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Journal of the ASEAN Federation of Endocrine Societies



Vol. 41 No. 1 April 2026 | eISSN 2308-118x (Online)

ORIGINAL ARTICLES

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The Prevalence and Risk Factors for Persistent Hyperparathyroidism in Post-Kidney Transplant Patients: A Single-Center Retrospective Study

Diagnostic Value of Key Clinical Characteristics and Baseline Cortisol in Assessing Adrenal Function in Patients Receiving Glucocorticoid Therapy

Retrospective Study of Clinical Characteristics, Natural History and Predictive Factors for Mild Autonomous Cortisol Secretion (MACS) in Patients with Adrenal Incidentalomas in Malaysia

Evaluating the Two-Step TSH Screening Protocol for Congenital Hypothyroidism: Prevalence and Diagnostic Accuracy in Ninh Binh, Vietnam

REVIEW ARTICLES

Living with Legacy: Outcomes and Future Implications for Offspring of Patients with MEN1

High Remnant Cholesterol Increased the Risk of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) or Non-Alcoholic Fatty Liver Disease (NAFLD): A Systematic Review and Meta-Analysis

Liver Enzyme Biomarkers Before or in Early Pregnancy as Predictors for Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis

Addressing Unmet Needs in the Management of Diabetes in Asia and Enhancing Diabetes Care Through the Use of Digital Technology: An Expert Opinion

CASE REPORTS

The Lingering Battle of Persistent Hypoaldosteronism Following Adrenalectomy for Primary Aldosteronism: A Case Report

A Rare Paediatric Adrenocortical Carcinoma with Aggressive Clinical Course

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Lingual Thyroid: An Ectopic Presentation at the Base of the Tongue





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Journal of the ASEAN Federation of Endocrine Societies

Vol. 41 No. 1 April 2026 | eISSN 2308-118x (Online)

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TABLE OF CONTENTS

Editorial

The Endocrine Window Widens: A New Chapter for JAFES **6**
Cecilia A. Jimeno

Passing the Baton: A Tribute to Dr. Elizabeth Paz-Pacheco **8**

ORIGINAL ARTICLES

Islet Autoantibody and Beta Cell Secretory Status at Diagnosis in Young Bangladeshi with Phenotypically Type 2 Diabetes **10**
Kishore Kumar Shil, Mashfiqul Hasan, Nusrat Sultana, Sayad Bin Abdus-Salam, Hafsa Mahrukh, Tahmina Ferdousi, Muhammad Abul Hasanat

Direct Medical Cost Analysis of Hyperglycemic Emergencies Among Patients with Diabetes Mellitus in a Tertiary Government Hospital in the Philippines **18**
Juan Paolo Abasolo, Aldrich Ivan Lois Burog, Margarette Rose Pajanel, Emilio Villanueva III, Celito Tamban

The Impact of Chronic Kidney Disease on Ulcer-Related Outcomes in Hospitalized Diabetic Foot Ulcers: A Retrospective Study from Thailand **32**
Jeeraphan Sripatpong, Sirinate Krittiyawong, Waralee Chatchomchuan, Ekgaluck Wanothayaroj, Taweesak Srikummoon, Poovasit Klinoubol, Phawinpon Chotwanvirat, Siriwan Butadej, Soontaree Nakasatien, Thep Himathongkam, Yotsapon Thewjitcharoen

Knowledge, Attitudes and Practices of Physicians on Diagnosis and Management of Diabetic Peripheral Neuropathy at the University of Santo Tomas Hospital **40**
Samantha Bernardine Reburiano, Dylan Jansen Taytayon, Dionise Ysabelle Bawal, Bien Matawaran

Guideline-Directed Medical Therapies for Diabetic Kidney Disease Among Thai People With Type 2 Diabetes: A Real-World Data Based on Theptarin Diabetes Staging **49**
Peachaphol Chongvoranond, Waralee Chatchomchaun, Ekgaluck Wanothayaroj, Siriwan Butadej, Soontaree Nakasatien, Thep Himathongkam, Yotsapon Thewjitcharoen

Effect of Baseline HbA1c and Inpatient Glycemic Control on Mortality and Organ Dysfunction among Patients with Diabetes Mellitus Hospitalized for COVID-19: A Multicenter Retrospective Cohort Study **60**
Mari Des San Juan, Jennifer Lourdes Ng, John Paul Martin Bagos, Marion Sarigumba, Jekrylei Cadeliña, Ronald Chua, Darius Enario, Margarita Katrina Amor Tan, Elizabeth Paz-Pacheco, Sahra May Paragas, Erick Mendoza, Maria Princess Kanapi, Christina Chua, Cindy Ceryl Tan, Cecille Dela Paz, Karla Kristine Fernando

COVID-19 Infection and Gut Microbial Dysbiosis Among Filipinos with Type 2 Diabetes Mellitus **72**
Adrian Jonathan Velasco and Leslie Michelle Dalmacio

Prevalence and Impact of Hypothyroidism on Glycaemic Control in Indian Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study **82**
J Rawat and Aviral Rawat

Prevalence and Factors Associated with Diabetes Related Emotional Distress (DRED) Among Filipino Adult Patients with Type 2 Diabetes Mellitus Using A Validated Filipino Version of the Diabetes Distress Scale (DDS) 87
Carissa Rae Mirano, Oliver Allan Dampil, Hanna Clementine Tan

The Association of Ramadan Fasting on Relative Leukocyte Telomere Length in Type 2 Diabetes Mellitus 100
Mona Hardika, Farid Kurniawan, Purwita Wijaya Laksmi, Syahidatul Wafa, Rheza Meida Marliau, Agian Jeffilano Barinda, Dante Harbuwono, Dicky Tahapary

How Filipinos View Obesity: Findings From the ACTION APAC Study 107
Nemencio Nicodemus Jr., Edgardo Juan Tolentino, Cecilia Jimeno, Joy Arabelle Fontanilla, Cyrus Pasamba, Danieson Lampano

The Prevalence and Risk Factors for Persistent Hyperparathyroidism in Post-Kidney Transplant Patients: A Single-Center Retrospective Study 121
Pamela Anne Gaerlan, Harold Henrison Chiu, Matt Jayson Fontarum, Jocelyn Cobankiat

Diagnostic Value of Key Clinical Characteristics and Baseline Cortisol in Assessing Adrenal Function in Patients Receiving Glucocorticoid Therapy 128
Dung Truc Nguyen, Tuan Thanh Nguyen, Khanh Quang Tran

Retrospective Study of Clinical Characteristics, Natural History and Predictive Factors for Mild Autonomous Cortisol Secretion (MACS) in Patients with Adrenal Incidentalomas in Malaysia 137
Vanusha Devaraja, Subashini Rajoo, Vijiya Mala Valayatham, Foo Siew Hui

Evaluating the Two-Step TSH Screening Protocol for Congenital Hypothyroidism: Prevalence and Diagnostic Accuracy in Ninh Binh, Vietnam 147
Nguyen Hoang Viet, Tran Khanh Hoa, Nguyen Bich Ngan, Bui Thi Bao, Nguyen Anh Ngoc, Van-Thao Ta

REVIEW ARTICLES

Living with Legacy: Outcomes and Future Implications for Offspring of Patients with MEN1 152
Dimuthu Tharanga Muthukuda, Kushalee Poornima Jayawickreme, Gayathri Wijeweera, Ashley Grossman

High Remnant Cholesterol Increased the Risk of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) or Non-Alcoholic Fatty Liver Disease (NAFLD): A Systematic Review and Meta-Analysis 160
Taufik Biya, Himawan Sanusi, Andi Makbul Aman

Liver Enzyme Biomarkers Before or in Early Pregnancy as Predictors for Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis 168
Samuel Pratama, Rizka Dwi Aulia, Indi Jazilah, Brigitta Cindy Lauren

Addressing Unmet Needs in the Management of Diabetes in Asia and Enhancing Diabetes Care Through the Use of Digital Technology: An Expert Opinion 184
Daphne SL Gardner, Julia K. Mader, Sanjay Kalra, Irene Kopp, Banshi Saboo, Kazuhiro Sugimoto, Michael Villa, Shailendra Bajpai

CASE REPORTS

The Lingering Battle of Persistent Hypoaldosteronism Following Adrenalectomy for Primary Aldosteronism: A Case Report 194
Jie En Tan, Nor Shaffinaz Yusoff Azmi Merican, Shartiyah Ismail, Noor Rafhati Adyani Abdullah

A Rare Paediatric Adrenocortical Carcinoma with Aggressive Clinical Course 200
Kah Yin Lim and Pian Pian Tee

LETTER TO THE EDITOR 205
Eisha Fatimah, Sarosh Usman, Muhammad Aqib Farooq Khan

IMAGES IN ENDOCRINOLOGY

Intraductal Papillary Mucinous Neoplasm of the Pancreas Presenting as Worsening Hyperglycemia in a 72-Year-Old Patient with Type 2 Diabetes 207
Yotsapon Thewjitcharoen, Nopparath Tongpoo, Veekij Veerasomboonsin, Soontaree Nakasatien, Thep Himathongkam

Lingual Thyroid: An Ectopic Presentation at the Base of the Tongue 209
Rizqi Rifani and Dicky Levenus Tahapary

Instructions to Authors 211
Editorial Policies 219
Cover Letter 223
Author Form 224
Patient Consent Form 227

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The Endocrine Window Widens: A New Chapter for JAFES



This April 2026 issue of the Journal of the ASEAN Federation of Endocrine Societies arrives at a moment of major transitions and subtle changes within the journal. After 15 years under the able leadership of Editor-in-Chief, Dr. Elizabeth Paz-Pacheco, the baton has been passed to yours truly. Building on this solid foundation, the journal forges onward with its commitment to serve as the "endocrine window between the ASEAN region and the world," by continuing to publish current and relevant research from the region and beyond. One of the changes that is being implemented is the expansion to three issues a year from the usual two as a result of the high volume of submissions to the journal reflecting the growing interest in and confidence of authors in this regional publication. For this, the journal leadership is grateful to the authors, our JAFES editorial team and the AFES leadership for their support.

This issue also arrives at a moment when the burden of endocrine disease in our region continues to outpace the capacity of our health systems to respond. Twenty-four contributions from ASEAN countries and our neighbors in Asia including Bangladesh, the Philippines, Thailand, Indonesia, Malaysia, Vietnam, India, and Sri Lanka populate this issue—an emphatic reminder that endocrinology in Asia is neither monolithic nor merely derivative of Western paradigms. It is, instead, a discipline shaped by distinct epidemiologic pressures, genetic predispositions, cultural practices, and resource realities that demand region-specific evidence.

Diabetes Mellitus: The Dominant Narrative

More than half of the original articles in this issue address diabetes mellitus, reflecting both its overwhelming prevalence and the multifaceted nature of its complications. The work of Bangladeshi investigators on islet autoantibody and beta cell secretory status in young adults with phenotypically type 2 diabetes challenges us to reconsider diagnostic categories that may obscure latent autoimmune disease in our populations. This question—what type of diabetes are we actually treating?—has profound implications for therapeutic selection and prognostication.

Several papers interrogate diabetes care along its complications cascade. The Thai cohort study on diabetic foot ulcers in patients with chronic kidney disease, the retrospective analysis of guideline-directed therapies for diabetic kidney disease using the Theptarin Diabetes Staging system and the assessment of physician knowledge and practice on diabetic peripheral neuropathy at the University of Santo Tomas Hospital in Manila together construct a sobering portrait: even where evidence-based care is well-defined, implementation gaps persist. The Filipino cost analysis of hyperglycemic emergencies in a tertiary government hospital quantifies what clinicians have long suspected—that the economic toll of poorly controlled diabetes falls heaviest on those least able to bear it.

The lingering shadow of the COVID-19 pandemic continues to inform our understanding of diabetes pathophysiology. The multicenter retrospective cohort study on baseline HbA1c and inpatient glycemic control in COVID-19 patients reaffirms that glycemic dysregulation is not merely a comorbidity but a determinant of survival. The companion study on gut microbial dysbiosis among Filipinos with type 2 diabetes and COVID-19 infection extends this inquiry into the microbiome, suggesting biological mechanisms that may yet yield therapeutic targets.

https://doi.org/10.15605/jafes.041.01.6480

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Equally important are the papers that move beyond biomedical reductionism. The validation and application of the Filipino version of the Diabetes Distress Scale to characterize diabetes-related emotional distress (DRED) in our patients is a welcome corrective to a literature that has too often treated psychological burden as peripheral. The Indonesian investigation of Ramadan fasting and relative leukocyte telomere length, meanwhile, exemplifies the kind of culturally embedded research that only investigators within our region can credibly undertake.

Beyond Glucose: The Breadth of Endocrine Practice

Although diabetes commands the most space in this issue, the breadth of endocrine practice is well represented. The Indian cross-sectional study on hypothyroidism and glycemic control reminds us that endocrine disorders rarely travel alone. The Filipino contribution to the ACTION APAC study on perceptions of obesity surfaces a uniquely complex challenge: how do we reconcile clinical urgency with cultural attitudes that may not regard adiposity as pathological?

The adrenal contributions are particularly noteworthy. The diagnostic value of clinical characteristics and baseline cortisol in assessing adrenal function during glucocorticoid therapy addresses a daily clinical dilemma. The Malaysian retrospective study on mild autonomous cortisol secretion in patients with adrenal incidentalomas advances our understanding of a condition whose clinical significance remains contested. The two case reports—on persistent hypoaldosteronism following adrenalectomy for primary aldosteronism, and on a rare pediatric adrenocortical carcinoma—illustrate the diagnostic and therapeutic challenges that define our subspecialty at its most demanding.

Thyroid disease is represented by the Vietnamese evaluation of the two-step TSH screening protocol for congenital hypothyroidism in Ninh Binh province—a study with direct implications for newborn screening policy across the region—and by an instructive image of lingual thyroid as an ectopic presentation. The study on persistent hyperparathyroidism in post-kidney transplant patients addresses an underappreciated complication of transplantation that endocrinologists are increasingly called upon to manage.

Synthesis, Hereditary Syndromes, and the Digital Frontier

The review articles in this issue gesture toward both the future and the foundational. The Sri Lankan review on outcomes and implications for offspring of patients with multiple endocrine neoplasia type 1 reminds us that endocrine genetics is a generational concern requiring sustained family-centered care. The two Indonesian meta-analyses—on remnant cholesterol and metabolic dysfunction-associated fatty liver disease, and on liver enzyme biomarkers as predictors of gestational diabetes—exemplify the kind of synthetic scholarship that can elevate regional evidence into globally relevant insight.

Of strategic importance is the expert opinion on addressing unmet needs in diabetes care in Asia through digital technology. As our region contemplates the integration of telemedicine, continuous glucose monitoring, artificial intelligence-assisted decision support, and electronic health records, we must do so with clear-eyed attention to equity. Digital tools that widen rather than narrow the gap between the well-resourced and the underserved would be a failure not of technology but of imagination and policy.

A Closing Reflection

What strikes me most about this issue is not any single paper, but the cumulative portrait it paints of a regional endocrine community coming into its own. The questions our investigators are asking—about genetic and immunologic heterogeneity in our populations, about the economic and emotional costs of chronic disease, about culturally appropriate care, about the unfinished business of pandemic-era endocrinology, and about the responsible deployment of digital health—are questions that cannot be adequately answered from outside our region. They are ours to investigate, and the evidence we generate must increasingly inform our own guidelines, training programs, and health policies.

I commend our authors for their scholarship, our reviewers for their rigor, and our readers for the clinical care that ultimately gives this work its meaning. The patients we serve—from Dhaka to Ho Chi Minh City, from Manila to Colombo—are the silent collaborators in every paper that follows. May this issue serve them well.

Cecilia A. Jimeno
Editor-in-Chief, JAFES

Disclosure: The author declares no conflict of interest relevant to this editorial.

Journal of the
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Passing the Baton: A Tribute to Dr. Elizabeth Paz-Pacheco

Editor-in-Chief, Journal of the ASEAN Federation of Endocrine Societies (2010–2025)

There are moments in the life of an organization when quiet stewardship shapes its future more profoundly than any single event. For the Journal of the ASEAN Federation of Endocrine Societies, that moment stretched across fifteen years, guided by the steady, visionary leadership of **Dr. Elizabeth Paz-Pacheco.**



When she assumed the role of Editor-in-Chief in 2010, JAFES was still finding its footing. JAFES was non–peer-reviewed, irregular in publication, and largely unseen beyond its immediate circles. What followed under her leadership was not merely improvement, but transformation.

With clarity of purpose and unwavering commitment to scientific integrity, Dr. Paz-Pacheco led the journal toward becoming a fully peer-reviewed publication, establishing regular biannual issues, and building a sustainable editorial process supported by an Open Journal Systems platform. These were not just operational milestones; they were foundational steps in redefining the journal's identity and credibility.

Perhaps most significantly, JAFES achieved indexing in major international databases: including PubMed, PubMed Central, Scopus, Web of Science, the WHO Western Pacific Region Index Medicus, and the Directory of Open Access Journals. These accomplishments are not easily won; they are the result of consistent editorial discipline, rigorous standards, and a deep respect for the scientific enterprise.

But beyond metrics and milestones lies a more enduring legacy. Dr. Paz-Pacheco cultivated a culture of excellence, one that valued not only quality research, but also mentorship, regional collaboration, and the elevation of Southeast Asian voices in global endocrinology. She transformed JAFES into a platform where local scholarship could stand confidently alongside international work.

Her leadership reminds us that journals are not merely repositories of knowledge, but rather, communities shaped by the values of those who guide them.

As she steps down from her role as Editor-in-Chief and passes the baton to Dr. Cecilia Jimeno, we do not simply mark the end of a tenure. We recognize the lasting imprint of her vision, her discipline, and her dedication. On behalf of the endocrine community, we extend our deepest gratitude to Dr. Elizabeth Paz-Pacheco, for re-establishing not just a journal, but building a legacy.









"As she steps down from her role as Editor-in-Chief and passes the baton to Dr. Cecilia Jimeno, we do not simply mark the end of a tenure. We recognize the lasting imprint of her vision, her discipline, and her dedication."



– "Passing the Baton"

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Islet Autoantibody and Beta Cell Secretory Status at Diagnosis in Young Bangladeshi with Phenotypically Type 2 Diabetes

Kishore Kumar Shil,[1] Mashfiqul Hasan,[2] Nusrat Sultana,[2] Sayad Bin Abdus-Salam,[2] Hafsa Mahrukh,[2] Tahmina Ferdousi,[2] Muhammad Abul Hasanat[2]

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Abstract

Background. The overlapping clinical features in young-onset type 2 diabetes (T2DM) present significant diagnostic difficulties. Variable autoimmunity and beta-cell dysfunction, which are related to the phenomenon, are not sufficiently consolidated to distinguish subclasses.

Objectives. To determine the frequency of islet autoantibodies and beta-cell secretory status in phenotypically young Bangladeshi with T2DM.

Methodology. This cross-sectional study enrolled 83 patients with newly diagnosed young-onset phenotypically T2DM, aged 10 to 29 years, comprising 34 males (41%) and 48 females (59%), using non-probability purposive sampling. The demographic and clinical features of the patients were recorded. A fasting blood sample was collected for C-peptide and islet antibodies (anti-glutamic acid decarboxylase [GAD], zinc transporter 8 [ZnT8], and Islet Antigen 2 [IA-2] antibodies). C-peptide, anti-GAD Ab and IA-2 Ab were measured by chemiluminescence, while the ZnT8 Ab was measured by enzyme-linked immunosorbent assay (ELISA).

Results. An adequate beta cell secretory reserve was present in 97.6% of participants (N = 82), with a median C-peptide level of 4.3 ng/mL (IQR: 3.0-6.7). Of the 82 patients included, GAD Ab was found to be positive in 17% (n = 14), ZnT8 Ab in 2.4% (n = 2), and none were positive for IA-2 Ab or a double antibody (ZnT8 Ab + GAD Ab). The frequency of double diabetes (DD) [GAD Ab positive subjects] was 17% (14/82). Comparing the GAD Ab positive to the negative group, the former had a significantly lower homeostasis model assessment of β-cell function (HOMA-B) at 24.7 (16.3-99.1) [versus 81.9 (30-154) in the latter (p = 0.02)] and a significantly higher fasting plasma glucose (FPG) median IQR at 16 mmol/L (10-19) [compared to 9.5 (6.7-14.5) (p = 0.04) in the negative group.] The body mass index (BMI) was the only significant predictor of C-peptide (β = 0.44, p <0.001).

Conclusion. GAD Ab was the most commonly detectable antibody in this study of young-onset phenotypically T2DM patients. The concentration of GAD Ab may influence the phenotypic presentation, but it is not a predictor of C-peptide levels. Beta-cell dysfunction in this subset of patients may depend on certain yet unexplored factors.

Key words: young diabetes, phenotypic T2DM, islet autoantibodies, C-peptide

INTRODUCTION

Diabetes is one of the most prevalent non-communicable diseases and one of the fastest-growing global health emergencies of the 21st century. Common factors for the high prevalence of diabetes are related to an increased prevalence of obesity, population aging, population growth, urbanization and physical inactivity.[1] Type 2 diabetes (T2DM) is the most prevalent form of diabetes and has increased with cultural and social changes. Not only is it highly prevalent in adults, but the prevalence of T2DM has also been rising in the young. It has been observed that Asians, compared to Western populations, develop diabetes at younger ages with a risk of developing complications in early adulthood.[2] South Asians have also increased abdominal visceral fat and greater insulin resistance (IR).[3] The prevalence of young-onset DM in Bangladesh is also rising.[4] Therefore, it is necessary to know the characteristics and nature of this group of diabetic patients in Bangladesh.

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Shil et al.
Received: February 16, 2025. Accepted: April 29, 2025.
Published online first: April 25, 2026.
https://doi.org/10.15605/jafes.041.01.5033

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The common underlying mechanism of all forms of DM is the dysfunction or destruction of pancreatic beta cells. Factors involved in this process include genetic predisposition, epigenetic processes, insulin resistance, autoimmunity, concurrent illnesses, inflammation and environmental factors. Understanding the beta cell status can help define subtypes of diabetes and guide their treatment.[5] Islet beta cell autoantibodies against glutamic acid decarboxylase (GAD), zinc transporter 8 (ZnT8) and Islet antigen 2 (IA-2) are implicated in the pathogenesis of autoimmune beta-cell destruction. Historically, T2DM has been considered primarily a metabolic disease of older individuals without involvement of the immune system. Over the years, investigations into the pathophysiology of T2DM have identified the presence of islet-specific T cells and islet autoimmunity in T2DM.[6] Using islet autoantibodies as a biomarker for islet autoimmunity in type 2 diabetes mellitus (T2DM), the prevalence of islet autoimmunity has been estimated to be between 5% and 30%.[7] One study showed that the frequency of autoimmunity was lower in T2DM compared to T1DM; however, there were still 8.1%, 30.3% and 34.8% of T2DM children and adolescents testing positive for anti-glutamic acid decarboxylase (GAD), Zn transporter 8 (ZnT8) and Islet Antigen 2 (IA-2) antibody, respectively.[8] Recently, the phenotypes of T1DM and T2DM have become less distinctive, which is why the World Health Organization (WHO) has revised the classification of diabetes and has recognized hybrid forms of DM, including slowly evolving immune-mediated DM and ketosis-prone diabetes as separate subtypes of DM. The American Diabetes Association (ADA) (2011) defined youth with type 2 diabetes as having evidence of islet cell autoimmunity with autoantibodies targeting beta cells typical of type 1 diabetes as "double diabetes" (DD). The term "double diabetes" (DD) refers to cases where a patient exhibits characteristics that are a combination of T1DM and T2DM.[9] Common symptoms of DD include obesity, insulin resistance, a positive family history and the presence of autoantibodies, specifically GAD56, IA-2 and insulin antibodies. Having DD is significant among young onset (11–19 years old) diabetic patients, because of weight gain and insulin resistance.[10] Identifying DD in children and adolescents is crucial as it affects the diagnostic method and choice of treatment.

The serum C-peptide level reflects insulin secretion from pancreatic islet cells and has been suggested as a valid parameter in classifying diabetes. Patients with DD need early treatment with insulin as they develop early beta cell failure and are more prone to develop ketosis. Nearly 65% of the DD group may require early insulin treatment.[11] In our country, there is no available data on the prevalence of DD and the percentage of positive islet antibodies in young T2DM patients. Hence, the objective of our study was to measure islet autoantibodies (GAD, ZnT8, and IA2) and to assess beta-cell secretory status through fasting C-peptide and HOMA-B in young-onset phenotypically T2DM individuals. Additionally, we also wanted to compare the clinical characteristics of participants with or without GAD Ab positivity and to correlate clinical and biochemical variables with GAD Ab, ZnT8 Ab levels and HOMA-B. Lastly, the study aimed to evaluate the ability of glycemic values to predict GAD antibody positivity using the Receiver Operating Characteristic (ROC) curve analysis.

METHODOLOGY

Study subjects and design

This cross-sectional study was conducted in the Department of Endocrinology at Bangabandhu Sheikh Mujib Medical University (BSMMU, Dhaka, Bangladesh). Eighty-three newly diagnosed (within 1 month of diagnosis) young patients with phenotypical T2DM, diagnosed according to the American Diabetes Association (ADA) criteria (age range: 10–29 years), were enrolled through non-probability purposive sampling. Phenotypical T2DM characteristics include: overweight/obesity, central obesity (abdominal obesity), features of insulin resistance (like acanthosis nigricans, obesity (central/ generalized), skin tags, double chin, lipodystrophy and, in females, features of androgen excess (androgenic alopecia, hirsutism, oligomenorrhea), positive family history and absence of ketosis at presentation.[12] Patients with gestational diabetes, chronic liver disease, chronic kidney disease, other endocrinopathies and current use of drugs interfering with endogenous insulin and C-peptide concentration were excluded from this study.

Sample size

Assuming a 21.2% prevalence of the most frequently detected islet autoantibody in young-onset T2DM (SEARCH for Diabetes in Youth Study Group, 2007), the required sample size was calculated with a 95% confidence level and a 10% margin of error using the following formula:

$$n = \frac{Z^2 pq}{d^2}$$

n = The desired sample size that would help to measure the different indicators.
z = The standard normal deviation, usually set at 1.96 at 5% level, which corresponds to a 95% confidence level.
p = The assumed target proportion.
q = 1-p
d = The degree of accuracy level considered as 10%. The degree of accuracy d, which is assumed, is 0.1

After calculation, the sample size was 65, but we recruited 83 young phenotypical T2DM patients.

Study procedure

A detailed history and thorough examination were done of each individual. Height was measured by using a stadiometer. Weight was measured by a balance on a hard, flat surface. Waist circumference (WC) was measured to the nearest centimeter with a flexible steel tape while

the participants were in a standing position at the end of gentle expiration. Hip circumference was measured at the level of the widest portion of the buttocks. Blood pressure (BP) was measured in millimeters of mercury by a standard sphygmomanometer. The demographic and clinical features of the patients (mode of presentation, physical activity level, family history, glycemic status, treatment history, anthropometric measurements, features of insulin resistance- acanthosis nigricans, obesity [central/generalized], skin tags, double chin, lipodystrophy and in females, features of androgen excess [androgenic alopecia, hirsutism, oligomenorrhea]) were recorded in a standard pre-tested structured datasheet. Physical activity level was defined as (1) vigorous, (2) moderate or (3) light physical activity. Vigorous activity was defined as any activity that caused a significant increase in breathing or heart rate, if continued for at least 10 minutes (e.g., running, carrying heavy loads, digging or construction work). Moderate activity was defined as any activity that caused a slight increase in breathing or heart rate, provided it was continued for at least 10 minutes (such as brisk walking or carrying light loads). Light physical activity was defined as activities such as office work.[13] Body mass index interpretation was done for those less than 18 years of age according to the growth charts of the US Centers for Disease Control and Prevention: children with normal weight (BMI from the 5th to the 85th percentile), overweight (BMI from the 85th to the 95th percentile) and obese (BMI above the 95th percentile).[14] For those 18 years and older, body mass index interpretation was done according to the WHO adult obesity category for Asians. An abnormal waist circumference in individuals under 18 years of age was defined as exceeding the 90th percentile for age and sex, according to the CDC's waist circumference growth charts for age. For those 18 years old and above, an abnormal WC was at least 90 cm in males and at least 80 cm in females.[15] A fasting blood sample (10 mL) was collected from each participant for the measurement of C-peptide and islet autoantibodies. C-peptide-based homeostasis model assessment[16] was determined using the following formulae: HOMA-B = 0.27 × fasting C-peptide (FCP)/(FPG-3.5) [If FCP in ng/mL then FPG in mg/dL; if FCP in pmol/L then FPG in mmol/L]; and, HOMA-IR = 1.5 + (FPG (mg/dL) x FCP (ng/mL)) / 2800, with a cut-off of 0.997 (sensitivity = 85.4, specificity = 52.4). Estimated glucose disposal rate (eGDR) (mg kg^{-1}/min) was calculated using the following formula: eGDR = 21.158 − (0.09 x WC) − (3.407 x HT) − (0.551 x HbA1c), where WC = waist circumference (cm), HT = hypertension (yes = 1/no = 0) and HbA1c = HbA1c (%).[17]

Analytic method

The quantitative determination of C-peptide was performed using a chemiluminescent immunometric assay with a measuring range of 0.01-20 ng/mL. The C-peptide assay is a sandwich chemiluminescence immunoassay in a single assay run. The intra-assay coefficient of variation (CV) was 5%. Quantitative determination of glutamic acid decarboxylase antibody (GAD65) measured through chemiluminescent immunometric assay, with a measuring range of 1.0-280 IU/mL, with sensitivity of 73% and specificity of 96%. Intra-assay CV was 3.6%. Also, quantitative determination of tyrosine phosphatase-like protein antibody (Anti-IA-2) was measured by the chemiluminescent immunometric assay with a measuring range of 2.5-280 U/mL. Intra-assay CV was 3.37%. The measurements of C-peptide, GAD65, and anti-IA-2 were performed on the Snibe MAGLUMI 2000 Plus Chemiluminescence Immunoassay (CLIA) System (China). Serum ZnT8 Ab was estimated by an ELISA kit by ElisaRSR™ ZnT8 Ab™, RSR Ltd. (Cardiff, UK) with a 72% sensitivity and a 99% specificity. Intra-assay CV was 4.39%.

A GAD Ab level greater than or equal to 5 U/mL, a ZnT8 Ab level greater than or equal to 15 U/mL and an IA-2 Ab level greater than or equal to 7 U/mL were considered positive. A C-peptide greater than or equal to 0.9 ng/mL was considered adequate.

Statistical analysis

Quantitative data were expressed as mean ± SD or median and interquartile range (IQR), whereas qualitative data were expressed in frequency distribution and percentages. Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 25.0). The association between categorical variables was analyzed using the $\chi 2$ test, and the continuous variables were analyzed using Student's *t*-test and one-way analysis of variance (ANOVA). A continuous variable with a skewed distribution was compared using the Mann–Whitney *U*-test. Correlation between the variables was done using Kendall's tau-b test. A *p*-value of less than 0.05 was considered statistically significant for all statistical tests.

Potential confounders of the assessment of beta cell secretory status and islet autoantibodies, such as chronic liver disease, chronic kidney disease, other endocrinopathies and the use of drugs that interfere with insulin secretion, were excluded from the study. An appropriate multivariable regression model was used to adjust for covariates associated with GAD antibody positivity.

Ethical considerations

The project commenced after approval of the Departmental Technical Committee and the Institutional Review Board (IRB). Voluntary, informed written consent was obtained from each subject and/or their legal guardian after a thorough explanation of the procedure and the purpose of the study. Each participant enjoyed the right to participate, refuse, or even withdraw from the study at any point in time. Proper medical services and advice were provided to all subjects, regardless of their enrollment status. Information about the patients was kept confidential. Proper counseling was done before the collection of blood samples. Adequate safety measures were taken at every step of sample collection.

RESULTS

The present study enrolled 83 young subjects with newly diagnosed phenotypic T2DM to assess their islet auto-antibodies and beta cell secretory status. Subsequently, one patient was diagnosed with fibrocalculus pancreatic diabetes and excluded from the study. No one fulfilled the criteria for T1DM based on auto-antibody positivity and C-peptide level, so we analyzed the data from 82 participants.

Table 1. Demographic and clinical characteristics of study participants (N=82)

Variables	n (%)	Median (IQR)
Age (years)		26.5 (22- 28.5)
Gender		
Male	34 (41%)	
Female	48 (59%)	
Family history†		
Present	49 (60%)	
Absent	33 (40%)	
Acanthosis Nigricans		
Present	55 (67%)	
Absent	27 (33%)	
WC (cm)		
Normal	27 (33%)	
High	55 (67%)	
Physical activity level		
Light	60 (73%)	
Moderate	21 (25.5%)	
Vigorous	1 (1.5%)	
Symptoms of hyperglycemia††		
Present	57 (69%)	
Absent	25 (31%)	
WHR		
Normal	7 (8.5%)	
High	75 (91.5%)	
BMI (kg/m²) (mean ± SD)		25.8 ± 5.2
Normal	23 (28%)	
Overweight/Obese	59 (72%)	

Mean ± SD for normally distributed data and median (IQR) for skewed data.

† Family history of DM in 10 relatives

†† Polyurea, polydipsia, weight loss, tiredness.

DM: diabetes mellitus of young; HC: hip circumference; BP: blood pressure; BMI: body mass index, WC: waist circumference; Obese, M>90, F>80; WHR: waist-hip ratio; Abdominal obesity, M>0.88, F>0.81

Clinical characteristics of the study subjects are presented in Table 1. The participants' ages varied from 10 to 29 years (median 26.5 [IQR 22-28.5]). Median glycemic values of the participants were: fasting plasma glucose of 10.4 mmol/L (IQR: 6.9-15.8), 2-hour plasma glucose after 75 g test of 18.0 mmol/L (IQR:12.9-23.7) and HbA1c of 8.5 % (IQR: 6.8-10.8). There was an adequate beta cell secretory reserve, with a median C-peptide of 4.3 ng/mL (IQR: 3.0-6.7), in the majority of participants (97.6%).

GAD Ab was found in 17% (14 out of 82) of patients, whereas ZnT8 Ab was found in 2.5% (2 out of 82). None of the participants were positive for IA-2 Ab or double antibody (ZnT8 Ab + GAD Ab). Subjects who were positive for GAD Ab were referred to as DD. There was a trend of a higher frequency of GAD Ab positivity in those under 18 years old (25% [3/12] vs. 15.7% [11/70], $p = 0.279$).

The clinico-biochemical characteristics between the GAD Ab-positive and negative groups are shown in Table 2. Beta cell secretory capacity assessed by HOMA-B was significantly lower [24.7 (16.3-99.1) vs. 81.9 (30- 154), $p = 0.02$] and fasting plasma glucose was significantly higher [16 (10-19) vs. 9.5 (6.7-14.5), $p = 0.04$] in the GAD Ab positive than those of the negative groups. The estimated glucose disposal rate (eGDR) was also significantly lower [6.49 (4.84-7.33) vs. 8.00 (6.35-9.11), $p = 0.013$] in the GAD Ab-positive groups.

There was a significant negative correlation between age (r = -0.18, $p = 0.02$) and HOMA-B (r = -0.17, $p = 0.02$) with GAD

Table 2. Clinical and biochemical characteristics in GAD Ab positive and negative participants (N=82)

Characteristics	Group		*P*
	GAD Ab Positive (n=14)	GAD Ab Negative (n=68)	
Age (years, median; IQR)	23 (18.7-28.2)	27 (22.2-28.7)	0.20
Sex; n (%)			
Male	7 (50 %)	27 (39.7%)	0.47
Female	7 (50 %)	41 (60.2%)	
BMI (kg/m², mean ± SD)	24.4 ± 6.7	25.9 ± 4.8	0.73
WHR (cm, median; IQR)	0.91 (0.88-0.97)	0.90 (0.88-0.95)	0.59
Acanthosis nigricans; n (%)	7 (50%)	48 (70%)	0.13
Family history of DM; n (%)	8 (57%)	41 (60%)	0.87
Symptoms of hyperglycemia; n (%)	11 (78.5%)	46 (67.5%)	0.41
FPG (mmol/L, median; IQR)	16 (10-19)	9.5 (6.7-14.5)	**0.04**
2h PG (mmol/L, median; IQR)	22.5 (13.9-27.9)	16.6 (12.8-22.9)	0.10
HbA1c (median; IQR)	10.6 (6.8-12.5)	8.4 (6.8-10.2)	0.16
HOMA-B (median; IQR)	24.7 (16.3-99.1)	81.9 (30- 154)	**0.02**
HOMA-IR (median; IQR)	1.81 (1.71-1.89)	1.80 (1.60-1.94)	0.97
eGDR (mg/kg/min, median; IQR)	6.49 (4.84-7.33)	8.00 (6.35-9.11)	**0.013**

Significance level was measured by $\chi 2$, Fisher's Exact test, and Mann-Whitney U test as applicable.

Within parentheses are percentages over the column total if not otherwise mentioned. HOMA-IR: homeostatic model assessment for insulin resistance; HOMA-B: homeostasis model assessment of β-cell function; WHR: waist-hip ratio; GAD Ab: glutamic acid decarboxylase antibody; BMI: body mass index; FPG: fasting plasma glucose; 2-hr PG: 2 hours after 75 g plasma glucose; HbA1c: glycated hemoglobin; eGDR: estimated glucose disposal rate.

Ab levels, and a positive correlation between HbA1c (r = 0.14, p = 0.04) and GAD Ab levels. However, there was no significant correlation between ZnT8 Ab level and any of the other variables (Table 3).

There was a significant positive correlation between BMI (r = 0.50, p <0.001) and symptoms of hyperglycemia (r = 0.26, p = 0.004) with HOMA-B and a negative correlation between HOMA-B and positive GAD Ab (r = -0.17, p = 0.02). There was no correlation between HOMA-B and ZnT8 Ab positivity (Table 4).

Multiple logistic regression (Table 5) was used to assess the ability of control measures (age, positive family history, BMI, Acanthosis nigricans, HOMA-B) to predict levels of GAD Ab positivity. Still, there were no statistically significant predictors of GAD Ab positivity.

Table 3. Correlation of GAD Ab and ZnT8 Ab level with clinical and biochemical characteristics

Determinants of 'r'	GAD Ab		ZnT8 Ab	
	r	*p*	r	*P*
Age (years)	-0.180	**0.02**	0.13	0.08
BMI (kg/m²)	-0.090	0.24	-0.01	0.81
HOMA-B	-0.178	**0.02**	0.04	0.57
HOMA-IR	-0.025	0.74	0.04	0.57
FPG (mmol/L)	0.122	0.11	-0.03	0.63
2h-PG (mmol/L)	0.143	0.06	-0.07	0.35
HbA1c (%)	0.148	**0.04**	-0.05	0.49

Correlation between variables was done by Kendall's tau-b.

r: correlation coefficient; HOMA-IR: homeostatic model assessment for insulin resistance; HOMA-B: homeostasis model assessment of β-cell function; FPG: fasting plasma glucose; 2h PG: 2 hours after 75 plasma glucose; HbA1c: glycated hemoglobin, BMI: body mass index; GAD Ab: glutamic acid decarboxylase antibody; ZnT8 Ab: zinc transporter 8 antibody.

Table 4. Correlation of HOMA-B with clinical characteristics and autoantibodies

Determinants of 'r'	r	*p*
HOMA-B vs BMI	0.50	**<0.001**
HOMA-B vs GAD Ab	-0.17	**0.02**
HOMA-B vs ZnT8 Ab	0.04	0.57
HOMA-B vs family history	0.15	0.09
HOMA-B vs. symptoms of hyperglycemia	0.26	**0.004**

Correlation between variables was done by Kendall's tau-b.

r: correlation coefficient; HOMA-B: homeostasis model assessment of β-cell function; BMI: body mass index, GAD Ab: glutamic acid decarboxylase antibody; ZnT8 Ab: zinc transporter-8 antibody.

Table 5. Multiple logistic regression for positive GAD Ab

Variables	OR	*P*	95% CI	
			Lower	Upper
Age (each year increase)	0.89	0.08	0.79	1.01
Family history of diabetes	1.20	0.78	0.31	4.6
BMI (kg/m²)	1.04	0.58	0.90	1.20
Acanthosis nigricans	0.21	0.07	0.44	1.05
HOMA-B	0.99	0.33	0.98	1.00

R^2 8.5-14.2%

OR: Exp(B); p <0.05 is significant; 95% CI: 95% confidence interval

HOMA-B: homeostasis model assessment of β-cell function; BMI: body mass index; GAD Ab: glutamic acid decarboxylase antibody.

Multiple regressions were used to assess the ability of control measures (age, positive family history, BMI, Acanthosis nigricans, waist-hip ratio, physical activity, GAD Ab, and ZnT8 Ab) to predict levels of C-peptide. BMI was a statistically significant predictor (B = 0.44, p <0.001). Every 1 kg/m^2 increase in BMI will increase 0.44 units of C-peptide.

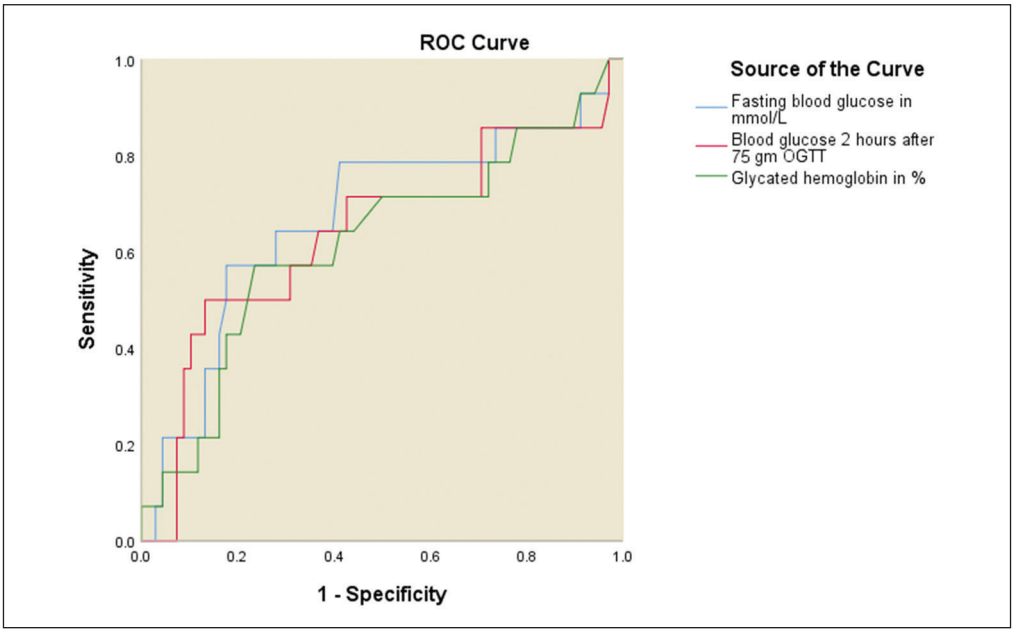
The ROC curve (Figure 1) analysis of glycemic values as a marker of GAD Ab positivity showed that the FPG value at a threshold of 11.3 mmol/L predicts the GAD Ab positivity with a sensitivity of 68% and specificity of 63%. Plasma glucose value 2 hours after a 75-gram glucose drink (2h-PG) at a threshold of 20.25 mmol/L predicts the GAD Ab positivity with a sensitivity of 56% and specificity of 72%. HbA1c at a threshold of 8.6% predicts the GAD Ab positivity with a sensitivity of 63% and specificity of 63%.

DISCUSSION

The classification of diabetes is crucial for developing an effective management plan for the condition. But considerable diagnostic hurdles exist in classifying young diabetic subjects due to overlapping clinical features, variable autoimmunity, and varying degrees of beta-cell dysfunction. Diabetes is often classified based on the presence of islet autoantibodies and C-peptide level. T2DM is the most polygenic and the most challenging to define because genetic, epigenetic, environmental variables, islet autoimmunity and islet-specific T cell response all play a role in its development. This ambiguity in diagnosis may contribute to a delay in initiating appropriate treatment, which leads to subsequent poor glycemic control.

The present study aimed to investigate the presence of islet-specific autoantibodies (GAD Ab, ZnT8 Ab and IA-2 Ab) and beta-cell secretory status in 83 young (aged 10-29 years) phenotypic T2DM subjects. GAD Ab was positive in one of six participants, ZnT8 Ab in one of twenty participants, while none were positive for IA-2 Ab or a double antibody (ZnT8 Ab+ GAD Ab). The frequency of double diabetes (GAD Ab positive) was 17% (14/82). GAD Ab-positive participants phenotypically simulated T1DM, with a lower BMI, less acanthosis nigricans, an infrequent family history of DM, and a higher prevalence of hyperglycemic symptoms. There were no independent predictors of GAD Ab positivity. HOMA-B had a significant positive correlation with BMI and symptoms of hyperglycemia. C-peptide concentration had an inverse relationship with GAD Ab titer, and BMI was the only statistically significant predictor of C-peptide level.

In the SEARCH study (2014), 21.2% of children aged 10 to 19 years diagnosed as T2DM tested positive for GAD-65 antibodies. However, in the TODAY study (2010), 9.8% (118 of 1,206) of young people with T2DM were positive for GAD-65 and/or IA-2 antibodies. In this study, GAD Ab was positive in 17% (14/82) of the participants. The higher rate of GAD Ab identified in young T2DM subjects in the



	Values	Area under curve	Sensitivity (%)	Specificity (%)	Youden index
FPG (mmol/L)	11.30	0.69	68	63	1.43
2h-PG (mmol/L)	20.25	0.67	56	72	1.40
HbA1c (%)	8.6	0.66	63	63	1.41

FPG: Fasting plasma glucose; 2h-PG: 2 hours after plasma glucose; HbA1c: glycated hemoglobin.
ROC curve: receiver operating characteristic curve

Figure 1. ROC curve analysis of glycemic values as a marker of GAD Ab positivity (N=82).

SEARCH study may be due to a higher background of the non-Hispanic white population. Tosur et al., also found that the proportion of autoantibody positivity varies by race/ethnic background, with the highest rates in white non-Hispanics, followed by Asians.[18]

Islet autoimmunity observed in T2DM possesses unique characteristics in terms of the presence of a single auto-antibody, ethnicity, age of onset of DM and insulin treatment. The presence of a single islet cell antibody is a unique feature of the Asian cohorts, whereas double antibody positivity was primarily observed in white Europeans.[19] ZnT8 Ab and IA-2 Ab positivity was present in 60–80% of individuals with new-onset T1DM compared to <2% of controls and <3% of individuals with phenotypic T2DM. ZnT8 Ab positivity is associated with older age, inflammation and acute metabolic complications in adults with both T1DM and phenotypic T2DM.[20] Wenzlau et al., found a low prevalence of ZnT8 Ab positivity (0.43%) in adolescents with T2DM.[21] We also found that ZnT8 Ab was positive in 2.4% (2/82) of participants, and none of the participants were positive for IA-2 Ab or double antibody (ZnT8 Ab + GAD Ab). In contrast, Mishra et al., found a 13% positivity rate for IA-2 Ab among DM participants under 25 years of age, where they included all DM subjects regardless of type; following antibody testing, 51% were identified with T1DM.[21] However, because this study only enrolled phenotypical T2DM patients, the observed low titer of IA-2 Ab in our study may be attributable to this. This low prevalence of ZnT8 Ab and IA-2 Ab indicates that ZnT8 and IA-2 Ab autoantibody positivity is not the etiology of a significant number of cases of T2DM in young people in our country.

The SEARCH study, TODAY study, and others found that GAD Ab-positive T2DM participants, denoted as "DD," were less likely to present with clinical and phenotypic traits of T2DM; instead, they were more likely to demonstrate a T1DM phenotype, characterized by hyperglycemic symptoms and a low BMI, among other manifestations.[19,22] We also found that GAD Ab-positive subjects had a lower BMI, fewer cases of acanthosis nigricans, a positive family history, and a higher frequency of symptoms of hyperglycemia compared to GAD Ab-negative subjects. Most studies found these phenotypic differences to be statistically significant. Since we only recruited phenotypic T2DM patients who had a high BMI and some signs of insulin resistance at the time of enrollment, they were not too likely to exhibit the phenomenon of positive GAD autoimmunity.

Tfayli et al., found that insulin sensitivity was significantly impaired in auto-antibody negative young T2DM compared with the young with islet autoimmunity and young obese controls.[23] Because the young patients with auto-immunity do not have the same level of insulin resistance as those with auto-antibody negative T2DM, the progression to diabetes must be due to a bigger component of beta cell failure than in auto-antibody negative young T2DM, presumably due to islet autoimmunity.

Hosen et al., from our study group found that C-peptide levels may not be low at diagnosis in young-onset DM subjects, which supports our findings of an adequate C-peptide level at diagnosis.[24] The GAD Ab positive T2DM group in SEARCH had a mean fasting C-peptide level of 2.83 ± 1.8 ng/mL, which was modestly higher than the TODAY study subjects (2.30 ± 1.62 ng/mL) but lower than that of the antibody-negative participants in both the TODAY study (4.13 ± 2.22 ng/mL) and SEARCH (3.71 ± 2.2 ng/mL). However, the C-peptide was substantially higher than that found in individuals with physician-diagnosed T1DM in SEARCH (fasting C-peptide 0.6 ng/mL). We found that HOMA-B and C-peptides were low, and fasting plasma glucose was significantly high in GAD Ab-positive groups. The median C-peptide concentration was slightly high in our study, as we measured C-peptide at diagnosis.

It was found that BMI (OR -0.11, p = 0.014), GAD Ab (OR 0.14, p = 0.007), C-peptide (OR -0.90, p = <0.001), and HOMA-IR (OR 0.92, p <0.001) were significant independent predictors for both fasting plasma glucose and 2-h plasma glucose. This indicates that both insulin resistance and beta-cell dysfunction contribute to glycemic status, with a prominent impairment in insulin secretion, as evidenced by a weak relationship (r = 0.23) with markers of insulin resistance (HOMA-IR) but a strong relationship (r = -0.73) with C-peptide. GAD Ab was a weak predictor, but HOMA-IR and C-peptide were strong predictors for the glycemic status of the participants. These findings are similar to other findings in Asians. Asian T2DM patients are generally non-obese, have a prominent impairment in insulin secretion and a better insulin sensitivity than non-Asians.[25] The steepest rates of glycemic deterioration were among those with young-onset T2DM, especially those diagnosed at age 20 years.[23] Aggressive glycemic deterioration in young-onset T2DM contributed to persistently increased HbA1c levels. A national Chinese cross-sectional survey of people with newly diagnosed T2DM showed that HOMA-β was similar across ages at diagnosis, but the difference in HOMA-β between people with T2DM and age-matched control individuals was much greater among people with young-onset than in people with usual-adult onset T2DM.[26]

In summary, the most commonly detectable antibody was the GAD Ab in our study of young-onset phenotypic T2DM subjects. The frequency of IA-2 Ab and ZnT8 Ab was lower, and none were positive for double-antibodies. The concentration of GAD Ab may dictate phenotypic presentation. The C-peptide level may be adequate at diagnosis, and GAD Ab may not be a reliable predictor of C-peptide level.

CONCLUSION

GAD Ab was the most commonly detectable antibody in young-onset phenotypic T2DM patients. The frequency of ZnT8 Ab and IA-2 Ab was very low to undetectable, and none were positive for double-antibodies, indicating that IA-2 Ab and ZnT8 Ab may not be characteristic of young-onset T2DM. The concentration of GAD Ab may dictate phenotypic presentation. Though GAD Ab may not be a predictor of C-peptide level, it may be concluded that beta cell dysfunction in young patients with diabetes might be dependent on other unexplored factors for classifying the early-onset T2DM.

Acknowledgment
The authors acknowledge the contribution of the Department of Microbiology, BSMMU, for their technical help.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
KKS: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration, Funding acquisition**;** **MH:** Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration; **NS:** Conceptualization, Methodology, Investigation; **SBAS:** Investigation, Resources; **HM:** Investigation, Resources; **TF:** Investigation, Resources, Writing – review and editing; **MAH:** Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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ORIGINAL ARTICLE

Direct Medical Cost Analysis of Hyperglycemic Emergencies Among Patients with Diabetes Mellitus in a Tertiary Government Hospital in the Philippines

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Abstract

Background. There is limited published local data on the direct medical costs of hyperglycemic emergencies. This study aimed to analyze direct medical costs incurred during hospitalization for hyperglycemic emergencies from a healthcare payer perspective.

Methodology. This is a retrospective cohort study done in a tertiary government hospital in the Philippines. The primary outcome measure was the median cost and distribution of direct medical costs (in Philippine Pesos) incurred during hospitalization.

Results. Among 319 patients with cost data, the median direct medical cost was PhP 79,331.50 (USD 1,375.02; USD 1: PhP 57.69), representing approximately 22.5% of the average annual family income and 7.2 times the average annual healthcare expenditure per capita. HHS incurred the highest costs (PhP 143,902.77; USD 2,494.21) with diagnostic fees as the largest expense (PhP 41,507.00; USD 719.42). The total costs exceeded the coverage provided by PhilHealth, the national health insurance in the Philippines.

Socioeconomic disparities were evident, with lower-income patients incurring higher expenses due to delayed presentation and more severe illness.

Conclusion. This study highlights the substantial economic burden of hyperglycemic emergencies in a public tertiary hospital. As one of the first of its kind locally, the study informs policy efforts to reduce financial risk for vulnerable populations and optimize resource allocation for diabetes-related emergencies.

Key words: health expenditure, direct medical cost, hyperglycemic emergencies

INTRODUCTION

Diabetes mellitus (DM) remains a growing public health concern. As of 2022, the World Health Organization (WHO) estimated that approximately 830 million people are living with DM, with a rapid rise noted in low- and middle-income countries.[1] In the Philippines, the prevalence of DM has been increasing and is currently estimated at 7.5% according to the International Diabetes Federation.[2] Alongside this growing prevalence, hyperglycemic emergencies have become a significant cause of morbidity and mortality. A local study has reported a higher-than-expected mortality rate.[3]

Hyperglycemic emergencies are acute, severe, life-threatening emergencies in individuals with Type 1 (T1DM) and Type 2 Diabetes Mellitus (T2DM). Diabetic ketoacidosis (DKA) is characterized by hyperglycemia, ketonemia/ketonuria and metabolic acidosis. Hyperglycemic Hyperosmolar State (HHS), on the other hand, is marked by severe hyperglycemia, hyperosmolality and dehydration without any major ketosis or acidosis.[4] These emergencies require urgent medical attention and are commonly managed with adequate fluid resuscitation, insulin therapy, correction of electrolyte imbalances, and close monitoring of patients.[4,5]

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Abasolo et al.
Received: June 29, 2025. Accepted: July 27, 2025.
Published online first: April 20, 2026.
https://doi.org/10.15605/jafes.041.01.5233

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Globally, the frequency of hyperglycemic emergencies is rising in both T1DM and T2DM populations.[4] In the Philippines, a 5% incidence rate for DKA and an 11% mortality rate have been reported.[3,6] These hyperglycemic emergencies impose a substantial clinical and financial burden, particularly in a resource-limited healthcare system. The global economic burden of diabetes is estimated at USD 1.31 trillion. Locally, the cost of managing T2DM varies considerably depending on the presence of complications, ranging from USD621 to USD3,226 annually per person with complications and USD127 to USD2,242 for those without.[7] However, specific data on the direct medical costs of hyperglycemic emergencies in the Philippines remain scarce.

In light of the Universal Health Care (UHC) Law, there is increasing demand from policymakers, healthcare payors and professional societies for reliable, context-specific cost data to inform reimbursement policies, optimize clinical resource allocation and support local guideline development. This study addresses this gap by evaluating the direct medical costs incurred during hospitalization for hyperglycemic emergencies among patients with diabetes mellitus in a tertiary government hospital in the Philippines. To provide clinical context to these costs, the study also examined key demographic, clinical and biochemical variables — including age, sex, diabetes type, comorbidities, identified etiologies (e.g., infection, non-adherence with medications), and biochemical markers such as pH, bicarbonate, anion gap, serum osmolality and glucose levels — as well as level of care received. These variables were selected based on existing literature demonstrating their association with disease severity, length of hospital stay and patient outcomes.[8]

OBJECTIVES

The main objective of this study is to analyze the direct medical costs incurred during hospital admissions of patients with DM treated for hyperglycemic emergencies (i.e., Diabetic Ketoacidosis or DKA, Hyperglycemic Hyperosmolar State or HHS, Diabetic Ketoacidosis-Hyperglycemic Hyperosmolar State Overlap or DKA-HHS, Euglycemic Diabetic Ketoacidosis).

Specifically, this study aims to:

1. Determine the median and distribution of direct medical costs incurred during hospital admissions of patients with DM treated for hyperglycemic emergencies.
2. Compare the median direct medical costs incurred across different socio-economic classifications.
3. Determine the association between selected factors – age, sex, etiology (i.e., infection, non-compliance with medications), presence of comorbidities, initial pH level, initial bicarbonate level, anion gap, type of diabetes, length of hospital stay) and direct medical costs among patients who had hyperglycemic emergencies.

METHODOLOGY

This paper was written following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. (Appendix B)

Study design

The researchers conducted a retrospective cohort study to evaluate the direct medical costs incurred by patients with diabetes mellitus admitted for hyperglycemic emergencies. This allowed assessment of cost accumulation during hospitalization and identification of factors associated with cost variation. The cost analysis was conducted from a healthcare payer perspective and was limited to direct medical costs, including diagnostics, medications, room charges and healthcare professional fees. Other categories of costs – indirect costs, out-of-pocket costs, administrative costs, long-term care costs, social costs, preventive care costs, legal and liability costs and behavioral health costs – were excluded. This focus on direct medical costs was a deliberate methodological choice reflecting the limited availability and reliability of non-medical cost data in the local setting. In the Philippine setting, where healthcare spending is largely out-of-pocket and the health system is fragmented, comprehensive tracking of indirect costs is challenging. Direct medical costs, routinely recorded in hospital billing and clinical records, provided the most feasible and consistent basis for analysis. Data were collected via retrospective review of medical records from January 1, 2017, to December 31, 2024.

Study setting

The study was conducted at East Avenue Medical Center, a tertiary government referral hospital in Quezon City. It is a 1,000-bed tertiary government hospital retained by the Department of Health in Quezon City. This facility serves as an apex referral center, offering medical services to a diverse patient population from multiple regions across the country, encompassing various socioeconomic backgrounds, the majority of which are indigents. The hospital has a well-established Department of Internal Medicine with dedicated subspecialty sections, including Endocrinology, which manages patients with diabetes mellitus and related complications. EAMC handles a high annual patient census, with diabetes consistently ranking among the leading causes of adult medical admissions.

Data gathering procedure

The researchers reviewed medical charts after obtaining permission from the Health Information Management Department of Medical Records and the Hospital Information System.

A review of databases from medical records from January 1, 2017, to December 31, 2024, was performed. The data-

base was searched using the following keywords: "DKA," "HHS," "DKA-HHS overlap," "diabetic ketoacidosis," "euglycemic DKA," and "hyperglycemic hyperosmolar state."

The following data were collected from medical records and recorded into the data abstraction form. Each patient received a unique identifier code. Demographics included age and sex. Clinical profile included type of DM (T1DM, T2DM, and others), duration of DM prior to onset of hyperglycemic emergency (in years), duration of symptoms (e.g., nausea, vomiting, abdominal pain, decreased sensorium) prior to presentation, vital signs (e.g., blood pressure, heart rate, respiratory rate, temperature), comorbidities (e.g., hypertension, pulmonary tuberculosis, autoimmune disorders, bronchial asthma, pregnancy), etiology (e.g., infection, non-compliance to medications), capillary blood glucose, random blood sugar, ketonuria, arterial blood gas (pH, pCO_2, HCO_3), anion gap, electrolytes (sodium, potassium, chloride), effective osmolality, level of care received (ward, ICU, ER) and type of hyperglycemic emergency (mild DKA, moderate DKA, severe DKA, HHS, DKA-HHS, Euglycemic DKA). Outcomes related to the patient included length of hospital stay, complications (e.g., hypoglycemia, hypokalemia, normal anion gap metabolic acidosis, thrombosis, cerebral edema, osmotic demyelination syndrome, acute kidney injury), and in-hospital mortality. Direct medical costs were extracted from medical and billing records and entered into a standardized data collection form. The cost components included medication expenses (e.g., intravenous fluids, electrolyte replacements, antibiotics, pressors, anti-diabetic medications), diagnostic fees, room charges and healthcare professional fees. These categories were selected based on their consistent availability and documentation in the patient records and were considered core components of inpatient care costs. However, some direct expenses not itemized or routinely documented may not have been fully captured. Consequently, the reported figures may underestimate the actual medical expenses incurred during hospitalization. The algorithm of the methodology is shown in Figure 1.

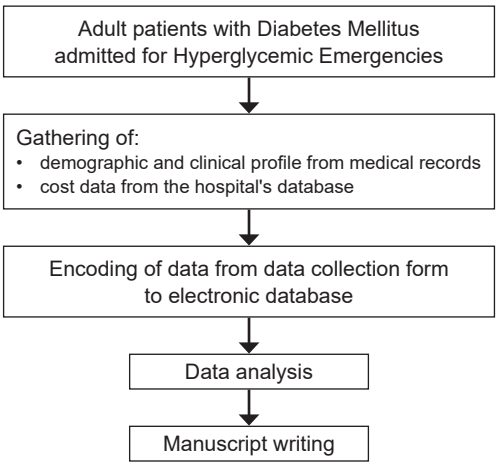


Figure 1. Algorithm of methodology.

Study participants

Adult patients who were clinically assessed to have hyperglycemic emergencies at East Avenue Medical Center from January 1, 2017, to December 31, 2024. The study period was selected based on the availability of accessible medical and billing records, with 2017 being the earliest year for which relevant data could be reliably retrieved.

Inclusion and exclusion criteria

The following individuals were included in the study: patients aged 18 years and above, diagnosed with DKA, HHS, DKA-HHS, or Euglycemic DKA, and admitted as service or private patients. Those with unavailable medical records were excluded.

Bias

Potential sources of bias included: selection bias due to incomplete or missing medical records and information bias related to inconsistencies in clinical documentation across the study period. To minimize bias in this study, the researchers utilized predefined inclusion and exclusion criteria to ensure objective patient selection and used a standardized data abstraction form to guide chart review.

Study outcome

The study's primary outcome of interest was the median cost and distribution of direct medical costs (in Philippine Peso) incurred during hospital admissions of patients with DM treated for hyperglycemic emergencies.

Sampling design

The researchers utilized a total enumeration technique. The study included all charts that met the inclusion and exclusion criteria.

Sample size

The sample size was computed using G*Power version 3.1. A minimum sample size of 395 was needed to achieve 80% power with a 5% level of significance in a multiple linear regression analysis with eight predictor variables of interest to detect a significant predictor of cost with a small effect size (Cohen's $f^2 = 0.02$). To ensure sufficient power for both objectives, a sample size of at least 395 participants was targeted for this study.

Data analysis

The data analysis involved descriptive statistics to summarize patient characteristics and direct medical costs of patients with diabetes mellitus treated for hyperglycemic emergencies seen at East Avenue Medical Center from January 1, 2017, to December 31, 2024. These were described across different types of hyperglycemic emergencies

and medical social service classifications. Box plots were generated to aid visual comparison between groups.

A generalized linear model with a gamma distribution and log-link function was used to analyze the relationship between total cost and the predictor variables of interest, adjusting for year of admission to account for inflation, policy changes, and the COVID-19 pandemic period. Length of hospital stay was log-transformed to address skewness, and influential data points were removed to improve model fit. The model was fitted using maximum likelihood estimation.

Data analysis was performed using Stata 17. The normality of distribution of numerical variables was checked using the Shapiro-Wilk test of normality. Missing values were neither replaced nor imputed. The generalized linear model excluded participants with missing data for total costs. Residual diagnostic plots were generated to check the fit of the generalized linear model. Statistical significance was set at $p < 0.05$.

In this retrospective cohort study, the researchers have opted not to perform sensitivity analyses. The primary focus is on the main outcomes as assessed by the predefined methodologies.

Ethical considerations

This study was approved by the EAMC institutional ethical review board (EAMC IERB 2024-150). The researchers adhered to ethical considerations and principles defined by relevant guidelines, including the Declaration of Helsinki, International Conference on Harmonization – Good Clinical Practice (ICH-GCP), National Ethical Guidelines for Research Involving Human Participants 2022, and the Data Privacy Act 2012.

RESULTS

A total of 377 patients with hyperglycemic emergencies were included in the analysis, as shown in Figure 2.

The demographics and clinical profiles of the study participants are presented in Table 1. Among the 377 patients, the majority presented with DKA, accounting for 69.5% of cases, with 38 classified as mild, 50 as moderate, and 174 as severe. This was followed by DKA-HHS overlap (19.4%) and HHS (10.9%). One case of euglycemic DKA was recorded. The median age of the cohort was 50 years (IQR: 24 years), with a male predominance (56.2%). Patients with HHS had the highest median age (65 years, IQR: 12 years), whereas DKA patients were generally younger (47 years, IQR: 23 years). T2DM was the most common diabetes type (83.6%), with all HHS patients diagnosed with T2DM. T1DM was more common in the DKA group (21.73%).

The median duration of diabetes was two years (IQR: 7 years), with patients experiencing symptoms for a median

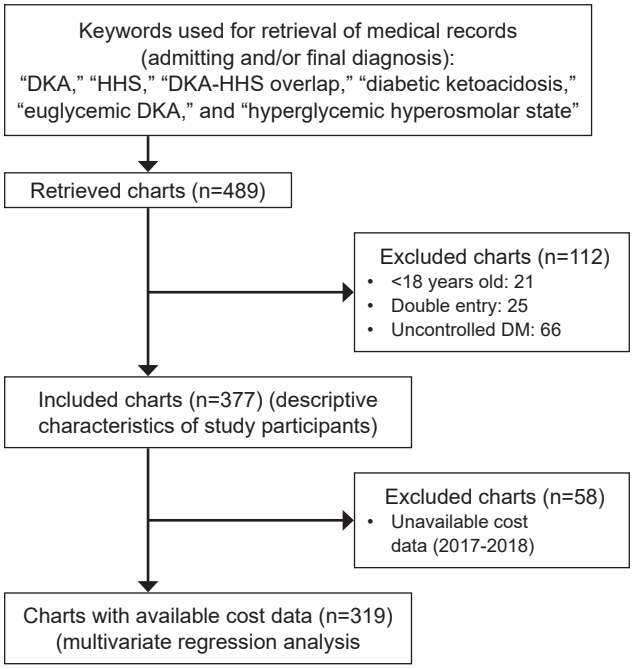


Figure 2. Participants flow diagram.

of three days (IQR: 6 days) before presenting to the hospital. The most common comorbidities were hypertension (37.7%) and pulmonary tuberculosis (16.2%). Infections (66.3%) and medication non-compliance (41.1%) were the most common precipitating factors.

On presentation, the median systolic and diastolic blood pressures were 120 mmHg (IQR: 30 mmHg) and 70 mmHg (IQR: 20 mmHg), respectively. Patients with HHS had higher median blood pressures compared to other groups. Random blood sugar was highest in DKA-HHS overlap (median: 702 mg/dL, IQR: 316 mg/dL) and lowest in DKA (median: 462 mg/dL, IQR: 258 mg/dL), consistent with the typical presentations of these conditions. The median glycosylated hemoglobin level was 12.7% (IQR: 4.18%), indicating poor glycemic control across all subgroups.

Patients with DKA had the lowest pH values (7.16, IQR: 0.29), while those with DKA-HHS overlap had the highest anion gap (28.7 mmol/L, IQR: 10.6 mmol/L), consistent with metabolic acidosis. The lowest bicarbonate levels were seen in DKA cases (HCO_3: 5.7 mmol/L, IQR: 7.2 mmol/L). Effective osmolality was highest in HHS patients (324 mOsm/kg, IQR: 30 mOsm/kg), confirming the hyperosmolar state characteristic of the condition. These findings support the diagnosis of each hyperglycemic emergency classification.

Most patients were managed in the emergency room (39.3%), while 24.9% were immediately transferred and managed in the intensive care unit (ICU). ICU admission was most frequent among patients with DKA-HHS overlap (31.5%). The median time to recovery was two days (IQR: 1 day) across all groups.

The most common in-hospital complications included acute kidney injury (48.0%), hypokalemia (36.7%) and hypoglycemia (26.8%). The incidence of acute kidney injury was highest among DKA-HHS overlap patients (69.9%), which may have contributed to the high mortality rate in this subgroup.

The overall in-hospital mortality rate was 35.0%, with the highest mortality observed in the DKA-HHS group (57.5%), followed by HHS (43.9%) and DKA (27.5%). The median length of hospital stay was seven days (IQR: 11 days), with prolonged hospitalization noted in patients with HHS (9 days, IQR: 12 days).

Table 1. Descriptive characteristics of study participants with diabetes mellitus treated for hyperglycemic emergencies seen at East Avenue Medical Center (n = 377)

Variables	Over all (n=377)	DKA (n=262)	HHS (n=41)	DKA-HHS (n=73)	Euglycemic DKA (n=1)
Age (years), median (IQR)	50 (24)	47 (23)	65 (12)	55 (22)	37
Sex, n (%)					
Male	212 (56.23%)	144 (54.96%)	20 (48.78%)	47 (64.38%)	1
Female	165 (43.77%)	118 (45.04%)	21 (51.22%)	26 (35.62%)	0
Type of diabetes mellitus, n (%)					
Type 1 DM	62 (16.4%)	56 (21.37%)	0	6 (8.22%)	0
Type 2 DM	315 (83.55%)	206 (78.63%)	41 (100.00%)	67 (91.78%)	1
Others	0	0	0	0	0
Duration of diabetes (years), median (IQR)	2 (7)	3 (8)	3 (7)	1 (6)	6
Duration of symptoms (days), median (IQR)	3 (6)	3 (6)	6 (8)	3 (6)	2
Comorbidities, n (%)					
Hypertension	142 (37.67%)	79 (30.15%)	27 (65.85%)	36 (49.32%)	0
Pulmonary tuberculosis	61 (16.18%)	44 (16.79%)	7 (17.07%)	10 (13.70%)	0
Autoimmune disorder	0	0	0	0	0
Bronchial asthma	14 (3.71%)	13 (4.96%)	0	1 (1.37%)	0
Pregnancy	3 (0.80%)	2 (0.76%)	0	1 (1.37%)	0
Etiology, n (%)					
Infection	250 (66.31%)	171 (65.27%)	29 (70.73%)	49 (67.12%)	1
Non-compliance to medications	155 (41.11%)	106 (40.46%)	18 (43.90%)	31 (42.47%)	0
Others	67 (17.77%)	45 (17.18%)	10 (24.39%)	12 (16.44%)	0
Systolic blood pressure (mmHg), median (IQR)	120 (30)	120 (30)	120 (40)	110 (30)	100
Diastolic blood pressure (mmHg), median (IQR)	70 (20)	70 (10)	80 (20)	70 (20)	60
Heart rate (bpm), median (IQR)	103 (23)	103 (22)	98 (22)	109 (22)	74
Respiratory rate (bpm), median (IQR)	22 (6)	22 (6)	20 (3)	23 (6)	20
Temperature (°C), median (IQR)	36.8 (0.4)	36.7 (0.4)	36.8 (0.4)	36.8 (0.4)	37.2
Capillary blood glucose (mg/dL), median (IQR)	452 (251.5)	403 (236)	563 (159)	600 (154)	178
Random blood sugar (mg/dL), median (IQR)	511 (336)	462 (258)	608 (365)	702.5 (316)	195
Ketonuria (+), median (IQR)	2 (1.5)	2 (2)	0 (0)	1 (1.75)	2
pH (mmol/L), median (IQR)	7.194 (0.286)	7.164 (0.299)	7.400 (0.083)	7.170 (0.262)	7.284
pCO2 (mmol/L), median (IQR)	18.1 (12.9)	16.1 (10.6)	28.6 (9.0)	21.0 (12.7)	21.5
HCO3 (mmol/L), median (IQR)	7.0 (9.2)	5.7 (7.2)	17.9 (7.0)	7.9 (7.3)	10
Anion gap (mmol/L), median (IQR)	26.6 (8.4)	27.0 (7.6)	19.9 (8.9)	28.7 (10.6)	21.8
Sodium (mmol/L), median (IQR)	135.70 (10.31)	133.40 (8.40)	148.00 (16.40)	146.57 (18.40)	136.2
Potassium (mmol/L), median (IQR)	4.33 (1.24)	4.40 (1.22)	4.06 (1.16)	4.21 (1.29)	3.54
Chloride (mmol/L), median (IQR)	101.0 (11.3)	99.6 (9.2)	110.3 (20.2)	109.3 (19.1)	104.4
Glycosylated hemoglobin (%), median (IQR)	12.70 (4.18)	12.66 (3.80)	10.80 (4.94)	14.30 (5.18)	13.8
Effective osmolality (mmol/L), median (IQR)	300 (27)	294 (17)	327 (32)	324 (30)	283
Time to recovery (days), median (IQR)	2 (1)	1 (1)	2 (1)	2 (2)	1
Level of care received, n (%)					
Emergency room	148 (39.26%)	95 (36.26%)	15 (36.59%)	38 (52.05%)	0
Ward	135 (35.81%)	106 (40.46%)	17 (41.46%)	12 (16.44%)	0
Intensive care unit	94 (24.93%)	61 (23.28%)	9 (21.95%)	23 (31.51%)	1
In-hospital complications, n (%)					
Hypoglycemia	101 (26.79%)	65 (24.81%)	16 (39.02%)	20 (27.40%)	0
Hypokalemia	139 (36.87%)	101 (38.55%)	15 (36.59%)	23 (31.51%)	0
Normal anion gap metabolic acidosis	1 (0.27%)	0	1 (2.44%)	0	0
Thrombosis	1 (0.27%)	0	0	1 (1.37%)	0
Cerebral edema	1 (0.27%)	1 (0.38%)	0	0	0
Osmotic demyelination syndrome	0	0	0	0	0
Acute kidney injury	181 (48.01%)	114 (43.51%)	16 (39.02%)	51 (69.86%)	0
Length of hospital stay (days), median (IQR)	7 (11)	8 (10)	9 (12)	5 (10)	6
In-hospital mortality, n (%)	132 (35.01%)	72 (27.48%)	18 (43.90%)	42 (57.53%)	0

The direct medical costs incurred during hospital admissions for hyperglycemic emergencies varied across the different clinical groups, as summarized in Table 2. Out of the 377 patients, cost data were available for only 319 patients due to the unavailability of cost data from 2017-2018. The overall median total cost was PhP 79,331.50 (IQR: 103,027.27). Among the subgroups, patients with HHS had the highest median total cost of PhP 143,902.77 (IQR: 184,655.35), followed by DKA cases at PhP 78,230.81 (IQR: 90,883.92) and DKA-HHS overlap cases at PhP 74,167.55 (IQR: 74,915.82). The single case of euglycemic DKA incurred a total cost of PhP 39,947.20.

The median medication costs were highest in HHS patients (PhP 13,209.46, IQR: 31,700.83), followed by DKA-HHS (PhP 7,361.34, IQR: 16,117.46), and lowest in DKA cases (PhP 5,460.74, IQR: 13,675.99). The costs of IV fluids and antibiotics were notably higher in HHS cases than in isolated DKA cases and DKA-HHS overlap cases. Patients with HHS had the highest antibiotic costs (PhP 2,105.87, IQR: 6,690.03), while the lowest was recorded in DKA patients (PhP 490.19, IQR: 4,646.51).

Diagnostic fees contributed significantly to the overall costs, with HHS patients incurring the highest median diagnostic expenses (PhP 74,250.86, IQR: 82,221.00), followed by DKA (PhP 41,898.50, IQR: 45,962.50) and DKA-HHS overlap cases (PhP 34,112.50, IQR: 47,235.00). Laboratory expenses accounted for a substantial portion of the diagnostic fees, with HHS patients paying a median of PhP 43,494.50 (IQR: 64,835.61), compared to PhP 27,955.00 (IQR: 39,552.00) in the overall cohort.

Room charges also varied across the subgroups, with the highest median cost recorded in HHS cases (PhP 8,400.00, IQR: 8,760.00). The costs for healthcare professional fees were highest among HHS cases, with a median of PhP 8,400.00 (IQR: 8,760.00).

The final model explained 18% of the deviance in total cost (AIC = 24.88, BIC = -1566.66). Model diagnostics indicated adequate fit with no evidence of systematic residual patterns (Appendix A). Log-transformed length of hospital stay showed a strong positive association with total cost (β = 0.5612, 95%CI [0.5170, 0.6053], p <0.001). This indicates that a 1% increase in length of hospital stay is associated with a 0.01% increase in expected median total cost. Age was positively associated with total cost (β = 0.0080, 95% CI [0.0036, 0.0124], p <0.001), with each additional year corresponding to a 0.80% increase in expected total cost. The presence of infection was a significant factor (β = 0.1571, 95% CI [0.0288, 0.2854, p = 0.016), as these patients had 17% higher expected median total cost than those without infection. Non-compliance with medication was also significant (β = -0.2096, 95% CI [-0.3251, -0.0940, p = 0.009) as non-compliant patients had 19% lower expected median total cost than those with other precipitating causes. Initial pH level was negatively associated with total cost (β = -0.7737, 95% CI [-1.1620, -0.3853], p <0.001), with each additional unit corresponding to a 53.87% decrease in expected total cost. Anion gap was negatively associated with total cost (β = -0.0130, 95% CI [-0.0213, -0.0047], p = 0.002), with each additional mmol/L corresponding to a 1.29% decrease in expected total cost. Table 3 shows the patient-related clinical predictors of direct medical costs incurred during hospital admissions of patients with diabetes mellitus treated for hyperglycemic emergencies.

Table 4 presents the comparison of direct medical costs incurred during hospital admissions for diabetic ketoacidosis (DKA) across different socioeconomic classifications. The median total costs varied significantly among the different socio-economic classes, with the highest costs observed in Class D (PhP 94,024.65, IQR: 114,872.00) and the lowest in Class A (PhP 40,449.56, IQR: 7,084.32).

Medication costs were also highest among Class B patients (PhP 9,938.47, IQR: 17,933.90), whereas Class A patients

Table 2. Summary of direct medical costs (in PhP) incurred during hospital admissions of patients with diabetes mellitus treated for hyperglycemic emergencies (n = 319)

Direct medical costs	Over all (n=319)	DKA (n=214)	HHS (n=40)	DKA-HHS (n=64)	Euglycemic DKA (n=1)
Total costs, median (IQR)	79,331.50 (103,027.27)	78,230.81 (90,883.92)	143,902.77 (184,655.35)	74,167.55 (74,915.82)	39,947.20
Medications cost, median (IQR)	6,572.17 (15,699.18)	5,460.74 (13,675.99)	13,209.46 (31,700.83)	7,361.34 (16.117.46)	2,682.18
IV fluids	792.05 (1,315.69)	770.32 (1,143.09)	1,497.63 (1.490.71)	705.17 (1,171.30)	997.22
Electrolyte replacement	403.00 (1,122.13)	444.87 (1,198.28)	245.78 (887.48)	370.80 (1,041.08)	520.00
Antibiotics	657.21 (4,584.37)	490.19 (4,646.51)	2,105.87 (6.690.03)	939.20 (3,758.50)	248.95
Pressors	0 (175.52)	0 (109.70)	0 (670.02)	103.40 (2,573.94)	0.00
Anti-diabetic medications	288.96 (351.25)	288.96 (368.52)	288.93 (380.60)	244.00 (159.12)	239.10
Others	9,555.14 (19,007.80)	8,173.99 (15,652.32)	16,493.83 (39,020.71)	13,478.55 (17,951.43)	5,185.02
Diagnostic fees (PhP), median (IQR)	41,507.00 (51,689.00)	41,898.50 (45,962.50)	74,250.86 (82,221.00)	34,112.50 (47,235.00)	15,340.00
Imaging	4,662.50 (6,990.50)	1,570.00 (5,117.50)	6,352.50 (7,602.50)	4,937.50 (7,222.50)	365.00
Laboratory	27,955.00 (39,552.00)	27,951.50 (36,577.00)	43,494.50 (64,835.61)	21,883.50 (35,495.00)	8,575.00
Arterial blood gas	8,400.00 (9,600.00)	9,600.00 (10,800.00)	6,000.00 (10,576.00)	6,600.00 (8,400.00)	6,000.00
Others	400.00 (400.00)	400.00 (400.00)	400.00 (3,600.00)	400.00 (400.00)	400.00
Room charges (PhP), median (IQR)	8,400.00 (20,000.00)	8,350.00 (18,000.00)	13,100.00 (23,650.00)	6,750.00 (20,700.00)	12,000.00
Healthcare professional (PhP), median (IQR)	4,740.00 (6,840.00)	4,740.00 (3,750.00)	8,400.00 (8,760.00)	4,740.00 (8,400.00)	4,740.00
Other costs, median (IQR)	9,555.14 (19,007.80)	8,173.99 (15,652.32)	16,493.83 (39,020.71)	13,478.55 (17,951.43)	5,185.02

incurred the least (PhP 1,879.99, IQR: 6,228.45). Diagnostic fees followed a similar trend, with Class D having the highest median cost (PhP 48,979.00, IQR: 45,723.00) and Class A the lowest (PhP 20,859.00, IQR: 8,008.29).

Room charges and healthcare professional fees also varied across socio-economic classes, with Class B patients incurring the highest room charges (PhP 12,300.00, IQR: 18,400.00), while Class C2 had the lowest (PhP 6,300.00, IQR: 17,350.00). Median healthcare professional fees remained relatively stable across all classes, ranging from PhP 4,545.00 to PhP 5,000.00.

Table 5 presents the comparison of direct medical costs incurred during hospital admissions for hyperosmolar hyperglycemic state (HHS) across different socio-economic classifications. The highest total costs were observed among Class B patients, with a median expenditure of PhP 192,289.90 (IQR: 210,735.30). The lowest median total cost was reported in Class C2 (PhP 33,062.67, IQR: 3,196.05).

Medication costs also varied among the groups, with Class B patients incurring the highest median expense (PhP 27,531.91, IQR: 47,365.02), while Class C2 had the lowest (PhP 615.70, IQR: 6,986.11). Diagnostic fees were highest in Class D (PhP 86,870.80, IQR: 60,423.50) and lowest in Class C2 (PhP 19,578.00, IQR: 6,396.00).

Room charges were highest for Class B (PhP 13,200.00, IQR: 22,000.00) and lowest for Class C2 (PhP 400.00, IQR: 2,600.00). Healthcare professional fees were relatively similar across most socio-economic classes, with a median range of PhP 1,560.00 to PhP 9,600.00, except for Class C1, which had a slightly higher median of PhP 9,135.00 (IQR: 11,745.00).

Table 6 presents the comparison of direct medical costs incurred during hospital admissions for diabetic ketoacidosis-hyperosmolar hyperglycemic state (DKA-HHS) across different socio-economic classifications. The highest median total costs were observed in Class B patients at PhP 121,036.70 (IQR: 74,033.64). The lowest total cost was seen in Class C1 (PhP 63,274.71, IQR: 65,184.36).

Medication costs were highest in Class B (PhP 21,266.39, IQR: 36,278.45) and lowest in Class C3 (PhP 4,985.14, IQR: 30,316.22). Diagnostic fees followed a similar trend, with Class B incurring the highest costs (PhP 32,930.50, IQR: 38,895.25), while Class C2 had the lowest (PhP 30,428.00, IQR: 65,876.27).

Room charges were highest in Class B (PhP 10,500.00, IQR: 14,800.00) and lowest in Class C2 (PhP 800.00, IQR: 17,100.00). Healthcare professional fees were highest in Class B (PhP 9,600.00, IQR: 2,880.00) and lowest in Class C3 (PhP 1,560.00, IQR: 7,200.00).

Figures 3A and 3B illustrate the total hospitalization costs (in PhP ×1,000) for patients admitted with diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and combined DKA-HHS, stratified by socio-economic classification. Figure 3A includes all observations,

Table 3. Patient-related clinical predictors of direct medical costs incurred during hospital admissions of patients with diabetes mellitus treated for hyperglycemic emergencies (n = 300)

Predictor variable	Coefficient (β)	Std. err.	95% CI	*p*-value
Age	0.0080	0.0022	0.0036, 0.0124	0.000
Female sex	-0.0319	0.0507	-0.1313, 0.0675	0.529
Infection	0.1571	0.0655	0.0288, 0.2854	0.016
Non-compliance	-0.2096	0.0590	-0.3251, -0.0940	0.000
Presence of any comorbidity	0.0460	0.0366	-0.0257, 0.1178	0.208
Initial pH level	-0.7737	0.1982	-1.1620, -0.3853	0.000
Initial bicarbonate level	0.0039	0.0073	-0.0104, 0.0182	0.593
Anion gap	-0.0130	0.0042	-0.0213, -0.0047	0.002
Type 2 diabetes	-0.0612	0.0944	-0.2462, 0.1238	0.517
Length of hospital stay	0.5612	0.0225	0.5170, 0.6053	0.000

Note: The model was adjusted for year of admission.

Table 4. Comparison of direct medical costs (in PHP) incurred during hospital admissions of patients with diabetes mellitus treated for DKA across different socio-economic classification (n = 214)

Direct medical costs	Class A (n=5)	Class B (n=26)	Class C1 (n=48)	Class C2 (n=43)	Class C3 (n=48)	Class D (n=92)
Total costs, median (IQR)	40,449.56 (7,084.32)	84,942.48 (72,771.93)	83,958.97 (75,436.46)	66,710.88 (79,568.38)	69,082.95 (78,608.75)	94,024.65 (114,872.20)
Medications cost, median (IQR)	1,879.99 (6,228.45)	9,938.47 (17,639.30)	6,055.02 (14,242.77)	4,333.29 (9,320.59)	5,507.23 (11,660.99)	4,795.59 (18,605.74)
Diagnostic fees, median (IQR)	20,859.00 (8,008.29)	40,221.00 (36,386.00)	45,404.00 (46,525.50)	34,414.13 (44,250.25)	41,496.50 (30,775.19)	48,979.00 (45,723.00)
Room charges, median (IQR)	10,000.00 (12,100.00)	12,300.00 (18,400.00)	10,400.00 (18,100.00)	6,300.00 (17,350.00)	8,100.00 (18,100.00)	7,750.00 (19,600.00)
Healthcare professional, median (IQR)	5,000.00 (1,622.00)	4,740.00 (1,662.00)	4,740.00 (3,642.00)	4,545.00 (4,776.00)	4,740.00 (3,540.00)	4,740.00 (4,590.00)

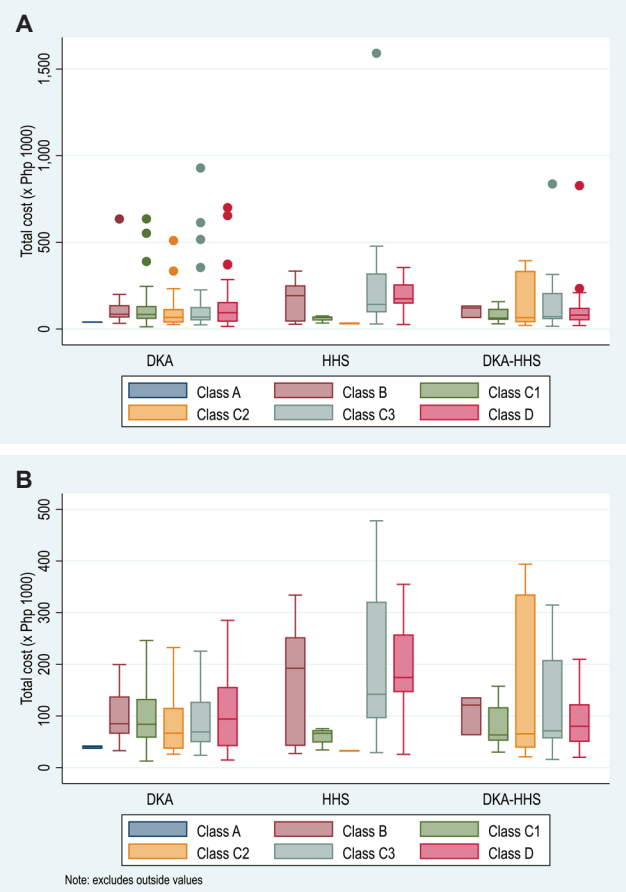


Figure 3. Box plots of total costs by hyperglycemic emergency across different socioeconomic classification **(A)**. Blow-out box plot by excluding outside values **(B)** for better visualization of the distribution.

including outliers, while Figure 3B presents the same data with outliers excluded to emphasize the distribution of typical costs.

Across all clinical categories, Class A patients—those classified as fully paying—incurred the lowest and most uniform costs. In contrast, patients from lower socioeconomic classes, particularly Classes C3 and D, exhibited greater cost variability, with several high-cost outliers observed in the HHS and DKA groups. The most extreme outlier, seen in a Class C3 patient with HHS, exceeded PhP 1.5 million in total costs (Figure 3A). When these outliers are excluded (Figure 3B), the data more clearly demonstrate that median costs were generally higher for Classes B, C3, and D compared to Classes C1 and C2.

Among the three clinical presentations, HHS was associated with the highest median and upper-quartile costs, followed by DKA-HHS and DKA. These findings suggest that both disease severity and socioeconomic classification significantly influence hospitalization costs. The wide cost variability among subsidized patients raises important considerations for resource allocation, especially in public healthcare settings aiming to deliver equitable care.

Post hoc power analysis

A simulation-based power analysis to estimate the minimum detectable effect size (β) for a Generalized Linear Model (GLM) with a Gamma distribution and log link, using approximately 300 eligible participants from the census. The outcome variable was total hospital cost,

Table 5. Comparison of direct medical costs (in PHP) incurred during hospital admissions of patients with diabetes mellitus treated for HHS across different socio-economic classification (n = 40)

Direct medical costs	Class A (n=0)	Class B (n=12)	Class C1 (n=4)	Class C2 (n=3)	Class C3 (n=9)	Class D (n=13)
Total costs, median (IQR)	-	192,289.90 (210,735.30)	66,487.14 (24,609.41)	33,062.67 (3,196.05)	141,926.20 (225,912.00)	174,541.00 (112,120.60)
Medications cost, median (IQR)	-	27,531.91 (47,365.02)	4,156.52 (4,769.56)	615.70 (6,986.11)	12,976.45 (33,724.16)	18,076.28 (30,920.38)
Diagnostic fees, median (IQR)	-	78,618.00 (98,657.75)	28,183.11 (13,131.61)	19,578.00 (6,396.00)	82,148.00 (81,733.50)	86,870.00 (60,423.50)
Room charges, median (IQR)	-	13,200.00 (22,000.00)	3,600.00 (6,200.00)	400.00 (2,600.00)	22,600.00 (21,600.00)	18,000.00 (17,900.00)
Healthcare professional, median (IQR)	-	9,600.00 (15,300.00)	9,135.00 (11,745.00)	1,560.00 (4,590.00)	5,790.00 (5,220.00)	9,600.00 (1,550.00)

Table 6. Comparison of direct medical costs (in PHP) incurred during hospital admissions of patients with diabetes mellitus treated for DKA-HHS across different socio-economic classification (n = 64)

Direct medical costs	Class A (n=0)	Class B (n=6)	Class C1 (n=13)	Class C2 (n=12)	Class C3 (n=11)	Class D (n=31)
Total costs, median (IQR)	-	121,036.70 (74,033.64)	63,274.71 (65,184.36)	65,364.28 (297,187.50)	71,214.21 (152,352.00)	80,036.89 (73,248.77)
Medications cost, median (IQR)	-	21,266.39 (36,278.45)	8,005.78 (11,403.74)	10,869.26 (48,548.39)	4,985.14 (30,316.22)	7,959.07 (11,661.35)
Diagnostic fees, median (IQR)	-	32,930.50 (38,895.25)	30,253.50 (33,462.50)	30,428.00 (65,876.27)	35,126.00 (56,574.50)	42,423.86 (49,882.00)
Room charges, median (IQR)	-	10,500.00 (14,800.00)	4,000.00 (16,800.00)	800.00 (17,100.00)	8,800.00 (37,800.00)	9,400.00 (24,600.00)
Healthcare professional, median (IQR)	-	9,600.00 (2,880.00)	5,790.00 (8,040.00)	4,740.00 (11,280.00)	1,560.00 (7,200.00)	4,740.00 (7,200.00)

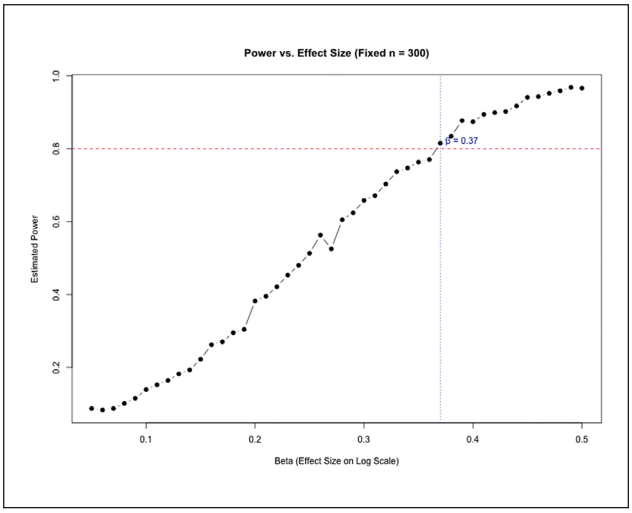


Figure 4. Power analysis of the approximately 300 eligible participants from the census.

modeled as Gamma-distributed with an assumed shape parameter of 1 (Figure 4).

The model included the following covariates of interest: age, sex, infection, non-compliance, comorbidity, pH, bicarbonate, anion gap, type 2 diabetes, length of hospital stay, and confounder: year of admission.

Using simulation (1,000 iterations per tested effect size), the β was varied, and the statistical power to detect it at a significance level of $\alpha = 0.05$ was recorded. The minimum detectable β with at least 80% power was estimated to be $\beta = 0.37$ on the log scale, corresponding to a relative increase of exp(β) = 45 % increase in total cost associated with a particular variable of interest while controlling the other factors constant.

DISCUSSION

This study evaluated the direct medical costs incurred during hospital admissions for hyperglycemic emergencies among patients with diabetes mellitus in a tertiary government hospital in the Philippines. Specifically, the study aimed to estimate the median cost of hospitalization, examine variations across socio-economic classifications, and identify clinical and biochemical factors associated with increased healthcare expenditures.

DKA was the most common hyperglycemic emergency in this cohort, accounting for nearly 70% of admissions. This finding is consistent with recent international reports noting the predominance of DKA over HHS, particularly in low- and middle-income countries. However, the incidence of DKA-HHS overlap was notably higher than reported in global literature and local studies conducted in private tertiary hospitals.[3,4] The variation in case distribution may reflect the role of the study institution as an apex hospital, receiving complex and severe cases from surrounding provinces and underserved communities.

HHS is classically seen in older patients with long -standing type 2 diabetes, yet in our cohort, DKA (69.5%) was far more common than HHS (10.9%) despite 83.6% having T2DM. This apparent paradox likely reflects a sizeable subgroup of adults with T2DM who manifest an insulin-deficient, ketosis-prone phenotype; the relatively short median diabetes duration (3 years) and the younger age of the DKA group (median 47 years versus 65 years for HHS) are consistent with this pattern.[9]

In this study, most DKA cases were severe (n = 174). This means that the majority of patients with DKA needed intensive care. ICU admission was mainly recommended for these severe DKA cases, as well as for patients with HHS and those with overlapping features of both conditions.

Infection (66.31%), including community-acquired pneumonia, hospital-acquired pneumonia, urinary tract infection and non-compliance with medication (41.11%), were identified as the predominant causes of hyperglycemic emergency, aligning with global data. Other precipitating causes include cerebrovascular disease, acute pancreatitis and upper gastrointestinal bleeding. The in-hospital mortality rate observed in this study (35.01%) aligns with global trends reported in low- and middle-income countries.[4] In this study, in-hospital mortality rates for DKA-HHS overlap at 57.53%, surpassing global trends of 3.6% in Nigeria, 5.3% in Japan, 8% in the United States, and 25% in Jamaica. This likely indicates systemic challenges such as delayed access to care, limited ICU resources, and elevated rates of acute kidney injury (48.01%), which is a recognized predictor of mortality.[10]

The median direct medical cost per admission for a hyperglycemic emergency was PhP 79,331.50 (USD 1,375.02), representing a substantial financial burden in the context of current household income and health expenditure patterns in the Philippines. To contextualize this burden, the 2023 estimated average annual family income was PhP 353,230 (USD 6,122.39),[11] meaning the median hospitalization represents approximately 22.5% of the estimated average annual family income. This figure far exceeds the average annual health expenditure per capita, estimated at PhP 11,083.00 (USD 192.10)[12] in 2023, suggesting that such emergencies can impose a strain on the health spending of families, particularly among lower-income groups.

To enable international comparisons, the median direct medical cost was converted using the 2023 World Bank Purchasing Power Parity (PPP) conversion factor for the Philippines (PhP 19.26 = International USD 1), resulting in an adjusted cost of approximately International (Int'l) USD 4,120. When adjusted for PPP to allow for valid cross-country comparisons, this cost is markedly higher than that reported in other low- and middle-income settings. For example, the direct medical cost per admission in Thailand was reported at USD 1,096.17,[13] which translates to **Int'l USD 1,045** using Thailand's PPP of 10.49. Similarly, in South Africa, a cost of USD 288.98[14] corresponds to **Int'l USD**

750 using a PPP of 3.85. These comparisons suggest that, relative to purchasing power, managing hyperglycemic emergencies in the Philippines imposes a heavier financial burden on both patients and the health system.[15]

This burden becomes even more significant when considered in the context of local income and health financing. Locally, the financial coverage provided by the national health insurance program, PhilHealth, remains limited. As of the latest schedule, PhilHealth provides a case rate of PhP 30,810.00 for diabetes mellitus with coma or ketosis (ICD code E10.1), covering only 38.8% of the observed median hospitalization cost. This leaves an average out-of-pocket expense of PhP 48,521.50, which constitutes roughly 13.7% of a household's annual income – far exceeding the World Health Organization's threshold for catastrophic health expenditure (10%).

The highest costs incurred by HHS amounted to PhP 143,902.77 (USD 2,493.21), likely attributable to extended ICU stays, complicated fluid and electrolyte management, and increased resource utilization associated with higher mortality rates. Diagnostic fees represented the most significant cost component (PhP 41,507.00, USD 719.42), primarily due to the necessity for regular laboratory monitoring (e.g., arterial blood gas analysis, electrolyte panel, random blood sugar). The cost incurred by DKA (PhP 78,230.81, USD 1,355.94) was lower than that for HHS, yet remained substantial. Euglycemic DKA resulted in the lowest costs (PhP 39,947.20, USD 692.39); however, the limited sample size (n = 1) restricts generalizability. This study reports lower direct medical costs per DKA admission than US-based studies, costing USD 1,343.70 (IQR: USD 1,561.04) versus USD 21,215.00 to USD 36,600. A UK-based study estimated the cost of DKA admission to be £2,064.00 (USD 2,568.54).[4] These discrepancies likely reflect differences in healthcare system structures, unit pricing, and availability of subsidized care. As this study was conducted in a public tertiary referral hospital with substantial government subsidies, the costs captured here represent a fraction of the actual economic burden. They are not directly comparable to costs in private or unsubsidized settings.

The median length of hospitalization for DKA was comparable to that of HHS, with durations of 8 and 9 days, respectively. However, room charges for DKA patients were significantly lower. This discrepancy may be attributed to the relatively lower mortality rate among DKA cases (27.5%) compared to HHS (43.9%) and overlap cases (57.5%). The reduced mortality rate in DKA patients was supported by a shorter median time to resolution of DKA — 1 day (IQR: 17) — versus 2 days (IQR: 21.5) observed in other groups. This equates to an earlier transition from intensive care to regular ward settings. Additionally, most patients in this cohort belonged to classes D and E, which may have contributed to extended hospitalization due to the time required for processing the discharge procedure, such that patients would seek further government help for financial aid. These findings are corroborated by the results of the final analytical model, which identified length of stay as a primary cost driver, with longer hospitalizations associated with increased total costs.

Socioeconomic stratification demonstrated disparities in healthcare expenses. In cases of DKA, patients classified as Class D (lower income) experienced greater costs (PhP 94,024.65) compared to Class A (PhP 40,449.56), likely attributable to delayed presentation necessitating more advanced interventions. In contrast, HHS costs were highest in Class B (PhP 192,289.90), indicating that middle-income groups may encounter obstacles to preventive care, resulting in significant decompensation of glycemic control and subsequent admission for such emergencies. Published studies on inequities in care costs associated with hyperglycemic emergencies are limited.

The final model used in this study accounted for 18% of the deviance in total direct medical costs for hyperglycemic emergencies, indicating modest explanatory power. Nonetheless, the model diagnostics demonstrated an adequate fit with no significant residual trends, supporting the validity of the identified associations.

In the analysis, length of hospital stay (LOS) emerged as the most significant driver of cost. The log-transformed length of hospital stay was used to account for the skewed distribution of LOS data and to model its association with median total costs. The median LOS in the cohort was 7 days, which served as the baseline reference point for interpretation. This means that the predicted costs are calculated relative to a patient with a 7-day stay. For example, an increase to 8 days (approximately 14.3% longer than the median) corresponds to an estimated 0.143% increase in total cost, while a stay of 10 days (43% longer) would be associated with approximately a 0.43% increase in costs. The estimated 0.143% per additional day was derived from the regression coefficient ($\beta = 0.5612$), indicating that each 1% increase in LOS results in a 0.01% increase in total cost. Since a one-day increase (from 7 to 8 days) represents approximately a 14.3% increase ($1/7 \times 100\%$), we multiply 14.3% by 0.01% to arrive at the 0.143% increase in total cost per additional day. This finding is consistent with prior studies, which consistently highlight prolonged hospitalization as a major determinant of cost in diabetes care due to higher utilization of intensive care and procedures. Efficient inpatient protocols—such as early recognition of metabolic stabilization, prompt transition to subcutaneous insulin, and timely discharge planning—may offer meaningful opportunities to reduce unnecessary expenditure.[16]

Age was also positively associated with total cost with each additional year of age corresponds to a 0.80% increase in expected total cost. Using the median age of 50 years as a reference point, this translates to meaningful cost variations across the age spectrum: a 60-year-old patient would incur approximately 8% higher costs compared to the median, while a 70-year-old would face roughly 16% higher costs.

This finding aligns with established healthcare economics literature and the recent published article by the American Diabetes Association last 2023.[17]

Infection as a precipitating factor was associated with a 17% increase in expected costs. This likely reflects the additive burden of managing concurrent infectious processes requiring more diagnostics, intravenous antibiotics, and potentially longer hospitalizations.[18]

Non-compliance with medications was associated with a 16% reduction in total costs. In our study, patients with DKA precipitated by non-compliance exhibited a lower mortality rate (32.9%) and a shorter median time to resolution (1 day vs. 2 days) compared to the compliant group. Despite experiencing a higher proportion of in-hospital complications (81.2% vs. 73.8%), both groups had a similar median hospital stay of 7 days. Notably, the lower costs linked to non-compliance may be explained by these faster resolution times and lower mortality rates, aligning with findings from other studies that indicate lower per-admission costs in non-compliance-related DKA episodes. However, they may contribute significantly to the overall economic burden due to their higher frequency.[19]

Initial pH level was negatively associated with total cost, with each additional unit corresponding to a 53.87% decrease in expected total cost. Higher initial pH can be seen in patients presenting with higher pH values around 7.5—more commonly observed in hyperosmolar hyperglycemic state (HHS) and DKA-HHS overlap cases—would demonstrate substantially lower total costs. This counterintuitive inverse relationship can be primarily attributed to the paradoxically higher early mortality rates observed in HHS and overlap presentations in this study, where severe hyperosmolarity and metabolic derangements lead to rapid clinical deterioration and early demise, thereby truncating the opportunity for prolonged intensive care utilization and cumulative cost accumulation.

Lastly, a small but statistically significant inverse relationship was observed between anion gap and total hospital cost, with each 1 mmol/L increase in anion gap associated with a 1.29% decrease in expected cost. Higher anion gaps are commonly used to classify the severity of DKA, with larger gaps indicating more severe metabolic disturbances.[4] At first glance, this counterintuitive finding may suggest that patients with more severe DKA — reflected by higher anion gaps — incur lower healthcare costs, potentially due to rapid deterioration leading to earlier mortality and shorter hospital stays. However, further analysis is needed to clarify whether this relationship is driven by mortality or other factors associated with disease severity.

Limitations of the study

This study has several limitations. Its retrospective design inherently limits the accuracy and completeness of the data, as it relied on how thoroughly physicians and other healthcare personnel documented a patient's clinical status and direct medical costs in the medical records. Some medical charts contained incomplete data, which may have affected data quality.

Notably, only 319 out of the initially planned 395 charts contained complete cost data and were included in the final analysis. While a post hoc GLM/Gamma simulation power analysis was conducted to estimate statistical power given the reduced sample size, this shortfall may have limited the study's ability to detect smaller effect sizes and increased the risk of type II error. It also raises the potential for selection bias, as missing cost data could be associated with patient characteristics or clinical outcomes not captured in the analysis.

Subgroup analyses were not performed in this study, which may have further limited the exploration of heterogeneity within the patient population. Further studies should consider incorporating subgroup analyses to understand differential cost drivers better.

This study was conducted at EAMC, a tertiary government hospital in the Philippines, primarily serving lower-to middle-income patients. As a result, the findings may be more applicable to public hospital settings and populations with limited healthcare access rather than private hospital settings or high-income populations. In addition, since the data were collected from a single institution, the results may not fully reflect cost variations in other hospitals, particularly private hospitals or rural healthcare settings.

The study only assessed direct medical costs from a healthcare payer perspective within the Philippine healthcare system. Since healthcare financing, insurance systems, and hospital financial structures vary across different countries, cost estimates in this study may not be directly related to other countries with different healthcare systems from those in the Philippines. However, the identified predictors of cost are likely relevant across different healthcare systems.

Since there is a relatively lower proportion of HHS compared to DKA in this study, in regions where HHS is more prevalent, or where care differs significantly, cost distributions and predictors may differ. Additionally, mortality and in-hospital complication rates are higher, suggesting more severe disease at presentation, limiting the applicability of the cost estimates in this study to settings where good glycemic control and good patient compliance are observed.

Lastly, the findings in this study may be more applicable to low-and middle-income countries where resource constraints and government-subsidized hospitalization significantly impact hospitalization costs.

CONCLUSION AND RECOMMENDATIONS

This study presents one of the first local estimates of direct medical costs associated with hyperglycemic emergencies in a Philippine public tertiary hospital, revealing a substantial financial burden on patients, particularly among lower-income groups. Key cost drivers included longer hospital stays and infections. In contrast, lower costs were associated with female sex, non-compliance with medications and higher anion gap—possibly reflecting differences in disease severity or early mortality. Despite study design and limitations, it offers relevant insights for health system planners and policy makers.

Future research should expand to multicenter settings, incorporate subgroup and sensitivity analysis, and explore cost variations based on DKA severity, level of care, and socioeconomic classification.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JPA: Conceptualization, Methodology, Validation, Investigation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **AILD:** Conceptualization, Methodology, Software, Validation, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization; **MRP:** Conceptualization, Methodology, Resources, Writing – original draft preparation, Writing – review and editing; **EQV:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, **CT:** Conceptualization, Methodology, Validation, Resources, Writing – original draft preparation, Writing – review and editing Supervision, Project administration.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
JPA, AILD, MRP, and CT declare no conflict of interest. EQV is a biostatistician and peer reviewer for JAFES and receives compensation from the same institution.

Funding Source
None.

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APPENDICES

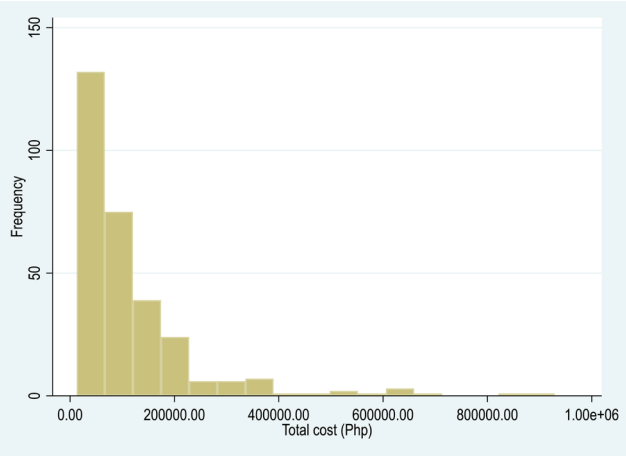


Figure A1. The histogram of the dependent variable total cost showing gamma distribution.

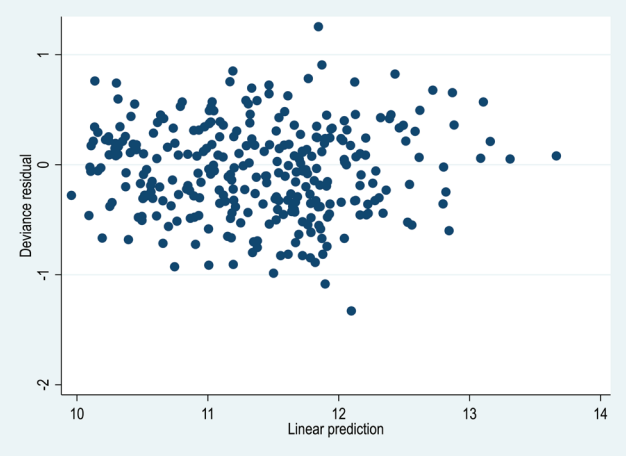


Figure A2. Deviance residual versus linear prediction plot shows random scatter indicating validity of the log link function.

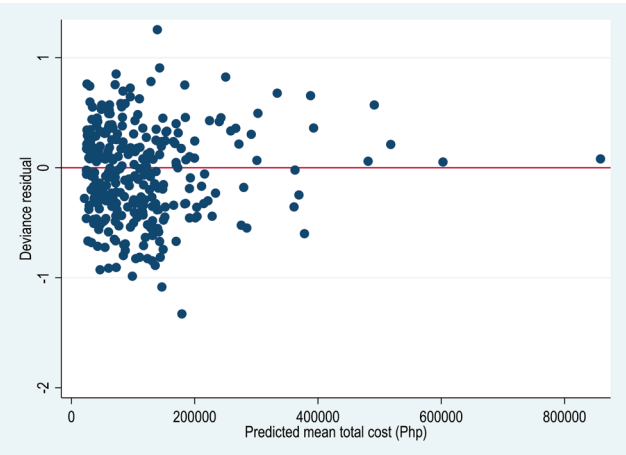


Figure A3. Deviance residual versus predicted plot shows random scattering around zero indicating homoskedasticity.

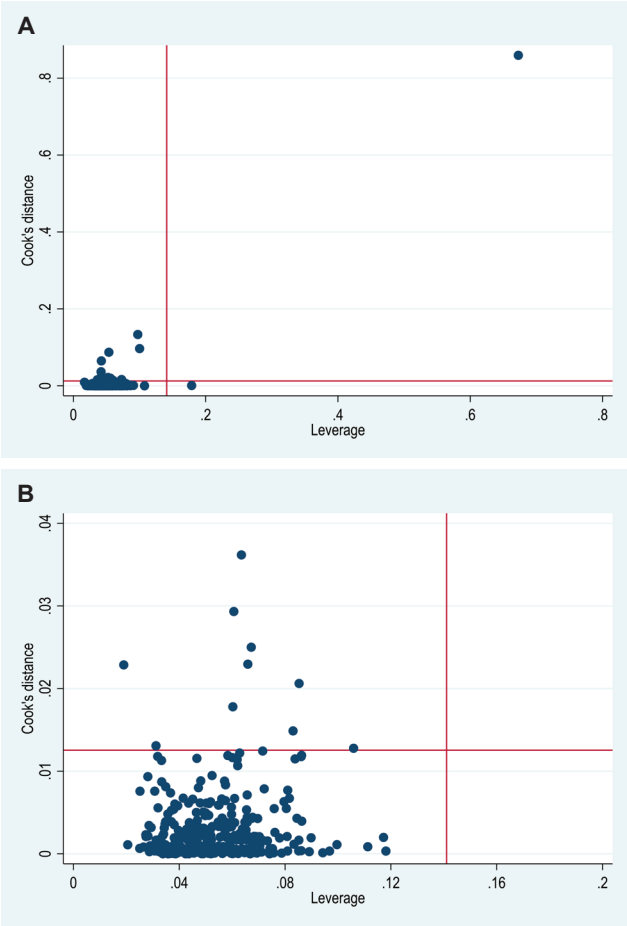


Figure A4. Cook's distance versus leverage plot showing before **(A, n=319)** and after **(B, n=300)** removing influential points.

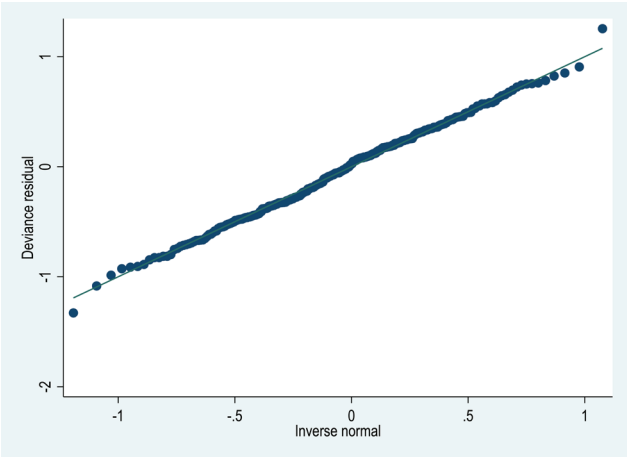


Figure A5. Normal Q-Q plot of deviance residual indicating normal distribution.

Appendix B. STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, explain how loss to follow-up was addressed	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (e.g., average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

The Impact of Chronic Kidney Disease on Ulcer-Related Outcomes in Hospitalized Diabetic Foot Ulcers: A Retrospective Study from Thailand

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Abstract

Objective. To explore the impact of chronic kidney disease (CKD) on hospitalized patients with diabetic foot ulcers (DFU) at a tertiary diabetes center in Thailand.

Methodology. A retrospective study reviewed hospitalized DFU admissions at Vimut-Theptarin Hospital from 2019 to 2023. Ulcer-related outcomes included complete wound healing at 12 months, major and minor amputations, and 1-year mortality.

Results. A total of 265 DFU admissions from 225 patients were included (male 60.4%; age, 66.7 ± 13.4 years; A1C, 8.2 ± 2.3%, advanced CKD, 26.1%, peripheral arterial disease, 54.7%). Severe DFU (Wagner grade ≥3) comprised 60.0% of all DFUs and almost one-third of patients had prior amputations. Complete healing occurred in 69.8%; major amputation in 4.9%; minor amputation in 30.9%; and 1-year mortality rate after discharge was 11.7%. Advanced CKD (stages 4-5) increased odds of non-healed ulcers (odds ratio OR, 2.69; 95% confidence interval CI, 1.46-4.98; *P* = 0.002) and 1-year mortality rate (21.7% vs 8.4%; *P* = 0.004).

Conclusion. Advanced chronic kidney disease (CKD) is associated with poorer ulcer-related outcomes in hospitalized patients with diabetic foot ulcers (DFU). Proactive foot care and early referral to multidisciplinary teams, particularly for dialysis-dependent patients, remain essential. Despite ongoing advances in DFU management, these patients continue to face higher rates of non-healing ulcers and mortality, underscoring the need for coordinated inter-institutional care and enhanced public education efforts.

Key words: diabetic foot ulcer, chronic kidney disease, Thailand

INTRODUCTION

Diabetic foot ulcer (DFU) causes a significant economic burden on healthcare systems all over the world and is one of the costliest diabetic complications, requiring multidisciplinary expertise from primary care to subspecialties.[1] Approximately 15% - 40% of individuals with diabetes develop a foot ulcer during their lifetime, with up to 10% progressing to lower extremity amputation, resulting in disability, prolonged hospitalization, and premature mortality.[2] Moreover, over 60% of these patients experience DFU recurrence within 5 years, accompanied by 5-year mortality rates of 50% to 70%.[3] The prevalence of co-morbidities is very high in DFU patients leading to increasingly complex wounds which affect the final treatment outcomes.[4-7]

Several studies demonstrated that chronic kidney disease (CKD) is associated with worse outcomes and mortality in DFU patients.[6-10] The presence of CKD accelerates more severe peripheral arterial diseases (PAD) by causing chronic inflammation and promoting a prothrombotic state.[11] A retrospective cohort study from the Netherlands found that DFU patients with advanced CKD had a 10-fold increased risk for major amputation compared to patients who have an estimated glomerular filtration rate (eGFR) of 30-59 ml/min/1.73 m^2.[5] Despite global declines in DFU-related major amputations, CKD prevalence in type 2 diabetes (T2D) has surged with rising life expectancy, though diabetic kidney disease mechanisms remain incompletely understood.[12] In Thailand, T2D is one of the common causes of dialysis.[13] Successful DFU management hinges on coordinated, holistic multidisciplinary care addressing all comorbidities.

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Sripatpong et al.
Received: July 10, 2025. Accepted: August 19, 2025.
Published online first: April 12, 2026.
https://doi.org/10.15605/jafes.041.01.5197

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Over the past 3 decades, our hospital – a tertiary diabetes center in Thailand – has been able to provide comprehensive diabetic foot care to the majority of complex patients referred to us from all over Thailand and neighboring countries. Prior data demonstrated achievement of limb salvage rates exceeding 90% and complete healing rates above 80% through dedicated multispecialty teams.[14] However, advanced CKD reduced complete healing by up to 33%, underscoring the role of comorbidities in this fragile population with DFU as a complex clinical syndrome.[15] More detailed analysis of the relationship between CKD staging and ulcer-related outcomes should be explored to better understand prognostic factors among hospitalized DFU patients. Therefore, this study examines the impact of The Kidney Disease: Improving Global Outcomes (KDIGO) categories for eGFR[16] on outcomes of hospitalized patients with DFU during the period of 2019-2023 at our hospital.

METHODOLOGY

Study design and study population

This retrospective cohort study examined all consecutive hospitalized DFU admissions from 2019 to 2023 at Vimut-Theptarin Hospital (formerly Theptarin Hospital), a private tertiary diabetes center in Bangkok. A dedicated foot clinic, established since 1995, follows uniform guidelines in accordance with international standards to triage the risk of DFU in all people with diabetes. Most hospitalized DFU patients were referral cases from all over Thailand and neighboring countries. DFU was defined as a full thickness wound below the ankle in an individual with diabetes. All hospitalized patients with DFU during the study period were included; exclusion criteria included ulcers above the ankle, absence of diabetes diagnosis, lack of laboratory data on renal function, missing glycated hemoglobin A1C results, and incomplete medical records.

The Wagner classification was used to assess the wound severity based on depth of ulceration and the extent of gangrene.[17] PAD was diagnosed if distal pulses were absent and/or the ankle brachial index (ABI) was <0.9. In patients whose ABI was >1.4 or in those with diagnostic uncertainty, a toe pressure of <55 mmHg or a toe brachial index (TBI) of <0.7 confirmed PAD.

The presence of CKD was defined as having eGFR <90 mL/min/1.73 m^2 with or without albuminuria. The stages of CKD followed standard classification: **Stage 1**: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2); **Stage 2**: Mild reduction in GFR (60-89 mL/min/1.73 m^2) **Stage 3a**: Moderate reduction in GFR (45-59 mL/min/1.73 m^2); **Stage 3b**: Moderate reduction in GFR (30-44 mL/min/1.73 m^2); **Stage 4**: Severe reduction in GFR (15-29 mL/min/1.73 m^2); **Stage 5**: Kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis). Renal function was categorized as: no chronic kidney disease (CKD), early-stage CKD (Stages 1–3), and advanced-stage CKD (Stages 4–5). Date of admission was defined as the index date for follow-up.

Sample size calculation

The sample size calculation was based on the study by Bonnet JB et al.,[10] which reported severe DFU in 64.8% of advanced CKD patients versus 24.7% in non-CKD patients. Assuming a two-sided α of 0.05, 80% power, and an approximate 1:1 ratio of advanced CKD to non-CKD patients, the minimum required sample size was 50 admissions. These assumptions provided sufficient statistical power to detect clinically meaningful differences in ulcer-related outcomes between groups.

Outcomes

The primary outcome was the rate of complete wound healing at 12 months post-admission. Secondary outcomes included rates of minor amputation, major amputation, and all-cause mortality at 12 months post-admission. Complete wound healing was defined as the complete epithelialization of the overlying soft-tissue wound within 12 months after admission. Amputations were classified into minor (up to below the ankle level) or major (above the ankle level). Patients who died before achieving wound healing were considered to have non-healing ulcers. This study was approved by the Institutional Review Board Committee of Vimut-Theptarin Hospital (EC No.01-2025).

Statistical analysis

Continuous variables were presented as mean ± SD or median (IQR), as appropriate and categorical variables were presented as proportions. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. If data was not normally distributed, non-parametric tests were applied. Comparisons among different stages of CKD were performed using one-way ANOVA or the Kruskal-Wallis test for continuous variables. Comparisons between healed and non-healed ulcers were conducted using the independent *t-test* or the Mann-Whitney U test for continuous variables, and the Chi-square test for categorical variables. Logistic regression analysis was used to evaluate the association between the transformed variables, clinical binary parameters, and ulcer-related outcomes. Variables with a univariate *P*-value <0.05, together with clinically important predictors (e.g., Wagner grade, PAD, advanced CKD status), were entered into the multivariate logistic regression model. Model diagnostics were performed to assess robustness. Multicollinearity was evaluated using variance inflation factors (VIFs). For further analysis, ulcer-related continuous variables were converted into categorical variables, including A1C (≥9%), age (≥60 years), BMI (≥25 kg/m^2), duration of diabetes (≥10 years), and high DFU severity (Wagner score ≥3). Fifteen variables were selected to assess multicollinearity. The type of DFU was excluded from the analysis due to a VIF greater than 2.0, while all other variables had VIF values below 2.0, leaving a total of fourteen variables. Logistic regression was used to evaluate the association between the transformed variables, clinical binary parameters, and ulcer-related outcomes.

A *P*-value <0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline characteristics of the patients

During the 5-year study period (2019–2023), a total of 272 admissions were reviewed; of these, 265 admissions met the inclusion criteria, as shown in Figure 1. A total of 265 DFU admissions from 225 patients were included (male 60.4%, age 66.7 ± 13.4 years, T2D 98.5%, glycated hemoglobin, A1C 8.2 ± 2.3%, advanced CKD 26.1%). DFUs were classified as neuropathic wounds (45.3%) or mixed neuro-ischemic wounds (54.7%). The median length of stay was 7 days (IQR 4, 13 days). Severe DFUs (Wagner grade 3–5) accounted for 60.0% of all DFUs, 63.4% of patients had a previous history of DFU, and 30.9% of patients had prior history of amputation. Patients with dialysis-dependent CKD composed of 13.2% of all patients. The detailed demographic data of DFU classified by non-CKD status, early stages of CKD (Stages 1-3), and advanced stages of CKD (Stages 4-5) were shown in Table 1.

Ulcer-related outcomes

Complete healing was achieved in 69.8% of all admissions. Major amputations were performed in 4.9% and minor amputations in 30.9%. The 1-year mortality rate was 11.7%. The most common causes of death were sepsis (46.9%), cardiovascular events (28.1%), and cancer (9.4%). Comparison of the clinical characteristics of the healed (including minor amputations) and non-healed patients were demonstrated in Table 2. When stratified by the severity of CKD, patients with advanced CKD had unfavorable outcomes in all ulcer-related outcomes as shown in Figure 2. Complete healing rates decreased from 75.9% for non-CKD patients to only 50.7% in patients with advanced stages of CKD (*P*-value = 0.021). Patients with advanced stages of CKD had higher 1-year mortality rate compared with those in the early stages of CKD (21.7% vs. 8.4%, *P*-value = 0.004). Ulcer-related outcomes stratified by type of ulcers and renal status were shown in Figure 3. Complete healing rate was higher in neuropathic ulcers compared with neuro-ischemic ulcers in all stages of renal function. Among advanced CKD patients with neuro-ischemic ulcers, complete healing rate was only 43.4%. Ulcer-related outcomes stratified by severe DFU (Wagner grade ≥3) across renal function groups are presented in

Table 1. Demographic data of hospitalized diabetic foot ulcer (DFU) classified by estimated glomerular filtration rate (eGFR) for the Kidney Disease: Improving Global Outcomes (KDIGO) staging system

	Total admissions (N = 265)	No CKD (N = 29, 10.9%)	Early CKD (N = 167, 63.0%)	Advanced CKD (N = 69, 26.1%)	*P*-value
Age (years)	66.7 ± 13.4	61.1 ± 13.5	66.6 ± 13.2	69.3 ± 13.1	**0.022** [a]
Male (%)	60.4%	62.1%	61.7%	56.5%	0.748 [b]
BMI (kg/m²)	24.5 (21.5, 27.4)	23.9 (20.1, 26.8)	24.7 (21.7, 27.8)	24.3 (21.3, 26.3)	0.432 [c]
T2D (%)	98.5%	93.1%	98.8%	100.0%	**0.034** [b]
Duration of DM (years)	20.0 (11.0, 28.0)	10.0 (2.0, 25.0)	20.0 (11.0, 29.0)	21.0 (12.0, 29.5)	**0.013** [c]
A1C (%)	7.7 (6.5, 9.5)	8.3 (6.8, 9.7)	8.0 (6.8, 10.0)	7.0 (6.0, 8.3)	**0.005** [c]
Serum creatinine (mg/dL)	1.2 (0.3, 2.1)	0.6 (0.5, 0.8)	1.0 (0.4, 1.4)	4.4 (2.4, 6.7)	**<0.001** [c]
eGFR (mL/min/1.73 m²)	57.0 (26.5, 87.0)	98.0 (93.5, 113.5)	67.0 (47.0, 86.0)	12.0 (7.0, 22.0)	**<0.001** [c]
Length of stay (days)	7 (4, 13)	7 (4, 10)	7 (4, 12)	9 (4, 17)	0.541 [c]
Type of DFU					**<0.001** [b]
Neuropathic	45.3%	69.0%	50.3%	23.2%	
Mixed	54.7%	31.0%	49.7%	76.8%	
Charcot foot (%)	7.9%	3.4%	8.4%	8.7%	0.637 [b]
Ischemic Heart Disease (%)	27.9%	13.8%	24.0%	43.5%	**0.002** [b]
Stroke (%)	8.3%	6.9%	10.2%	4.3%	0.322 [b]
Severe DFU (Wagner grades 3–5) (%)	60.0%	51.7%	58.7%	66.7%	0.329 [b]
Previous DFU (%)	63.4%	58.6%	56.3%	82.6%	**0.001** [b]
Previous Amputation (%)	30.9%	24.1%	32.3%	30.4%	0.674 [b]
Diabetic Retinopathy (%) *					0.121 [b]
No DR	26.1%	47.4%	27.0%	11.8%	
Mild NPDR	3.9%	0.0%	5.0%	2.9%	
Moderate to Severe NPDR	19.0%	15.8%	20.0%	17.6%	
PDR	51.0%	36.8%	48.0%	67.6%	
Active smoking (%)	8.7%	3.4%	9.6%	8.7%	0.465 [b]
Wound location (%)					0.089 [b]
Toe	45.3%	34.5%	46.1%	47.8%	
Forefoot	40.8%	41.4%	42.5%	36.2%	
Heel	7.5%	20.7%	5.4%	7.2%	
Ankle	3.8%	0.0%	4.2%	4.3%	
Midfoot	1.9%	3.4%	1.8%	1.4%	
Whole foot	0.7%	0.0%	0.0%	3.1%	

* Available data 153/265 (57.7%)

[a] One-way ANOVA; [b] Chi-square test; [c] Kruskal-Wallis test

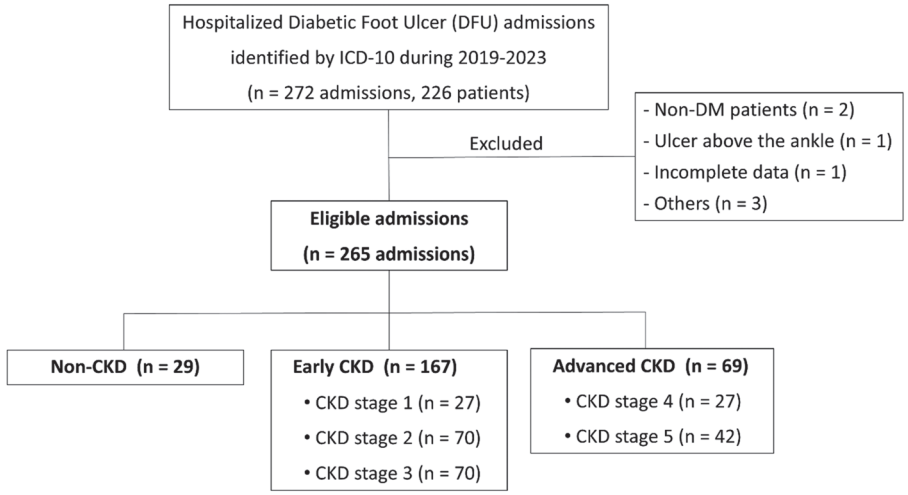


Figure 1. Study flowchart of patient selection.

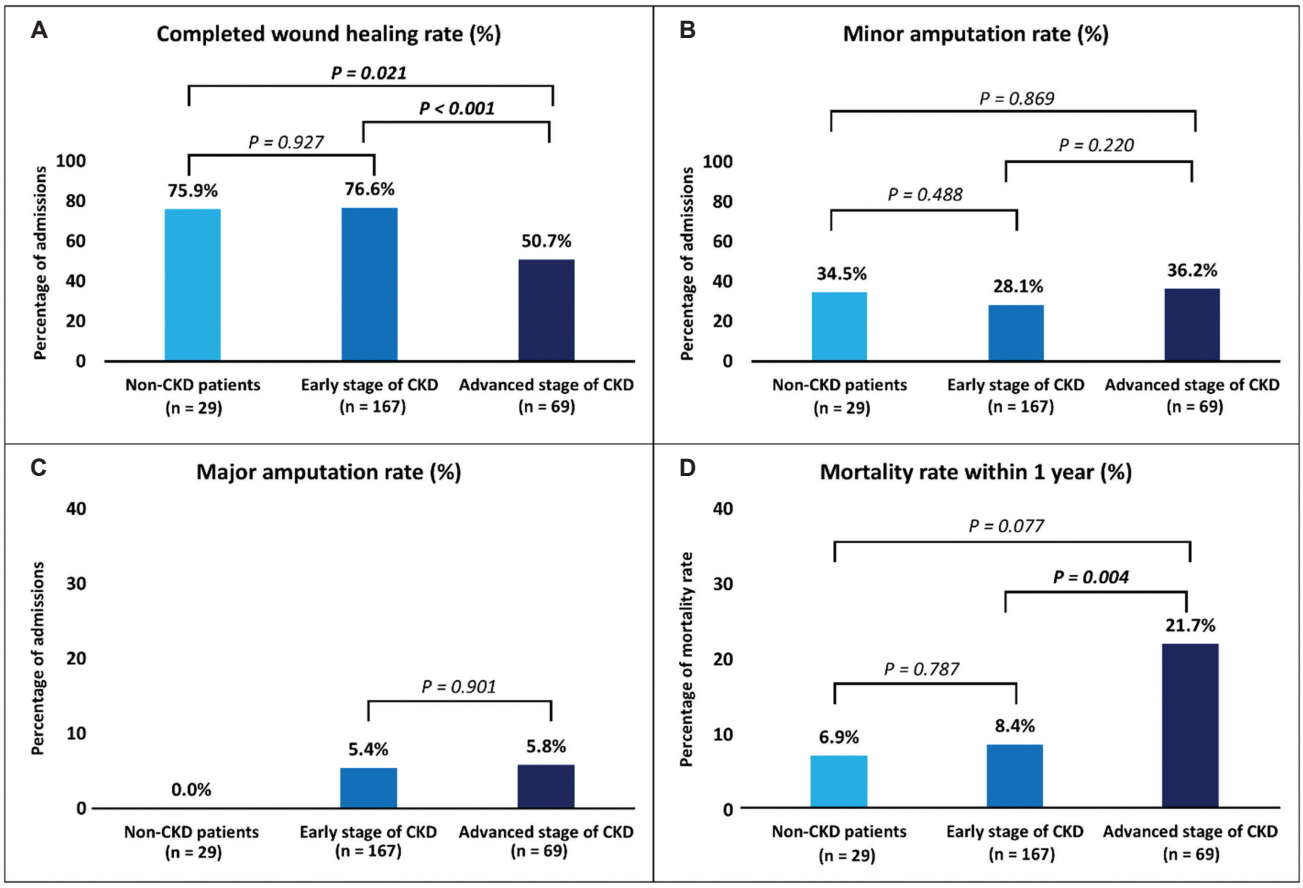


Figure 2. Ulcer-related outcomes stratified by renal status. **(A)** Completed wound healing rate. **(B)** Minor amputation rate. **(C)** Major amputation rate. **(D)** Mortality rate within 1 year.

Figure 4. Advanced renal dysfunction with severe DFU was associated with unfavorable ulcer-related outcomes in terms of complete healing and minor amputation rates, but differences in in major amputation rate and mortality rate were not statistically significant.

Results of univariate and multivariate logistic regression analysis of the complete healing rate are demonstrated in Table 3. More advanced Wagner's grades (≥3) were found more in non-healed group than healed group (70.0% vs. 55.7%, *P*-value 0.029) but this factor did not reach statistically significant levels after multivariate analysis as shown in Table 3. According to multivariate analysis for associated factors to predict non-healed ulcers, patients with advanced stages of CKD had increased odds of having a non-healed ulcer (Odd ratio 2.69, 95% Confidence Interval: 1.46-4.98, *P*-value = 0.002).

Comparisons with our previous published data

Compared with our previously published data from 2009 to 2013[14] and from 2014 to 2018,[15] the rates of ischemic ulcers and/or neuro-ischemic ulcers, advanced CKD, and severity of DFU increased in this study period (2019-2023) as shown in Table 4. Major amputation rate slightly increased from 4.2% to 4.9% but minor amputation rate markedly rose from 18.7% to 30.9%.

DISCUSSION

The present study demonstrates the impact of advanced CKD on various outcomes of hospitalized DFU patients. These findings were consistent with previous studies reporting higher odds of amputation and an increase in resource utilization due to prolonged length of stay among CKD patients with DFU.[4-10] Co-existing advanced CKD with the presence of PAD were the main drivers of these poor ulcer-related outcomes. Most patients with complicated DFUs at our center presented late for appropriate treatment. Longer delays before evaluation by diabetic foot specialists contributed to greater DFU severity.[18] Moreover, PAD has become an increasingly common cause of DFU, adversely affecting healing rates and amputation-free survival.[19] PAD prevalence is higher in the elderly, and increases exponentially with aging of the population.[20]

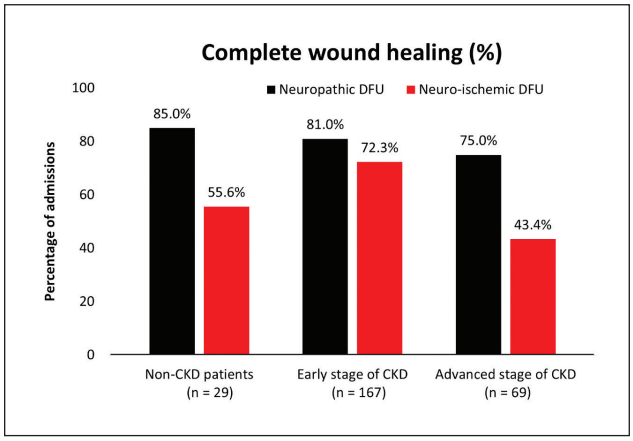


Figure 3. Ulcer-related outcomes stratified by type of ulcers.

Table 2. Clinical characteristics of patients with healed (including minor amputations) versus non-healed ulcers

	Healed ulcer (N = 185, 69.8%)	Non-healed ulcer (N = 80, 30.2%)	*P*-value
Age (years)	65.3 ± 13.1	69.9 ± 13.5	**0.008** [a]
Male (%)	62.7%	55.0%	0.239 [b]
BMI (kg/m²)	24.9 (22.3, 28.1)	23.4 (20.1, 25.5)	**0.001** [c]
T2D (%)	97.8%	100.0%	0.416 [b]
Duration of DM (years)	19.5 (11.0, 27.0)	20.0 (10.0, 30.0)	0.490 [c]
A1C (%)	7.9 (6.7, 9.7)	7.3 (6.0, 9.1)	**0.048** [c]
Serum creatinine (mg/dL)	1.1 (0.8, 1.8)	1.5 (0.9, 3.3)	**0.014** [c]
eGFR (mL/min/1.73 m²)	61.0 (36.0, 87.5)	42.5 (16.3, 86.8)	**0.015** [c]
Severe DFU (Wagner grades 3–5) (%)	55.7%	70.0%	**0.029** [b]
Wound location (%)			0.074 [b]
Toe	46.0%	43.7%	
Forefoot	43.2%	35.0%	
Heel	5.4%	12.5%	
Ankle	3.2%	5.0%	
Mid Foot	2.2%	1.3%	
Whole Foot	0.0%	2.5%	

[a] Independent t-test; [b] Chi-square test; [c] Mann-Whitney U test

Table 3. Factors associated with non-healed diabetic foot ulcer by logistic regression analysis

Variables	Univariate analysis			Multivariate analysis		
	Odds	*P*-value	95% CI	Odds	*P*-value	95% CI
Male	1.38	0.240	0.81 - 2.34			
A1C ≥9%	0.70	0.262	0.38 - 1.30			
Age ≥60 years	1.65	0.105	0.90 - 3.04			
BMI ≥25 kg/m²	0.46	0.006	0.26 - 0.80	0.57	0.070	0.31 - 1.05
Duration of DM ≥10 years	0.67	0.225	0.35 - 1.28			
Presence of Charcot foot	0.70	0.509	0.25 - 1.99			
Presence of IHD	1.77	0.048	1.00 - 3.12	1.02	0.943	0.53 - 1.99
Presence of PAD	2.73	<0.001	1.56 - 4.80	1.38	0.391	0.66 - 2.90
Previous Amputation	1.20	0.516	0.69 - 2.11			
Wagner grade ≥3	1.86	0.030	1.06 - 3.25	1.37	0.304	0.75 - 2.52
Wound site at heel	2.50	0.051	0.99 - 6.27			
Advanced CKD	3.17	<0.001	1.78 - 5.64	**2.69**	**0.002**	**1.46 - 4.98**
Severe DR	1.54	0.301	0.68 - 3.47			
Active Smoking	0.62	0.359	0.22 - 1.73			

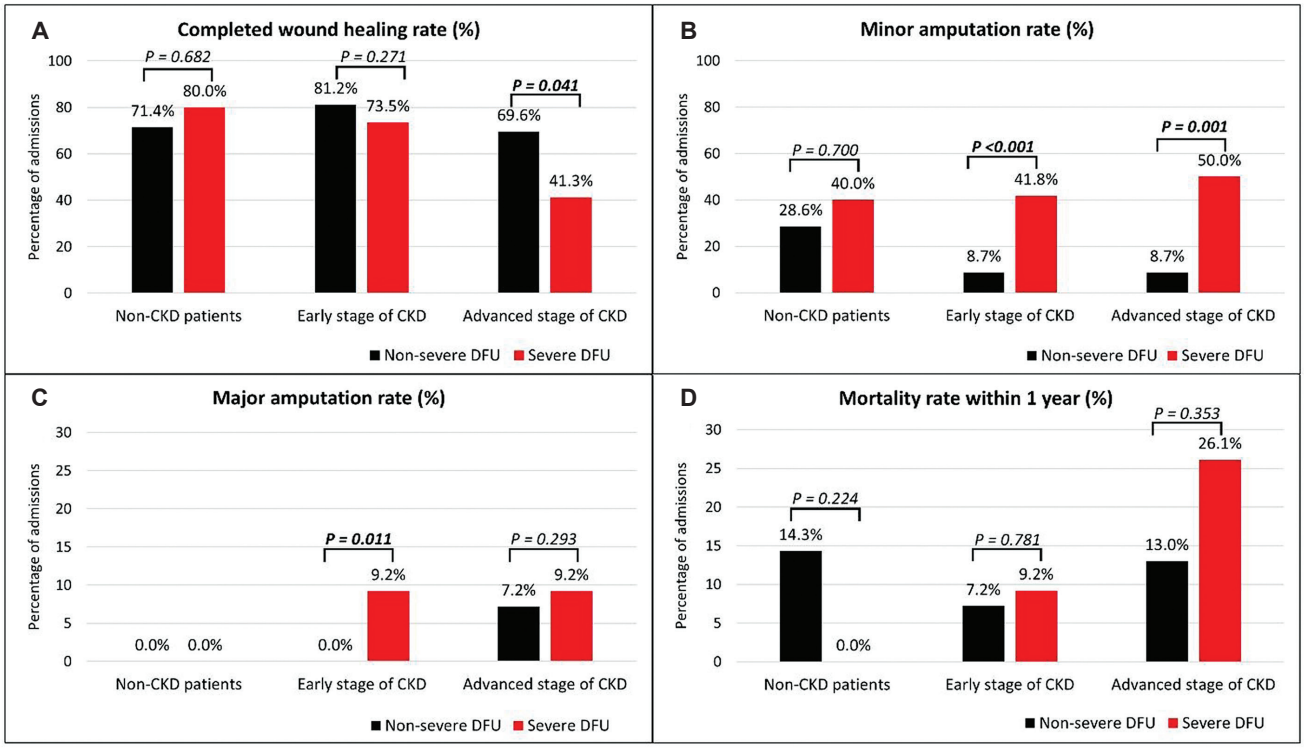


Figure 4. Ulcer-related outcomes stratified by severe diabetic foot ulcer (Wagner grade ≥3) in each renal status. **(A)** Completed wound healing rate. **(B)** Minor amputation rate. **(C)** Major amputation rate. **(D)** Mortality rate within 1 year.

Table 4. Comparison of clinical characteristic data and ulcer-related outcomes for this study period (2019-2023) with our previous published studies in 2009-2013 and 2014-2018

Study period	2009-2013* (N = 262)	2014-2018# (N = 350)	2019-2023 (N = 265)	*P*-value
Age (years)	65.6 ± 11.9	65.4 ± 13.4	66.7 ± 13.4	0.416
Duration of DM (years)	17.2 ± 9.9	18.8 ± 11.5	20.0 ± 10.9	0.017
A1C (%)	8.9 ± 2.4	8.6 ± 2.3	8.2 ± 2.3	0.003
PAD (%)	43.1%	62.0%	54.7%	<0.001
Advanced CKD (%)	18.5%	27.0%	26.1%	**0.029**
Major Amputation (%)	4.2%	4.6%	4.9%	0.927
Minor Amputation (%)	18.7%	22.3%	30.9%	**0.003**
Non-healing rate (%)	17.9%	26.6%	30.2%	**0.004**
Dead within 1 year (%)	5.7%	12.0%	11.7%	**0.021**

*J Clin Transl Endocrinol. 2014;1:187-91. #BMC Endocr Disord. 2020;20:89.

Previous studies have reported that beyond ulcer severity, several factors – particularly the renal function – are important predictors of amputation risk.[9,21,22] Our findings indicate that advanced renal dysfunction is associated with unfavorable ulcer-related outcomes, independent of DFU severity. These results highlight the importance of recognizing advanced renal impairment as a key risk factor for poor outcomes, even in patients who present with less severe DFU at initial evaluation.

Identifying individuals at risk for foot ulceration is the first step to prevent the vicious cycle of DFU.[23] The latest International Working Group on the Diabetic Foot (IWGDF) guideline designated end-stage renal failure as the highest podiatric risk category for worse outcomes.[24] This update in the IWGDF underscores the relationship between DFU and CKD. Patients receiving dialysis still have significantly greater odds ratio of undergoing major amputation even after adjusting for the presence of PAD.[25,26] It has been postulated that dialysis treatment itself might decrease tissue oxygenation and blood flow to the foot.[27] Therefore, active annual foot ulcer screening and prompt referral to a multidisciplinary diabetic foot team should be emphasized in people with diabetes who are on dialysis. Delayed referral to multidisciplinary care and the lack of a dedicated follow-up pathway can lead to lower extremity amputations. The national diabetes foot care audit in England reported that more than 10% of patients who did not self-present were not seen for 2 months or more after initial healthcare contact.[28] Our center, a referral facility for complex DFU cases for three decades, has also observed the continuing trend of delayed hospital presentation in several patients. More efforts are required to educate patients with high-risk foot if the ulcer develops to improve the future outcomes.

DFU complicated with PAD is highly prevalent among CKD patients and revascularization by angioplasty or bypass surgery in advanced tertiary centers are often needed in these patients. CKD patients tended to have PAD with characteristic lesions that significantly reduce long-term patency rate after revascularization such as long vascular segments, serious calcification, poor collateral circulation, and more involvement of small vessels under the knee.[20] Recently, transcatheter arterialization of the deep veins – a percutaneous approach that creates an artery-to-vein connection for delivery of oxygenated blood by means of the venous system to the ischemic foot has emerged to as a promising therapy in patients with no-option chronic limb threatening ischemia.[29] This advanced intervention, however, was not yet available in our center. Poor glycemic control is associated with worse outcomes following revascularization and optimal glycemic management including nutritional intervention, is very important factors to aid wound healing process in patients with complex DFU.[30]

Several limitations may have influenced our results. First, the retrospective design limits the generalizability of our findings to populations with different demographics and health care systems.. Various confounding factors like socioeconomic status, location of ulcers, smoking status, and other co-morbidities were not considered in our study due to incomplete data. Economic constraints were the main hindrance for patients with low socio-economic capacity from achieving the best results. Second, the use of a single definition of chronic kidney disease (CKD), based solely on estimated glomerular filtration rate (eGFR) without incorporating other markers of kidney damage, may have led to misclassification of CKD status. Third, consistent with prior studies, we classified patients who died within 12 months of admission as having non-healing ulcers; however, some of these patients may have died from unrelated causes after complete wound healing had been achieved. Fourth, we did not apply correction methods for multiple testing which could affect the significance level in our data. Fifth, our analysis was conducted at the level of hospital admissions rather than individual patients. Although repeated admissions represented only 17.7% of the sample and largely corresponded to distinct DFU episodes with differing severity and management, the non-independence of observations could affect the validity of our results. Given the relatively small sample size and sparse clustering, attempts to employ mixed-effects or generalized estimating equation models risked non-convergence or unstable estimates. Therefore, we performed admission-level analysis while explicitly acknowledging this methodological limitation. Finally, the presence of PAD might be underreported from inherent limitations of ABI in patients with calcified vessels.

CONCLUSION

Our data is consistent with other studies reporting an increase in morbidity and mortality in CKD patients who develop DFU. It is important to maintain a proactive approach to foot care and early referral for DFU in patients with advanced CKD, especially if the patients are on dialysis. Despite continuous improvements in DFU management, advanced CKD patients still had unfavorable ulcer-related outcomes and increased mortality. Coordinated care between institutes and better efforts at public education are required to improve future outcomes.

Acknowledgments
The authors express their gratitude to the staff at the THEPTARIN Diabetes, Thyroid and Endocrine Center (TDTEC) and Foot Clinic and Wound Care, Vimut-Theptarin Hospital, Bangkok, Thailand for their dedicated and compassionate patient care. We also acknowledge the meticulous proofreading and editing provided by Dr. Tinapa Himathongkam and Professor Rajata Rajatanavin. Parts of this manuscript has previously been presented as a poster at IDF World Diabetes Congress 2025 at Bangkok, Thailand.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JS and YT: Conceptualization, Software, Formal analysis, Data Curation, Visualization; **JS, SN, SB, and PC:** Methodology, Validation, Investigation, Writing – original draft preparation; **JS and SN:** Resources, Project administration; **SK, WC, EW, TS, PK, and PC:** Writing – review and editing; **YT:** Writing – review and editing; **TH:** Supervision, Funding acquisition.

Data Availability Statement
Datasets analyzed in the study are under license and not publicly available for sharing.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Knowledge, Attitudes and Practices of Physicians on Diagnosis and Management of Diabetic Peripheral Neuropathy at the University of Santo Tomas Hospital

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Abstract

Background. Diabetic peripheral neuropathy (DPN) is a prevalent chronic complication of diabetes, resulting in significant morbidity and mortality. Despite its impact, DPN remains an underdiagnosed and undertreated entity, further underscoring the need for improved physician awareness and timely intervention.

Objective. The study aimed to determine physicians' knowledge, attitudes and practices (KAP) in the diagnosis and management of DPN and the association between knowledge and attitude to practice.

Methodology. This was a cross-sectional study involving 211 physicians from the University of Santo Tomas Hospital (USTH). Chi-square test was employed to compare physician characteristics based on KAP. The association of knowledge and attitude with practice regarding DPN was analyzed using multiple logistic regression analysis.

Result. Median knowledge level was 81.3%, indicating good knowledge on DPN diagnosis and management. Most had favorable attitude and reported appropriate practice. Only attitude was shown to be significantly associated with practice.

Conclusion. Despite good knowledge about DPN, attitude was the only key influencer on appropriate practice. Enhancing positive attitudes in screening and management is essential to improve patient care and outcomes.

Key words: diabetic neuropathy, diabetes complications, knowledge, attitudes, practice, peripheral neuropathy

INTRODUCTION

Based on the International Diabetes Federation estimate in 2021, the prevalence of diabetes mellitus (DM) in the Philippines was 7.5%, affecting 4,303,899 individuals.[1] It continues to be the fourth leading cause of death in the country based on 2022 statistics.[2]

Diabetic peripheral neuropathy (DPN) as a complication of DM significantly contributes to morbidity and mortality. Approximately one in two patients with diabetes suffers from symptoms of DPN; 80% remain undiagnosed and untreated despite being symptomatic.

Early screening is of utmost importance to allow timely intervention. Patients may be unable to recognize symptoms of DPN and these may remain unreported to their healthcare providers. Up to 50% of these patients may not experience any noticeable symptoms.[3] A study by Tanirlar, et. al., on the knowledge, attitudes and practices of primary health care institutions in Turkey showed there were deficiencies in the knowledge level and approaches of physicians regarding DPN.[4] Assessing the adequacy of knowledge of physicians to provide comprehensive care in terms of prevention and treatment will help reduce morbidity and mortality. Educating patients about DPN will help them understand signs and symptoms and ensure timely intervention. The role of specialists is essential in the management of diabetes, particularly early complicaiton detection and intervention.

To our knowledge, there is a paucity of studies done on DPN in the Philippines. Consequently, the objective of this research was to assess the knowledge, attitude, and practices of physicians and identify gaps in the diagnosis and management of DPN. It also aims to compare the characteristics of physicians between good and poor knowledge levels; favorable and unfavorable attitudes; and appropriate versus inappropriate practices; to identify barriers to the diagnosis and management of diabetic

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Reburiano et al.
Received: June 13, 2025. Accepted: August 11, 2025.
Published online first: April 27, 2026.
https://doi.org/10.15605/jafes.041.01.5097

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peripheral neuropathy. Lastly, this study also aims to determine the relationship of knowledge and attitude of physicians to their practice in diagnosis and management of diabetic peripheral neuropathy (Appendix A).

Data obtained will allow identification of barriers in early diagnosis and appropriate management of patients with DPN. Understanding the KAP related to DPN can facilitate development of strategies to improve these domains, and ultimately patient management.

The results of this study will further strengthen measures to ensure adequate knowledge of physicians in providing comprehensive care to patients with DM. Understanding the KAP of physicians may also foster collaboration with other healthcare professionals in terms of timely referrals, ultimately leading to a more comprehensive and coordinated approach regarding DPN management. This will also benefit the institution since determining KAP of physicians helps the healthcare systems identify gaps that may require additional training. Hence, proper allocation of resources, such as educational programs or workshops, can be directed towards addressing these gaps and enhancing physician competence. Continuous assessment also allows quality improvement in the management of DPN. Data that may be provided by this research may also strengthen research on healthcare practices, contributing to the development of evidence-based guidelines.

METHODOLOGY

This research was an analytical, cross-sectional, questionnaire-based study done at the University of Santo Tomas Hospital. Research ethics committee approval was obtained.

This study included residents, fellows and consultants from the Departments of Internal Medicine, Family Medicine, Neurology and Psychiatry, Dermatology, ENT-HNS, Obstetrics and Gynecology, Ophthalmology, Rehabilitation Medicine and Surgery who completed at least one year residency in their respective specialties to ensure adequate patient experience. Residents, fellows and consultants from the Department of Anesthesiology, Clinical and Anatomic Pathology, Nuclear Medicine, and Radiological Sciences were excluded from the study since they were not expected to participate in the direct management of patients with DM, such that recognition and diagnosis of diabetes and diabetic neuropathy are beyond their area of focus (Figure 1).

OpenEpi sample size calculator was used to calculate the minimum sample size requirement. Based on a previous study, the proportion of good knowledge, favorable attitude and appropriate practice were 48.3%, 66.7% and 43.3%, respectively.[5] Using a maximum tolerable error of 5%, alpha of 0.05 and a finite population of 466, the sample size requirement was calculated as 198 to 211.The largest sample size obtained was used for this study. To account for 10% potential non-response, the minimum sample size was increased to 235.

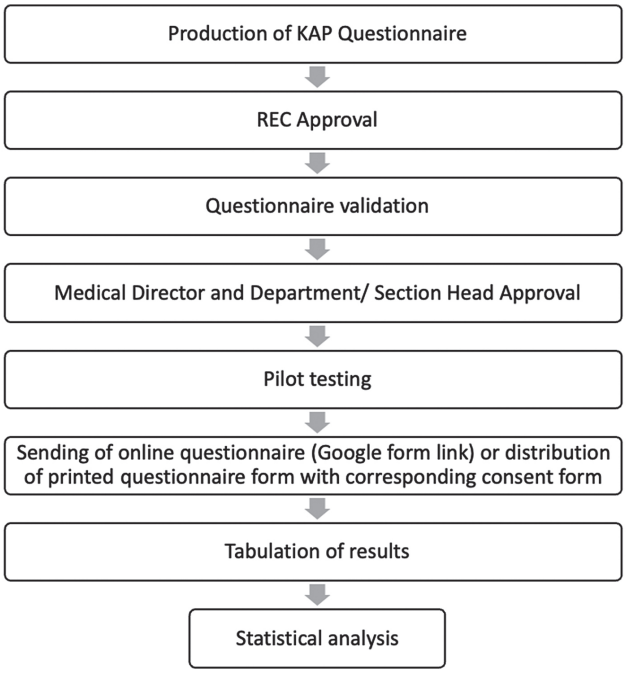


Figure 1. Flowchart of the study

Since *a priori* sample size computation for the objective examining the association of knowledge and practice was not available due to the lack of similar studies, *post hoc* power analysis using PASS 2021 software was performed instead. *Post hoc* power analysis revealed low statistical power for the regression analysis: only 77% for attitude and 8% for knowledge.

Stratified random sampling proportional to sample size was employed to select study participants. The strata consisted of residents, fellows and consultants. This ensured that the study population was a sample that is proportionally representative to the target population based on designation (Appendix C). OpenEpi Random Number Generator was used to create the list of random numbers per strata. The list of all trainees and consultants in USTH fulfilling inclusion criteria obtained from the Medical Director's Office and the UST Department of Medical Education and Research were used as the sampling frame.

Data gathering

A Knowledge, Attitudes and Practices questionnaire was formulated by the investigators. Questions were formulated based on the 2022 American Diabetes Association (ADA) clinical compendia on the Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy and the ADA Standards of Care 2023.[5,6] These guidelines discuss the recommendations on comprehensive diabetes management strategies for complications like DPN. These emphasize appropriate screening, diagnosis and management of DPN based on evidence and practice.

Content validity of the questionnaire was done by three content experts, consisting of two endocrinologists and

a neurologist. They were given a standardized form to determine the relevance of each item of the tool. The item-content validity index (I-CVI) was calculated (range: 0-1), and was categorized as follows: item is relevant (I-CVI >0.79), item needs revisions (I-CVI 0.70 to 0.79), and item is removed (I-CVI <0.70). The average of the I-CVI scores for all items on the scale (S-CVI/Ave) and the proportion of items on the scale that achieved a relevance scale of 3 or 4 by all experts (S-CVI/UA) was calculated. Excellent content validity was defined as S-CVI/UA ≥ 0.8 and S-CVI/Ave ≥ 0.97. Content validity and Cronbach's alpha was calculated to determine the validity and reliability of the tool (Appendix D).

The study was started following approval from the research ethics committee. The questionnaire was reproduced, and a pilot study was conducted among 10% of the total population. The questionnaire was finalized after the modification of the questions based on the pilot study. Appropriate correspondence with hospital administration and training committees were done to secure permission in distribution of questionnaires. Once informed consent was obtained, and questionnaires were then distributed both via paper form and Google form based on the preference of participant. Demographic characteristics were also collected: including age, gender, years in practice, specialty, designation, total number of patients seen per week, additional training in DPN (if applicable) and attendance in update lectures on DPN.

Data were encoded in Microsoft Excel by the researcher. Stata/MP version 17 software was used for data processing and analysis. Continuous variables were presented as median/interquartile range (IQR) due to the non-normal data distribution based on the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Comparison of physician characteristics based on KAP was performed using Mann -Whitney U test for continuous variables, and chi-square test or Fisher's Exact test for categorical variables. To determine the association of knowledge and attitude with practice regarding DPN, multiple logistic regression analysis was performed. Screening of potential confounders was based on the $p<0.20$ criteria, and significant confounders were identified based on the change-in-estimate criteria of >10%.[7] P values ≤0.05 were considered statistically significant. Missing data were neither replaced nor estimated.

RESULTS

Table 1 illustrates the demographic characteristics of the included participants. A total of 235 physicians were invited initially to participate in the study, of which 211 agreed. The median age was 34 years, and more than half were male. The median years in practice was six years. Most were non-internal medicine (IM) physicians, and about half of the participants were consultants. The median number of patients with DM seen per week for all physicians was eight.

Table 1. Characteristics of included physicians (n = 211)

Characteristic	Frequency (% or IQR[a])
Age (in years), median	34 (30-41)
Gender	
Male	119 (56)
Female	92 (44)
Years in practice, median	6 (3-10)
Specialty	
General practitioner	0
General IM[b]	13 (6)
IM[b] sub-specialist	66 (31)
Non-IM[b]	132 (63)
Designation	
Consultant	101 (48)
Fellow	41 (19)
Resident	69 (33)
Number of patients with DM per week, median	8 (4-12)
Additional training, % yes	76 (36)
Attendance on update lecture regarding DPN	
0-5 months ago	27 (13)
6-11 months ago	25 (12)
12-23 months ago	40 (19)
2-5 years ago	20 (9)
More than 5 years ago	15 (7)
Never attended	84 (40)

[a] IQR, interquartile range; [b] IM, internal medicine

Table 2. KAP on DPN diagnosis and management (n = 211)

Domain	Frequency (% or IQR[a])
Knowledge level, median	81.3 (71.9-90.6)
Good	204 (97)
Poor	7 (3)
Attitude score, median	80 (75.6-88.9)
Favorable	130 (62)
Unfavorable	81 (39)
Practice score, median	73.3 (53.3-86.7)
Appropriate	157 (74)
Inappropriate	54 (26)

[a] IQR, interquartile range

More than a third had additional training/attended lectures in DPN management. The most common source of additional information were books (72%). Other sources of information were clinical practice guidelines (66%), journals (58%), social media resources (57%), continuing medical education/workshops/conferences/webinars (51%), colleagues (45%), pharmaceutical representatives (41%), undergraduate training (38%), postgraduate training (38%), UpToDate® (33%) and Medscape (4%). On the other hand, most of the participants (40%) had never attended an update lecture on management of DPN.

Table 2 presents the knowledge on DPN diagnosis and management among included physicians. Median knowledge level was 81.3%. Only three were noted to attain a perfect score. Except for seven participants, all had good knowledge about DPN diagnosis and management. Median attitude level was 80%. 12% attained an attitude score of 100% and most had favorable attitude towards DPN diagnosis and management. Median practice score was 73.3%. Majority had appropriate practice of DPN diagnosis and management.

Table 3 compares the characteristics of physicians with good versus poor knowledge on DPN diagnosis and management. Analyses showed that between the two groups, only additional training was significantly different between the two groups. A higher proportion of physicians with good knowledge had additional training in the management of DPN compared to those with poor knowledge. Among the 132 non-IM physicians, 65 did not attend lectures on DPN. Of these, 89% had good knowledge.

Table 4 compares the characteristics of physicians with favorable and unfavorable attitude towards DPN diagnosis and management. Gender, specialty and additional training significantly differed between the two groups. Compared to those with unfavorable attitude, a higher proportion of those with favorable attitude were males, non-IM and had additional training in management of DPN.

Table 5 compares the characteristics of physicians with appropriate versus inappropriate practice of DPN

Table 3. Characteristics of included physicians: good vs. poor knowledge about DPN diagnosis and management (n = 211)

Characteristic	Good knowledge (n = 204)	Poor knowledge (n = 7)	*P* value
	Frequency (% or IQR[a])		
Age (year), median	34 (30-41)	35 (32-55)	0.3441[b]
Gender			
Male	114 (56)	5 (71)	0.473[c]
Female	80 (44)	2 (29)	
Years in practice, median	6 (3-10)	6 (5-20)	0.4811[b]
Specialty			
General IM	13 (6)	0	0.179[c]
IM sub-specialist	66 (32)	0	
Non-IM	125 (61)	7 (100)	
Designation			
Consultant	97 (48)	4 (57)	0.679[c]
Fellow	39 (19)	2 (29)	
Resident	68 (33)	1 (14)	
Number of patients with DM per week, median	8 (4-15)	8 (5-10)	0.7948[b]
Additional training, % yes	76 (37)	0	0.050*[c]
Attendance on update lecture regarding DPN			
0-5 months ago	27 (13)	0	0.142[c]
6-11 months ago	25 (12)	0	
12-23 months ago	40 (20)	0	
2-5 years ago	20 (10)	0	
More than 5 years ago	15 (7)	0	
Never attended	77 (38)	7 (100)	

[a] IQR, interquartile range; [b] Mann-Whitney U test; [c] Fisher's exact test

Table 4. Characteristics of included physicians: favorable vs. unfavorable attitude towards DPN (n = 211)

Characteristic	Favorable attitude (n = 130)	Unfavorable attitude (n = 81)	*P* value
	Frequency (% or IQR[a])		
Age (in years), median	33 (30-38)	34 (31-49)	0.0691[b]
Gender			
Male	84 (65)	35 (43)	0.002*[c]
Female	46 (35)	46 (57)	
Years in practice, median	6 (3-10)	7 (4-20)	0.0672[b]
Specialty			
General IM	5 (4)	8 (10)	0.044*[c]
IM sub-specialist	36 (28)	30 (37)	
Non-IM	89 (68)	43 (53)	
Designation			
Consultant	60 (46)	41 (51)	0.607[c]
Fellow	28 (22)	13 (16)	
Resident	42 (32)	27 (33)	
Number of patients with DM per week, median	10 (4-15)	6 (4-12)	0.2376[b]
Additional training, % yes	57 (44)	19 (23)	0.003*[c]
Attendance on update lecture regarding DPN			
0-5 months ago	19 (15)	8 (10)	0.245[c]
6-11 months ago	20 (15)	5 (6)	
12-23 months ago	21 (16)	19 (23)	
2-5 years ago	11 (8)	9 (11)	
More than 5 years ago	8 (6)	7 (9)	
Never attended	51 (39)	33 (41)	

[a] IQR, interquartile range; [b] Mann -Whitney U test; [c] chi-square test

diagnosis and management. Only additional training and attendance in update lectures regarding DPN were significantly different between the two groups. A higher proportion of physicians with appropriate practice had additional training in management of DPN than those with inappropriate practice. On the other hand, a higher proportion of physicians with inappropriate practice had never attended an update lecture regarding DPN compared to those with appropriate practice.

Based on the univariate analysis, the following were considered as probable confounders (i.e., satisfied $p<0.20$ criteria) and were entered into the multivariable model together with knowledge and attitude: age, years in practice, number of diabetic patients per week, additional training and attendance on update lecture regarding DPN (Table 6). However, based on the change-in-estimate criterion of >10% during multivariable analysis, only attendance in lectures regarding DPN was retained. Thus, this was

Table 5. Characteristics of included physicians: appropriate vs. inappropriate practice regarding DPN (n = 211)

Characteristic	Appropriate practice (n = 157)	Inappropriate practice (n = 54)	*P* value
	Frequency (% or IQR[a])		
Age (in years), median	34 (30-40)	35 (31-47)	0.0691[b]
Gender			
Male	86 (55)	33 (61)	0.418[c]
Female	71 (45)	21 (39)	
Years in practice, median	6 (3-10)	7.5 (4-15)	0.0672[b]
Specialty			
General IM	11 (7)	2 (4)	0.680[c]
IM sub-specialist	49 (31)	17 (31)	
Non-IM	97 (62)	35 (65)	
Designation			
Consultant	73 (47)	28 (52)	0.756[c]
Fellow	32 (20)	9 (17)	
Resident	52 (33)	17 (31)	
Number of patients with DM per week, median	10 (4-15)	5 (2-10)	0.2376
Additional training, % yes	63 (40)	13 (24)	0.034*[c]
Attendance on update lecture regarding DPN			
0-5 months ago	24 (15)	3 (6)	0.001*[c]
6-11 months ago	22 (14)	3 (6)	
12-23 months ago	36 (23)	4 (7)	
2-5 years ago	14 (9)	6 (11)	
More than 5 years ago	11 (7)	4 (7)	
Never attended	50 (32)	34 (63)	

[a] IQR, interquartile range; [b] Mann -Whitney U test; [c] chi-square test

Table 6. Association of knowledge and attitude towards DPN diagnosis and management and appropriate practice

	Crude OR[a] (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Knowledge about DPN diagnosis and management				
Poor	Ref	Ref	Ref	Ref
Good	1.17 (0.22-6.21)	0.854	0.53 (0.09-3.00)	0.471
Attitude towards DPN diagnosis and management				
Unfavorable	Ref	Ref	Ref	Ref
Favorable	2.34 (1.25-4.37)	0.008*	2.49 (1.29-4.83)	0.007*
Age (in years), median	0.98 (0.97-1.01)	0.183	-	-
Gender				
Male	Ref	Ref	-	-
Female	0.77 (0.41-1.45)	0.419	-	-
Years in practice, median	0.98 (0.95-1.01)	0.173	-	-
Specialty				
General IM	Ref	Ref	-	-
IM sub-specialist	0.52 (0.11-2.61)	0.430	-	-
Non-IM	0.50 (0.11-2.39)	0.388	-	-
Designation				
Consultant	Ref	Ref	-	-
Fellow	1.36 (0.58-3.22)	0.479	-	-
Resident	1.17 (0.58-2.36)	0.655	-	-
Number of diabetic patients per week, median	1.06 (1.01-1.11)	0.026*	-	-
Additional training, % yes	2.11 (1.05-4.26)	0.036*	-	-
Attendance on update lecture regarding DPN				
Never attended	Ref	Ref	Ref	Ref
Attended	3.64 (1.91-6.94)	<0.0001*	3.78 (1.95-7.32)	<0.0001*

[a] OR, odds ratio

Table 7. Barriers to DPN screening and management (n = 211)

Barrier	Yes	No	Not applicable
	Frequency (%)		
1. Lack of doctor-patient time	146 (69)	59 (28)	6 (3)
2. Inaccessibility of tools such as 10 g monofilament or tuning fork	184 (87)	17 (8)	10 (5)
3. Patients' coexisting multiple medical conditions that need more priority	180 (85)	29 (14)	2 (1)
4. Patients' refusal for screening and management	124 (59)	77 (36)	10 (5)
5. Others	4 (2)	28 (13)	179 (85)

the only variable that was considered as a significant confounder. Knowledge was not significantly associated with appropriate practice. Attitude was significantly associated with practice. Participants with favorable attitude towards DPN diagnosis and management had two times higher odds of appropriate practice than those with unfavorable attitude. Even after controlling for the effects of significant confounder, attitude remains significantly associated with practice.

The most commonly cited barrier to DPN screening and management was the inaccessibility of tools, such as 10 g monofilament or tuning fork (87%), followed by patients' coexisting multiple medical conditions that need more priority (85%) (Table 7). There were a few participants who also cited other barriers including financial issues, patients believing in Google, and cost of tests (e.g., nerve conduction velocity, electromyography, physical therapy occupational therapy).

DISCUSSION

The outcomes of this research have provided insight into the knowledge, attitudes and practices of physicians regarding DPN. The most common source of additional information/training regarding DPN were books (72%) and CPGs (66%), followed by journals (58%) and social media resources (57%). A study by Tanirlar, et. al. on the knowledge, attitudes and practices of primary health care institutions in Turkey showed there were deficiencies in the knowledge level and approaches of physicians regarding DPN.[4] In our study, most (40%) reported to have never attended an update lecture on management of DPN. Consequently, additional training was consistently associated with good knowledge, favorable attitude and appropriate practice. This was similar to the results in a study by Tanirlar et al., wherein the knowledge score of family physicians who underwent specialty training was statistically higher than those who did not.[4] This was attributed to more exposure to the care of patients with diabetic neuropathy during their residency training. The median knowledge level determined in the current study was 81.3% which showed a markedly higher level of proficiency in comparison to the clinical gaps identified by Al-Geffari[8] where only a small minority of practitioners were found to be knowledgeable in using screening tools.

In contrast, these were better than the results in a study by Peimani et al. which reported good knowledge scores in only 29% among the total number of physicians involved in the study.[9]

In the item analysis on knowledge about screening, all participants were able to attain a knowledge score of more than 50% regarding screening tools for DPN. One of the screening tests mentioned included monofilament testing. In contrast to our results, Tanirlar et al. reported that only 4.6% of the physicians in their study had knowledge about this specific test.[4]

In the attitude domain, 84% of the participants agreed that all patients with DM will benefit from DPN screening. Despite this, 64% of the participants claimed to have never screened patients with DM for DPN in their daily practice. Only 46% of the participants were confident in performing screening tests for DPN. Tanirlar et al. reported more than half of their participants were not confident in screening and managing diabetic neuropathy themselves.[4] Overall, our study showed that 74% had appropriate practice regarding DPN diagnosis and management.

In a study by Malik et al., the diagnosis and treatment of DPN were regarded as low priority by physicians, indicating a lack of awareness regarding DPN.[10] Inaccessibility of tools, such as 10 g monofilament or tuning fork, was the most identified barrier to DPN screening and management.

While there was good knowledge among most physicians, this did not translate to attitudes and practice. Good knowledge may be due to the wide availability of resources such as online materials and conferences. Aside from continuing medical education seminars and training courses to further strengthen knowledge, workshops may also done so as to empower physicians in adapting appropriate practice. Since one of the barriers identified includes unavailability of tools or materials for screening, it is important for the stakeholders to ensure availability of such resources (e.g., 10 g monofilament, questionnaires, tuning fork) for the physician to utilize to encourage regular screening for patients with DM.

Although this is the first study assessing the knowledge, attitudes and practices of physicians regarding DPN in the Philippines, there are still limitations to this research. These include the potential for recall bias and possible social desirability bias. Given its reliance on self-reported

data, there is a possibility of overestimation in terms of favorable attitude and good practice. Due to the lack of similar studies, *a priori* sample size computation was mainly based on assumptions. *Post hoc* power analysis revealed low statistical power for the regression analysis, especially for knowledge (8%). The findings that were not statistically significant for knowledge could have been due to the high beta error attributed to the low power. Moreover, the comparison of characteristics by knowledge, attitudes and practice was purely exploratory. The non-significant findings could be due to the low statistical power. Since this was a single-center study, characteristics, knowledge, attitudes and practices of physicians from other institutions may be different. A multi-center study may capture variations across different demographics, which would help in making the results more generalizable.

CONCLUSION

This study showed that majority of the participants involved had good knowledge, favorable attitudes and appropriate practice. It was also seen that attitude was significantly associated with practice. Hence, interventions aiming to improve health practices should focus on enhancing positive attitudes, as they may significantly influence practice outcomes. Strategies focused on attitudes may be key mediators in translating knowledge into practice.

Similarly, additional training was seen to significantly influence attitude and clinical practice. Regular updates and training, whether via literature, CPGs or conferences will help further strengthen knowledge and empower application in practice to address gaps in the comprehensive management of DPN patients.

This is the first study to assess knowledge, attitude, and practices of physicians in the Philippines regarding DPN. Although the findings demonstrate generally good knowledge and favorable attitudes, there are certain limitations that must be considered. This includes use of self-reported date that introduces potential for recall and social desirability bias, which may have resulted to overestimation of positive attitude and reported practices. As a single-center study, the results may not have been representative of other institutions.

Acknowledgments
The authors would like to acknowledge Lady Ann Cuevas, RN, for her contribution to the study as research assistant and Ms. Marla Briones for her assistance as biostatistician.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
SBR: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **DVT:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **DVB:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **BJM:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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APPENDICES

Appendix A. Operational definition of variables

Variable	Operational Definition	Categories
Knowledge about DPN	Measured using a questionnaire composed of 10 items. Each correct answer is given a score of 1. Knowledge score is the percentage of correct answers for knowledge items.	• Good knowledge level ≥50% correct answers • Poor knowledge level <50% correct answers
Attitude towards DPN	Measured using a questionnaire composed of 10 items, answerable using a 5-point Likert Scale. The following points will be applied, and the total attitude score will be calculated: 5=strongly agree, 4=agree, 3=neutral, 2=disagree, 1=strongly disagree. Attitude score is the percentage of correct answers for attitude items.	• Favorable attitude ≥80% of total score • Unfavorable attitude <80%
Practice of DPN screening and management	Measured using 3 general questions that are composed of a 4-point Likert scale. The following points will be applied, and the total practice score will be calculated: 3=always, 2=often, 1=seldom, 0=never. Practice score is the percentage of correct answers for practice items.	• Appropriate practice ≥60% of total score • Inappropriate if <60%
Specialty	Field of chosen specialization/subspecialization	• General Practitioner: Licensed medical doctor by the PRC[a], not currently undergoing residency training • General IM[b]: currently undergoing residency training in IM, or finished at least 3 years residency in IM and certified by the PCP[c], not undergoing fellowship training in any subspecialty • Sub-specialist: currently undergoing fellowship training in chosen field of sub-specialty (cardiology, pulmonology, endocrinology, nephrology, gastroenterology, hematology, oncology, rheumatology, infectious diseases; or completed fellowship training inchosen sub-specialty • Non-IM: Other services not included in internal medicine (family medicine, neurology and psychiatry, surgery, dermatology, ophthalmology, ENT-HNS[d], rehabilitation medicine
Years of practice	Years since licensed MD[e]	

[a] PRC, Professional Regulation Commission; [b] IM, internal medicine; [c] PCP, Philippine Colege of Physicians; [d] ENT-HNS, ear nose and throat - head and neck surgery; [e] MD, medical doctor

Appendix B. Sample size computation

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Tests for One Coefficient Alpha

Numeric Results

Hypotheses: H0: CA = CA0 vs. H1: CA ≠ CA0

Power	Sample Size N	Number of Items K	Coefficient Alpha|H0 CA0	Actual Coefficient Alpha CA1	Alpha	Beta
0.90743	16	39	0	0.7	0.05	0.09257

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Report Definitions

Power is the probability of rejecting a false null hypothesis.
N is the total sample size.
K is the number of items or raters.
CA0 is the value of coefficient alpha under the null hypothesis.
CA1 is the value of coefficient alpha at which the power is computed.
Alpha is the probability of rejecting a true null hypothesis. It should be small.
Beta is the probability of accepting a false null hypothesis. It should be small.

Summary Statements

A sample of 16 subjects each responding to 39 items achieves 91% power to detect the difference between the actual coefficient alpha of 0.7 and the coefficient alpha under the null hypothesis of 0 using a two-sided F-test with a significance level of 0.05.

Appendix C. Sample size determination per study objective

Objective	Parameter	Sample size
Proportion of good knowledge level about DPN, including diagnosis and management	P[a] = 48.3% d[b] = 5% alpha = 5% finite population = 466	211
Proportion of favorable attitude towards DPN, including diagnosis and management	P[a] = 66.7% d[b] = 5% alpha = 5% finite population = 466	198
Proportion of appropriate practice regarding DPN, including diagnosis and management	P[a] = 43.3% d[b] = 5% alpha = 5% finite population = 466	209
Association of knowledge and attitude with practice	Cohens f^2 (effect size) = 0.15 Power = 90% Alpha = 5%	91

[a] P, prevalence; [b] d, maximum tolerable error

Stratified distribution of population and sample size

Strata	Total number	% of population	Sample size
Resident	137	29.4%	78
Fellow	85	18.2%	48
Consultant	244	52.4%	138
Total	466	100%	264

Appendix D. Reliability of the questionnaire domains

Domain	Cronbach's alpha	
	Version 1	Version 2
Knowledge	0.79	0.79
Attitude	0.66	0.71
Practice	0.73	0.73
Barrier	0.64	0.70

ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Guideline-Directed Medical Therapies for Diabetic Kidney Disease Among Thai People With Type 2 Diabetes: A Real-World Data Based on Theptarin Diabetes Staging

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Abstract

Background. The "pillar approach" was recently proposed to holistically address diabetic kidney disease (DKD). Theptarin Diabetes Staging (TDS) is a staging system for type 2 diabetes (T2D) designed to prevent or delay the progression to advanced stages.

Objective. To evaluate the rate of guideline-directed medical therapies (GDMT) among individuals with DKD from 2021 to 2025 according to the TDS system.

Methodology. A retrospective review of medical records of T2D patients with TDS stage 4Ka (moderately increased persistent albuminuria), Stage 4Kb (severely increased persistent albuminuria), and stage 5Ka (eGFR <45 mL/min/1.73 m^2) was conducted. The rates of RASi, SGLT2i, GLP-1 RA, and finerenone use, along with achievement of metabolic targets, were evaluated prospectively from 2021 to 2025.

Results. A total of 206 medical records were reviewed (mean age 64.1 ± 10.3 years, A1C 7.3 ± 1.2%, mean eGFR 71.6 ± 24.5 mL/min/1.73 m^2). In 2021, the use of RASi was 78.2%, 51.5% for SGLT2i and 13.6% for GLP-1 RA among all patients. Four years later, rates of GDMT improved as follows: RASi 79.7%, SGLT2i 59.3%, GLP-1 RA 19.8% and finerenone 2.8%. However, only 1.1% of all patients in 2025 received all 4 GDMT items. More stable or improved TDS were observed in patients who received GDMT ≥3 classes across all 4 medication classes, compared with those who received GDMT <3 classes (96.2% vs. 78.8%, *P*-value = 0.036).

Conclusion. The real-world implementation of GDMT among DKD patients remains inadequate, and more efforts are required to improve GDMT adoption. Regular reviews and feedback are warranted to improve attainment of treatment targets and better clinical outcomes.

Key words: guideline-directed medical therapies (GDMT) prescription rates, diabetic kidney disease, Theptarin Diabetes Staging, Thai

INTRODUCTION

Diabetic kidney disease (DKD) is a common complication of type 2 diabetes (T2D) that significantly impacts quality of life and shortens life expectancy.[1] Over the past few decades, cardiovascular and renal outcome trials have reshaped diabetes care by demonstrating the vascular protective effects of certain novel anti-diabetic agents and some organ-protective medications. The concept of the cardiovascular-kidney metabolic (CKM) continuum was introduced in the 2020s, leading to a new era of combination therapy in T2D with chronic kidney disease (CKD), often referred to as a "*pillar approach*" as a result of collaborative care frameworks across various specialties.[2-6] The pillar approach for DKD medications involves a combination of four medication classes with proven benefits, namely renin-angiotensin system inhibitors (RASi), sodium-glucose cotransporter-2 inhibitors (SGLT2i), non-steroidal mineralocorticoid receptor antagonists (nsMRA), and glucagon-like peptide-1 receptor agonists (GLP-1 RA). However, the use of these foundation medications for DKD in clinical practice remains unacceptably low for various reasons.[7,8] While these developments represent major therapeutic advancements, they also introduce greater complexity and cost to DKD management, especially nsMRA and GLP-1 RA medications.

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Chongvoranond et al.
Received: January 16, 2026. Accepted: February 23, 2026.
Published online first: April 29, 2026.
https://doi.org/10.15605/jafes.041.01.6239

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Suboptimal usage of these medications is widespread, due to clinical therapeutic inertia. Therapeutic inertia is common and driven by various factors from clinicians, patients and health care systems. Clinician-associated barriers to treatment intensification include time and resource constraints, as well as overly cautious prescribing practices to avoid side effects. Moreover, these patients are often seen by multiple health care providers, and inadequate medication reconciliation procedures could affect treatment adherence.[9,10] In our previous study, we found that the prescription rate of SGLT2i was less than 60% among T2D patients with albuminuric DKA.[11] While medication cost contributed to the suboptimal usage, clinical inertia among diabetologists was the most common barrier causing low prescription rates for SGLT2i. The structure of routine clinic visits often discourages proactive treatment intensification in stable patients and promotes therapeutic clinical inertia.[12] Audit and feedback, together with educational outreach to clinicians, are important quality improvement initiatives to increase adherence to clinical practice guidelines.[13] Since 2010, the Theptarin Diabetes Staging (TDS) system, which was conceptualized by stratifying T2D patients based on the severity of diabetes complications and target organ damage, has been developed and implemented to prevent or delay the progression to advanced stages in individuals with diabetes.[14] The details of the TDS system were illustrated in Supplement Figure 1. Individuals with T2D and target organ damage were categorized as TDS stage 4, and those with advanced diabetes complications were categorized as TDS stage 5. TDS stage 4K (K = kidney), and TDS stage 5Ka (estimated glomerular filtration rate, eGFR <45 mL/min/1.73 m^2) represented the opportunity to monitor long-term adherence to guideline-directed medical therapies (GDMT) in T2D with CKD, as shown in Supplement Figure 2. When compared with the Kidney Disease Improving Global Outcomes (KDIGO) staging system, the TDS system focused more on the severity of increased albuminuria in the early stage of DKD and designated end-organ damage at a lower estimated glomerular filtration rate than the KDIGO system (eGFR <45 mL/min/1.73 m^2 versus eGFR <60 mL/min/1.73 m^2). Our TDS system had previously been validated for quality improvement initiatives at our hospital.[14]

There is a lack of real-world clinical studies on the uptake of GDMT among DKD patients in Southeast Asia. While the landscape of DKD treatment in persons with T2D has changed tremendously in the last 5 years, the use of these therapies remains unknown in routine clinical practice. Therefore, this study aimed to: 1) evaluate the rate of GDMT from each class of DKD medications in the pillar approach concept; 2) determine the proportion of patients with DKD according to TDS system who attained various multiple treatment targets from 2021 to 2025 in our hospital; and 3) identify the proportion of patients with DKD who could achieve stabilized or improved TDS five years later.

METHODOLOGY

Study design

The present study is a retrospective analysis of people with T2D who regularly visited the THEPTARIN Diabetes, Thyroid and Endocrine Center, Vimut-Theptarin Hospital, one of the largest diabetes centers in Thailand. Over 1,500 people with T2D regularly follow up at our hospital. Annual medical audit retrieved all data from medical records for the last quarter of each year. Patients with TDS stage 4Ka (moderately increased persistent albuminuria or previously known as microalbuminuria), stage 4Kb (severely increased persistent albuminuria or previously known as overt albuminuria), and stage 5Ka (eGFR <45 mL/min/1.73 m^2) were reviewed.

Patient selection

Inclusion criteria included patients with TDS stage 4Ka, 4Kb, and 5Ka as defined in Supplement Figure 1, who regularly followed up at least 3 times in 2021. Patients aged <15 years or >80 years, patients with normoalbuminuria, eGFR <20 mL/min/1.73 m^2, patients with a duration of follow-up less than 24 months, with acute kidney injury during the follow-up period, patients with type 1 diabetes mellitus and other types of diabetes were excluded. The severity of increased albuminuria was categorized into moderately increased albuminuria (urine albumin-creatinine ratio, UACR 30-300 mg/g) and severely increased albuminuria (UACR >300 mg/g). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for eGFR were used to calculate GFR from serum creatinine and eGFR was categorized according to KDIGO guidelines.[4]

Study procedure

Information on patient characteristics, including demographics, comorbidities, prescribed medications and laboratory data, was retrieved in the last quarter of 2021. Finerenone, which is the only approved nsMRA to reduce the risk of CKD progression and cardiovascular events, has been approved in Thailand since late 2023. Therefore, the prescription rate of finerenone was evaluated in 2024 and 2025. The rates of RASi, SGLT2i, GLP-1 RA and finerenone use, together with metabolic attainment targets, were evaluated prospectively in consecutive cases from 2021 to 2025. GDMT uptake was stratified into patients who received ≥2 classes or ≥3 classes from 4 classes and patients who received <2 classes or <3 classes from 4 classes. At the last follow-up in 2025, outcomes evaluated included progression or regression of the TDS system, new-onset macrovascular complications and achievement of treatment targets. The primary outcome was the annual rate of RASi, SGLT2i, GLP-1 RA, and finerenone use from 2021 to 2025. Secondary outcomes included attainment of metabolic targets from 2021 to 2025 and the proportion of patients who could stabilize or improve TDS in 2025 if GDMT uptake was ≥2/4 classes or ≥3/4 classes. This study

was approved by the Institutional Review Board (IRB) committee of Vimut-Theptarin Hospital (EC No.2-2025).

Sample size calculation

According to previous studies,[15-17] the prescription rates of RASi, SGLT2i, GLP-1 RA, and finerenone were 40.4%, 17.8%, 11.3%, and 33%, respectively. Based on these rates, the sample size was based on a prevalence-based calculation, and minimum required sample sizes were calculated using OpenEpi software: 369 for RASi, 227 for SGLT2i, 150 for GLP-1 RA, and 340 for finerenone. The largest calculated sample size (N = 369) was adopted to ensure adequate precision for all prevalence estimates. As this was a retrospective/cross-sectional study based on existing medical records with inclusion and exclusion criteria, attrition was not applicable. All calculations assumed a two-sided significance level (α) of 0.05, power ($1-\beta$) of 0.80, and a 95% confidence interval.

Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Categorical variables were presented as proportions. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. If the data were not normally distributed, non-parametric tests were applied. Comparisons among different stages of TDS were performed using one-way ANOVA or the Kruskal-Wallis test for continuous variables. The *t-test* or analysis of variance was used to compare differences in means among groups. The *Chi-squared* test was used to compare differences in percentages between groups. Fisher's Exact test was used alternatively if the expected value in any cell of a contingency table is less than 5. Variables analyzed in the univariate analysis included age ≥65 years, gender, duration of diabetes ≥10 years, body mass index (BMI) ≥25 kg/m^2, eGFR <45 mL/min/1.73 m^2 (TDS Stage 5Ka), the presence of diabetic retinopathy (DR), glycated hemoglobin (A1C) <7.0%, and severely increased albuminuria (>300 mg/g) based on previous literatures for associated factors in GDMT uptake among patients with DKD. Factors such as achieving a *P-value* <0.20 were included in the multivariate models to determine associated factors with ≥2 classes at baseline or ≥3 classes at the last follow-up among DKD patients. Multivariable logistic regression was used to identify factors associated with GDMT prescriptions. Results are presented as adjusted odds ratios (aOR) with 95% confidence intervals. Model fit and multicollinearity were assessed using the Hosmer-Lemeshow test and variance inflation factors, respectively. Comparisons of proportions between patients who could stabilize or improve TDS, stratified by the number of GDMT medication classes were performed using the two-proportion Z-test. A *P*-value of <0.05 was considered statistically significant. Given the exploratory nature of this study, no formal adjustment for multiple comparisons was applied. Patients were retained in analyses where data were available and excluded from analyses of variables with missing values. Therefore, no statistical imputation was performed. All analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline demographic and clinical characteristics

The study cohort comprised 206 eligible patients from 1,232 patients who were audited in 2021, as shown in Figure 1. Of the eligible audited patients, the baseline characteristics

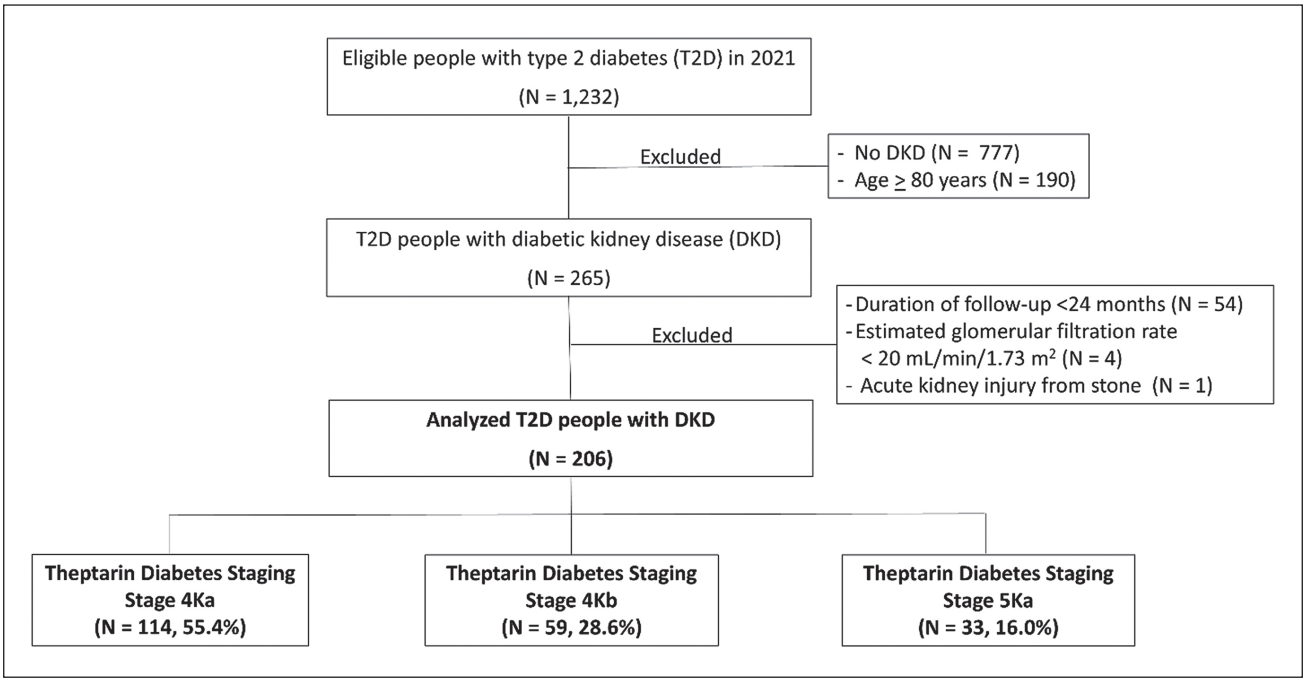


Figure 1. Flow diagram for studied patients' selection.

are shown in Table 1 (mean age 64.1 ± 10.3 years, A1C 7.3 ± 1.2%, mean eGFR 71.6 ± 24.5 mL/min/1.73 m^2). Compared with patients TDS stage 4Ka and 4Kb, TDS stage 5Ka patients were older, had heart failure, had higher insulin use, but less SGLT2i/GLP-1RA usage. In 2021, the rates of RASi were 78.2%, SGLT2i was 51.5%, GLP-1 RA was 13.6%, among all patients. None of these patients used finerenone in 2021, as it was not available yet. The mean follow-up duration for the entire cohort was 42.1 ± 4.6 months.

Long-term adherence to GDMT from 2021 to 2025

As shown in Figure 2, the proportion of prescriptions of GDMT classes improved every year. The rate of GDMT uptake ≥2 classes increased from 42.7% in 2021 to 55.9% in 2025, and GDMT uptake ≥3 classes increased from 7.3% in 2021 to 14.7% in 2025. However, the overall number of patients who received a combination of four medication classes for the pillar approach after finerenone became available in Thailand in 2024 remained low at 1.1% in 2025. At the last follow-up, the rate of GDMT was improved as follows: RASi 79.7%, SGLT2i 59.3%, GLP-1 RA 19.8%, finerenone 2.8%. The most common drug combinations for 2-class GDMT in both 2021 and 2025 were RASi and SGLT2i, and the most common drug combinations for 3-class GDMT in both 2021 and 2025 were RASi, SGLT2i and GLP-1 RA, as shown in Supplement Figure 3. The least common drug combinations for 3-class GDMT in 2025 were SGLT2i, GLP-1 RA and finerenone. When stratified by TDS system, TDS stage 5Ka received fewer GDMT medications than TDS stages 4Ka and 4Kb, as shown in Figure 3, but with improvement over time. Details of each class of DKD medication among individuals with TDS stage 5Ka in 2025, compared with the baseline in 202,1 are shown in Supplement Figure 3.

Outcomes of care based on TDS staging

The proportion of patients in each TDS system who attained multiple treatment targets was shown in Figure 4. While the overall treatment attainment targets were below 60% across all parameters, the LDL-cholesterol target of <70 mg/dL improved from 26.7% at baseline to 55.3% at the last follow-up. From 2021 to 2025, migration of the TDS staging system from the overall cohort is shown in Figure 5. Among patients in TDS stage 4Ka to TDS stage 5Ka, stable, improved, and worsening stages were found in 63.1%, 18.0%, and 18.9% respectively. Among all patients, 4

Table 1. Baseline characteristics of studied participants (N = 206 cases)

	Total cases (N = 206)	TDS Stage 4Ka (N = 114, 55.3%)	TDS Stage 4Kb (N = 59, 28.7%)	TDS Stage 5Ka (N = 33, 16.0%)	*P*-value
Female (%)	87 (42.2%)	49 (43.0%)	24 (40.7%)	14 (42.4%)	0.96*
Age (years)	64.1 ± 10.3	63.1 ± 10.7	63.0 ± 10.2	69.8 ± 6.9	<0.01[a]
<65 years	89 (43.2%)	52 (45.6%)	29 (49.1%)	8 (24.2%)	
65-74 years	88 (42.7%)	47 (41.2%)	26 (44.1%)	15 (45.5%)	
≥75-80 years	29 (14.1%)	15 (13.2%)	4 (6.8%)	10 (30.3%)	
Duration of diabetes (years)	18.2 ± 10.3	16.8 ± 9.6	19.8 ± 10.9	19.9 ± 10.5	0.10[a]
Duration ≥10 years (%)	161 (78.2%)	85 (74.6%)	48 (81.4%)	28 (84.8%)	
BMI (kg/m²)	27.5 ± 4.7	27.5 ± 4.9	27.3 ± 4.5	28.0 ± 4.5	0.78[a]
Active or ex-smoking (%)	36 (17.5%)	19 (16.7%)	13 (22.0%)	4 (12.1%)	0.46*
Hypertension (%)	146 (70.9%)	79 (69.3%)	45 (76.3%)	22 (66.7%)	0.54*
Heart failure (%)	10 (4.9%)	3 (2.6%)	3 (5.1%)	4 (25.0%)	0.08*
Coronary artery disease (%)	29 (14.1%)	16 (14.0%)	7 (11.9%)	6 (18.2%)	0.71*
Stroke (%)	10 (4.9%)	6 (5.3%)	4 (6.8%)	0 (0.0%)	0.33*
Peripheral artery disease (%)	9 (4.4%)	4 (3.5%)	4 (6.8%)	1 (3.0%)	0.56*
Diabetic retinopathy (%) [*]	67 (32.5%)	31 (27.2%)	23 (39.0%)	13 (39.4%)	0.19*
A1C (%)	7.3 ± 1.2	7.2 ± 1.1	7.5 ± 1.3	7.4 ± 1.2	0.20[a]
LDL (mg/dL)	85.0 ± 25.1	84.5 ± 24.0	84.5 ± 24.4	87.8 ± 30.2	0.79[a]
estimated GFR (mL/min/1.73 m²)	71.6 ± 24.5	79.2 ± 21.6	76.7 ± 18.5	36.2 ± 6.3	<0.01[a]
Stage 1 eGFR ≥90 mL/min/1.73 m^2 (%)	53 (25.7%)	39 (34.2%)	14 (23.7%)	0	
Stage 2 eGFR = 60-89 mL/min/1.73 m^2 (%)	84 (40.8%)	53 (46.5%)	31 (52.6%)	0	
Stage 3a eGFR = 45-59 mL/min/1.73 m^2 (%)	36 (17.5%)	22 (19.3%)	14 (23.7%)	0	
Stage 3b eGFR = 30-44 mL/min/1.73 m^2 (%)	27 (13.1%)	0	0	27 (81.8%)	
Stage 4 eGFR = 15-29 mL/min/1.73 m^2 (%)	6 (2.9%)	0	0	6 (18.2%)	
Albuminuria (Median/IQR)	139.1 (326.3)	77.8 (79.7)	529.3 (685.1)	147.2 (333.2)	0.47[#]
Normal to mildly increased (<30 mg/g)	2 (1.0%)	0	0	2 (6.0%)	
Moderately increased (30-300 mg/g)	136 (66.0%)	114 (100%)	0	22 (66.7%)	
Severely increased (>300 mg/g)	68 (33.0%)	0	59 (100%)	9 (27.3%)	
RAS inhibitors (%)	161 (78.2%)	88 (77.2%)	49 (83.1%)	24 (72.7%)	0.72*
Statin (%)	193 (93.7%)	106 (93.0%)	55 (93.2%)	32 (97.0%)	0.70*
Anti-diabetic medication (%)					
SGLT2i	106 (51.5%)	54 (47.4%)	38 (64.4%)	14 (42.4%)	0.06*
GLP-1 RA	28 (13.6%)	12 (10.5%)	14 (23.7%)	2 (6.1%)	0.02*
Metformin	171 (83.0%)	98 (86.0%)	52 (88.1%)	21 (63.6%)	0.01*
Sulfonylurea	79 (38.3%)	44 (38.6%)	22 (37.2%)	13 (39.4%)	0.97*
Thiazolidinedione	38 (18.4%)	24 (21.1%)	7 (11.9%)	7 (21.2%)	0.30*
DPP4 inhibitor	106 (51.5%)	59 (51.8%)	29 (49.2%)	18 (54.5%)	0.88*
Insulin	64 (31.1%)	26 (22.8%)	23 (39.0%)	15 (45.5%)	0.01*

Available data 198/206 (96.1%). [#] Kruskal-Wallis test was performed. * Chi-square test was performed. [a] Analysis of Variance was performed.

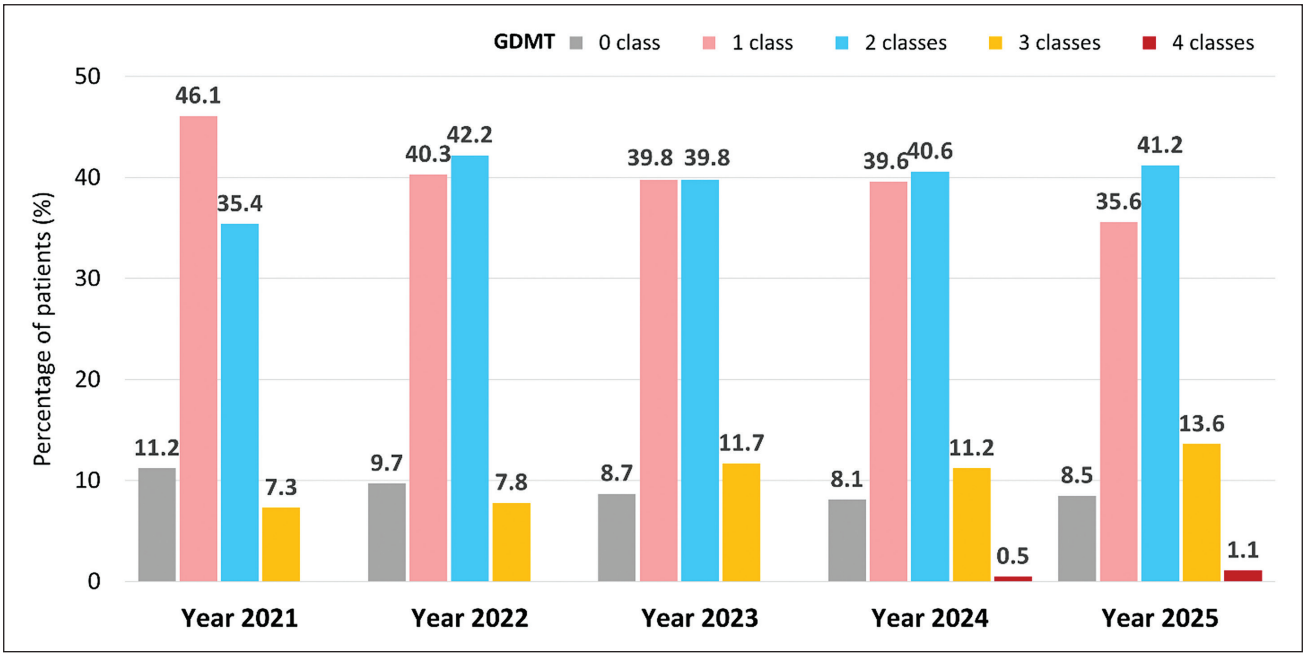


Figure 2. The proportion of numbers of pillar therapies for diabetic kidney disease from 2021 to 2025.

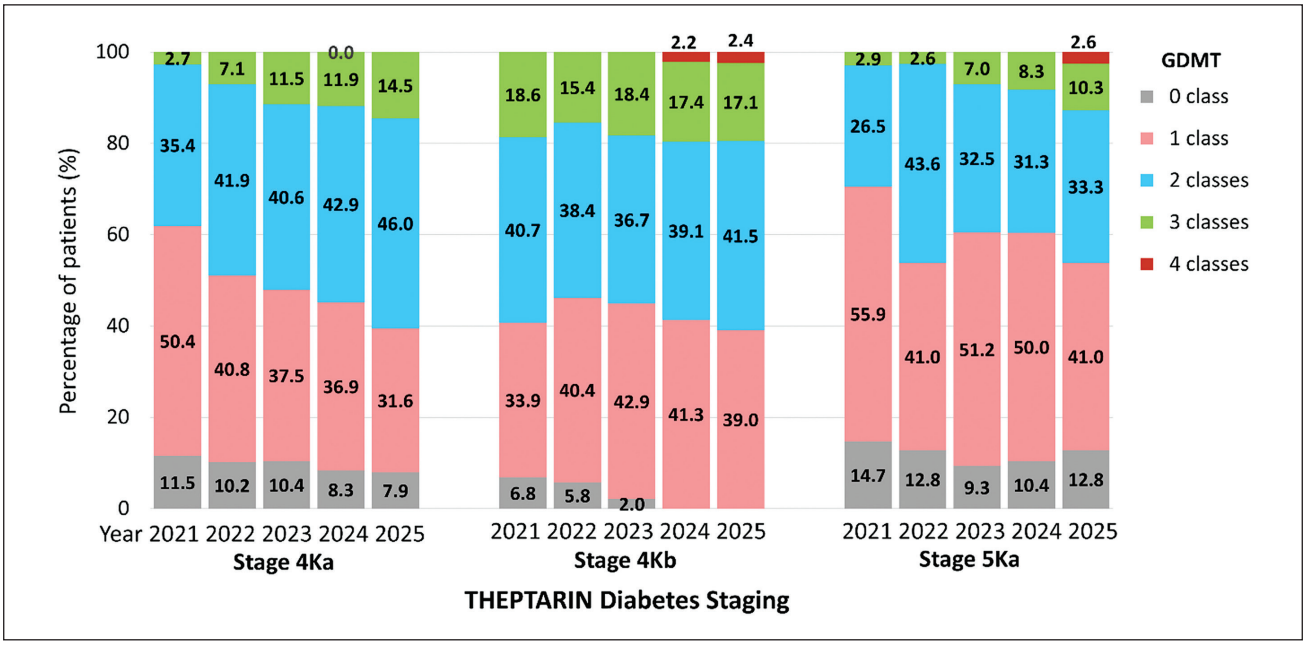


Figure 3. The proportion of prescriptions of each class of guideline-directed medical therapies (GDMT) from the baseline in 2021 to the latest follow-up in 2025 according to the Theptarin Diabetes Staging (TDS) system.

deaths (1.9%) occurred during the mean follow-up period of 3.6 years. The causes of death included cardiovascular events (50%), kidney failure (25%) and hepatobiliary infection (25%).

More TDS patients were stabilized or improved when they received GDMT ≥3 classes from all 4 medication classes when compared with those who received GDMT <3 classes (96.2% vs. 78.8%, *P*-value = 0.036), as shown in Figure 6. Female gender and elderly (aged ≥65 years) were associated with GDMT <2 classes in baseline (OR = 0.35; CI 95% 0.20-0.64 and OR = 0.46; CI 95% 0.25-0.83, respectively), as shown in Table 2. At the last follow-up, only BMI ≥25 kg/m^2 was associated with receiving GDMT ≥3 classes (OR = 3.40; CI 95% 0.93-12.36) as shown in Table 3.

DISCUSSION

In this retrospective study, we highlighted significant delays in transitioning from the evidence-based pillar approach for DKD management in T2D to real-world implementation of GDMT. Metabolic attainments among people with chronic kidney disease and T2D treated by specialists were still inadequate, and more efforts are required to

improve GDMT prescription rates in routine practice. Our findings identify opportunities for improvement in the management of T2D patients with both albuminuric DKD and normoalbuminuric DKD.

CKD is itself a major risk factor for cardiovascular disease, with reduced eGFR and albuminuria both independently associated with cardiovascular morbidity and mortality.[18] In addition to lifestyle modification, the management of DKD emphasized on the four 'pillars' of treatment.[6] Each pillar of pharmacotherapy has different mechanisms of

Table 2. Univariate and multivariate analysis of factors associated with receiving guideline-directed medical therapies (GDMT) ≥2 classes at the baseline

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Female	0.39	0.22-0.68	<0.01#	0.35	0.20-0.64	<0.01*
Age ≥65 years	0.48	0.27-0.84	0.01#	0.46	0.25-0.83	0.01*
Duration of diabetes ≥10 years	0.81	0.42-1.57	0.53#			
BMI (≥25 kg/m²)	1.72	0.95-3.12	0.08#	1.60	0.86-3.00	0.14*
TDS Stage 5Ka	0.61	0.29-1.28	0.19#			
Heart Failure	0.56	0.14-2.23	0.41#			
Diabetic retinopathy	1.12	0.69-1.82	0.66#			
Optimal A1C <7.0 %	0.81	0.46-1.43	0.47#			
Severely increased albuminuria	0.66	0.35-1.22	0.19#			

Binary logistic regression test was performed. * Multivariable logistic regression test was performed.

Table 3. Univariate and multivariate analysis of factors associated with receiving guideline-directed medical therapies (GDMT) ≥3 classes at the last follow-up in year 2025

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Female	0.59	0.24-1.44	0.24#			
Age ≥65 years	0.46	0.20-1.08	0.07#	0.50	0.21-1.19	0.12*
Duration of diabetes ≥10 years	1.04	0.36-2.99	0.94#			
BMI (≥25 kg/m²)	3.68	1.05-12.86	0.04#	3.40	0.93-12.36	0.06*
TDS Stage 5Ka	1.19	0.46-3.07	0.72#			
Diabetic retinopathy	1.57	0.67-3.68	0.30#			
Optimal A1C <7.0 %	0.90	0.39-2.09	0.80#			
Severely increased albuminuria	1.25	0.52-3.00	0.62#			

Binary logistic regression test was performed. * Multivariable logistic regression test was performed.

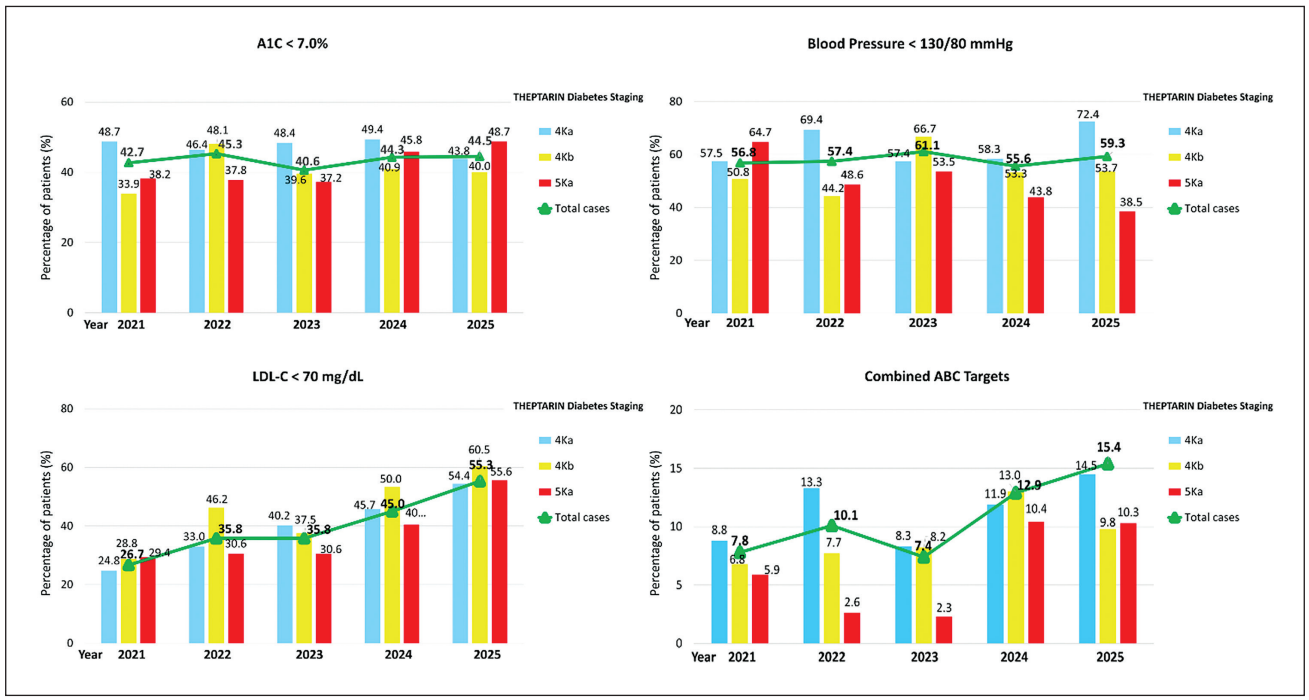


Figure 4. The proportion of patients in each Theptarin Diabetes Staging (TDS) system who attained various multiple treatment targets from 2021 to 2025

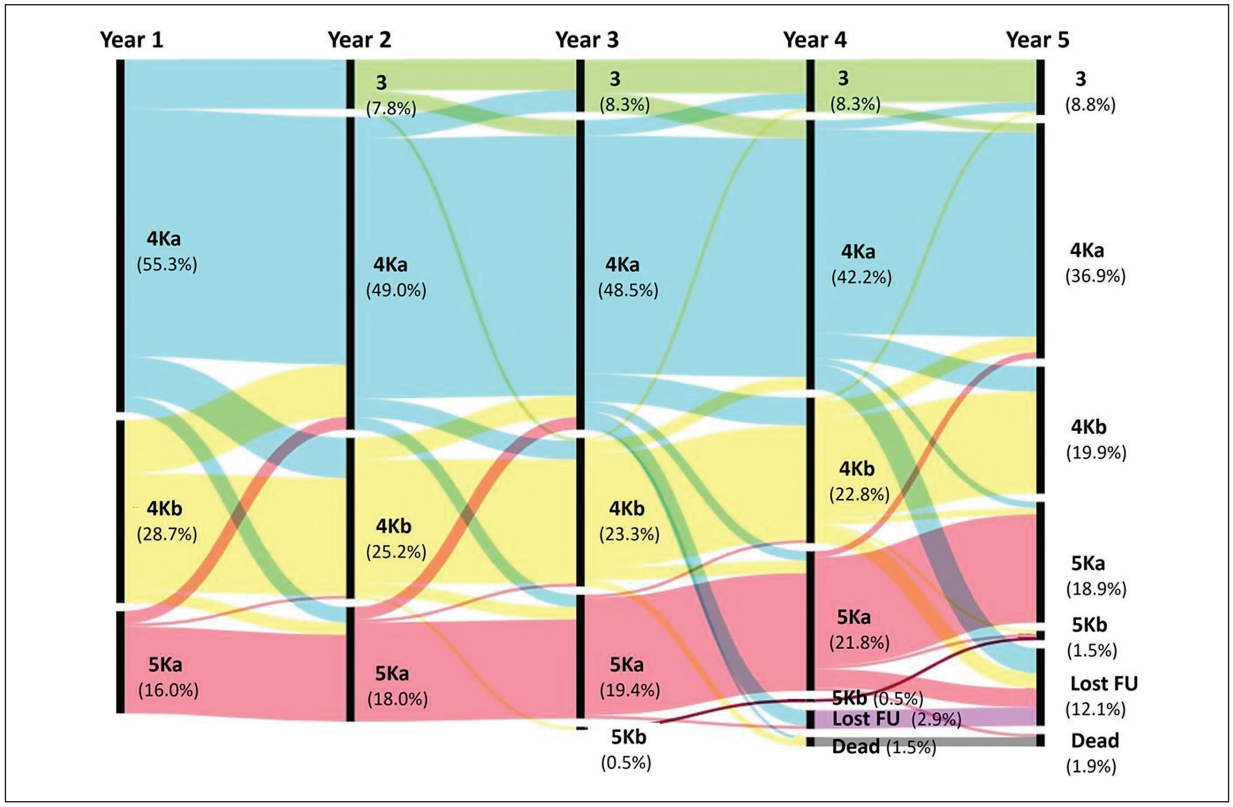


Figure 5. The migration of Theptarin Diabetes Staging (TDS) staging system from overall cohort from 2021 to 2025.

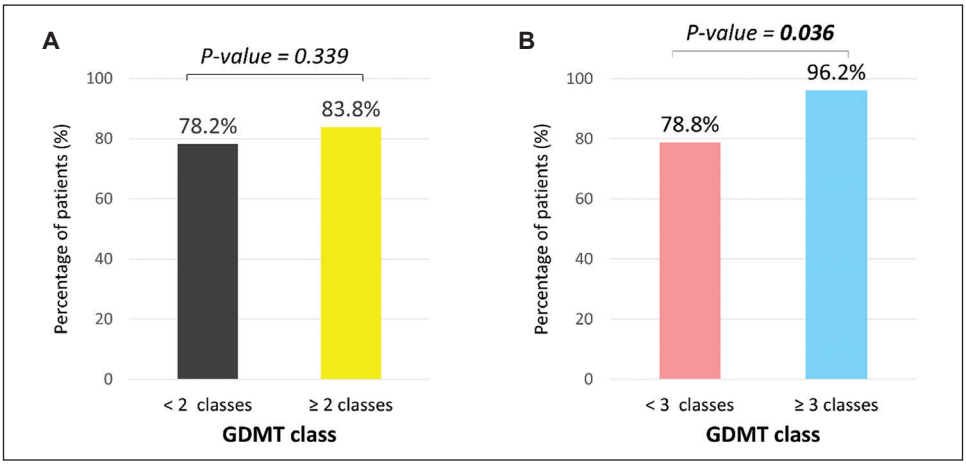


Figure 6. Comparisons the proportion of patients who could stabilize or improve Theptarin Diabetes Staging (TDS) at the last follow-up with numbers of guideline-directed medical therapies (GDMT) **(A)** patients who received GDMT <2 classes versus ≥2 classes **(B)** patients who received GDMT <3 classes versus ≥3 classes (the two-proportion Z-test was used to determine if the difference between two proportions is statistically significant).

action to address the abnormalities in hemodynamics, metabolism, inflammation and fibrosis that characterize the progression of DKD. Early implementation of these therapies is likely to confer substantial long-term gains in survival, free from cardiovascular and kidney disease.[19] It is important to stress that these medications reduced major adverse cardiovascular events, kidney events, and all-cause mortality, irrespective of baseline glycemic control. Despite conventional treatment for DKD, high-risk patients may have a decline in eGFR of up to 5 mL/min/1.73 m^2 per year. This underscores the need for additional therapies to further reduce the rate of kidney function decline to the level of normal healthy aging (about 1 mL/min/1.73 m^2 per year).[20] A recent study showed that if individuals were using all four pillars of therapy, it delays the progression of CKD for at least 5 years compared with conventional use of RASi alone.[21] However, despite this remarkable progress in the evidence-based treatment landscape, access to these therapies remains a challenge in low to middle-income countries. While RASi have been a backbone therapy for

CKD for almost 3 decades in T2D patients with DKD, and generic SGLT2is are now available, finerenone and GLP-1 RA are still unaffordable for most patients with economic difficulties. Primary physicians, especially diabetologists, play a vital role in the management of most T2D patients with DKD, while nephrologists typically oversee those at higher risk and with advanced disease.[22] Therefore, clinical inertia among diabetologists should be addressed with regular reviews and feedback. Our present study showed a detectable increase in GDMT uptake over the past 5 years, as seen in annual audits and feedback.

A further analysis in this study showed that when individuals used at least 3 medication classes, clinical staging could be stabilized or improved in some cases. Clinical staging of type 2 diabetes (T2D) might play a role in more individualized diabetes treatment and would permit timely implementation of effective strategies to prevent or delay progression to advanced stages in individuals with diabetes. Our TDS system had been used locally for more than 10 years to holistically address microvascular and macrovascular complications of diabetes.[14] The TDS system offers clinicians and other healthcare personnel a useful tool for understanding the concept of T2D continuum and defining needs for each patient. The TDS stage 5Ka (eGFR <45 mL/min/1.73 m^2) spanned both albuminuric and normoalbuminuric DKD. Previous studies showed that normoalbuminuric DKD is closely associated with prior RASi use and is more common in older patients with good glycemic control.[23] Unfortunately, the pillar approach is currently unclear since no trials have been conducted specifically on patients with eGFR reduction alone. However, SGLT2i and GLP-1 RA should already be used in patients with established atherosclerotic cardiovascular disease (ASCVD) or high risk for ASCVD. As shown in our present study, most patients with TDS stage 5Ka had a long duration of diabetes and higher rates of macrovascular complications. Both renal and cardiovascular risks should be addressed holistically, using proven pharmacotherapies when affordable.

Concerns about polypharmacy and adverse events should be addressed among patients and multi-disciplinary teams, especially elderly patients with frailty. The presence of multiple comorbidities in patients with CKD requires more comprehensive clinical assessments, not only pharmacotherapy, but also on the optimal control of other comorbidities and nutritional status.[5] While GLP-1 RA has dramatically altered the treatment of patients with obesity, elderly patients are at increased risk for sarcopenia if protein intake and exercise training are inadequate.[24] In patients started on finerenone, careful monitoring of blood pressure, serum potassium level and eGFR is necessary to mitigate adverse events from this new medication. Like RASi and SGLT2i, finerenone can cause a predictable slight drop in eGFR within a few weeks after initiation, but kidney function is expected to recover and stabilize.[25] Additional efforts for patient counseling before introducing this new medication should be emphasized.

There is a substantial opportunity to increase adherence to GDMT uptakes in DKD patients. The TDS system addressed this gap by stratifying patients into subgroups with distinct complication profiles, enabling more focused monitoring and preventive strategies. Improved and stabilized staging between baseline and the last follow-up cohort at 4 years later in patients with TDS stage 4K and TDS stage 5A provided indirect evidence that risk stratification could lead to timely management of DKD. Therefore, regular reviews and feedback are warranted to improve treatment target attainment and outcomes. Electronically delivered activation tools to intensify medications in suitable patients could be one option to remind treating clinicians. Previous study among DKD patients showed that patient empowerment with team-based care assisted by personalized reports to estimate the 5-year probability of major clinical events could improve risk factor control and clinical outcomes in Asians with DKD.[26] Emerging evidence also suggested that accelerated initiation of multiple therapies within a compressed timeframe, rather than a stepwise sequential approach could benefit patients at high risk of CKD progression and prevent clinical inertia.[27] This method of implementation has drawn parallels with the pillars of GDMT for heart failure.[28] Assessment of the overall cardiovascular-kidney-metabolic risk profile in each patient to match the intensity of treatments is an important step for successful DKD management. The collection and delivery of performance data to quality improvement teams and clinicians, along with educational outreach to clinicians, are also a critical step to increase adherence to clinical practice guidelines. Addressing therapeutic inertia and promoting the timely initiation of GDMT are continuous processes to overcome complex barriers at multiple levels across the health care ecosystem.

Our study has several limitations. First, a substantial proportion of individuals after implementation of the TDS system to track outcomes of care were excluded due to missing data or lost to follow-up. Routine assessment of associated complications is a prerequisite for designating the TDS system, but care deficits arising from the COVID-19 pandemic resulted in missing data. Those who were lost to follow-up before 24 months had a follow-up duration of less than 6 months in 2022 during the COVID-19 pandemic. We excluded them from further analysis due to short follow-up period to track the benefits of GDMT effectiveness. As a result, our single-center retrospective cohort is smaller than the sample sizes required to detect an absolute ± 5% difference with 80% power for several medication classes. Consequently, estimates for some medication classes have limited power and precision. Nonetheless, these real-world data offer important clinical insights into contemporary prescribing patterns and are informative for planning larger or multicenter studies. Despite the challenges associated with delivering and documenting care in the follow-up cohort, our current data can verify the usefulness and stage migration in the remaining patients receiving care after the TDS implementation. Second, due to the inherent

limitations of retrospective data and the relatively short follow-up period from a single tertiary private diabetes center in Thailand, our present study should be interpreted with caution. Third, the variability in UACR values and eGFR levels can misclassify some patients, but both tests are considered valid surrogates for CKD progression and reflect a real-world scenario for a single timepoint collection. Fourth, the main purpose of the TDS is to stratify the patients with T2D complications in the busy clinic and facilitate communication between multi-disciplinary teams. Our TDS system was different from the KDIGO guidelines, which used stage-specific recommendations. Therefore, stage-specific DKD guidelines should still adhere to the KDIGO guidelines. However, the UACR-centric TDS stage 4 and KDIGO system were similar and should prompt physicians to consider kidney-protective medications. Finally, other potential confounders, including lifestyle factors, therapy adherence, and socioeconomic status, were not evaluated which may have influenced the outcomes.

CONCLUSION

The landscape of DKD treatment has changed dramatically with the four pillars of pharmacotherapy (RASi, SGLT2i, nsMRA, and GLP-1 RA) in conjunction with comprehensive lifestyle modification. The real-world implementation of GDMT among Thai DKD patients remained inadequate and further efforts are required to improve GDMT uptake in routine practice. Regular reviews and feedback are warranted to improve treatment target attainment and outcomes. Stratifying risk of disease progression with the TDS system could enable more focused monitoring and preventive strategies.

Acknowledgments
The authors wish to thank all the staff in the THEPTARIN Diabetes, Thyroid and Endocrine Center, Vimut-Theptarin Hospital for taking care of all patients. We also acknowledge the meticulous proofreading and editing provided by Dr.Tinapa Himathongkam.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CP: Conceptualization, Formal analysis, Data curation, Writing – original draft preparation; **CW**: Writing – review and editing, Visualization; **WE**: Investigation, Writing – review and editing; **BS**: Validation; **NS**: Software, Resources, Visualization, Project administration; **HT:** Funding acquisition; **TY**: Methodology, Writing – review and editing, Supervision.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
This work was supported by the grant for promoting research in Vimut-Theptarin Hospital (Grant No. 2/2568).

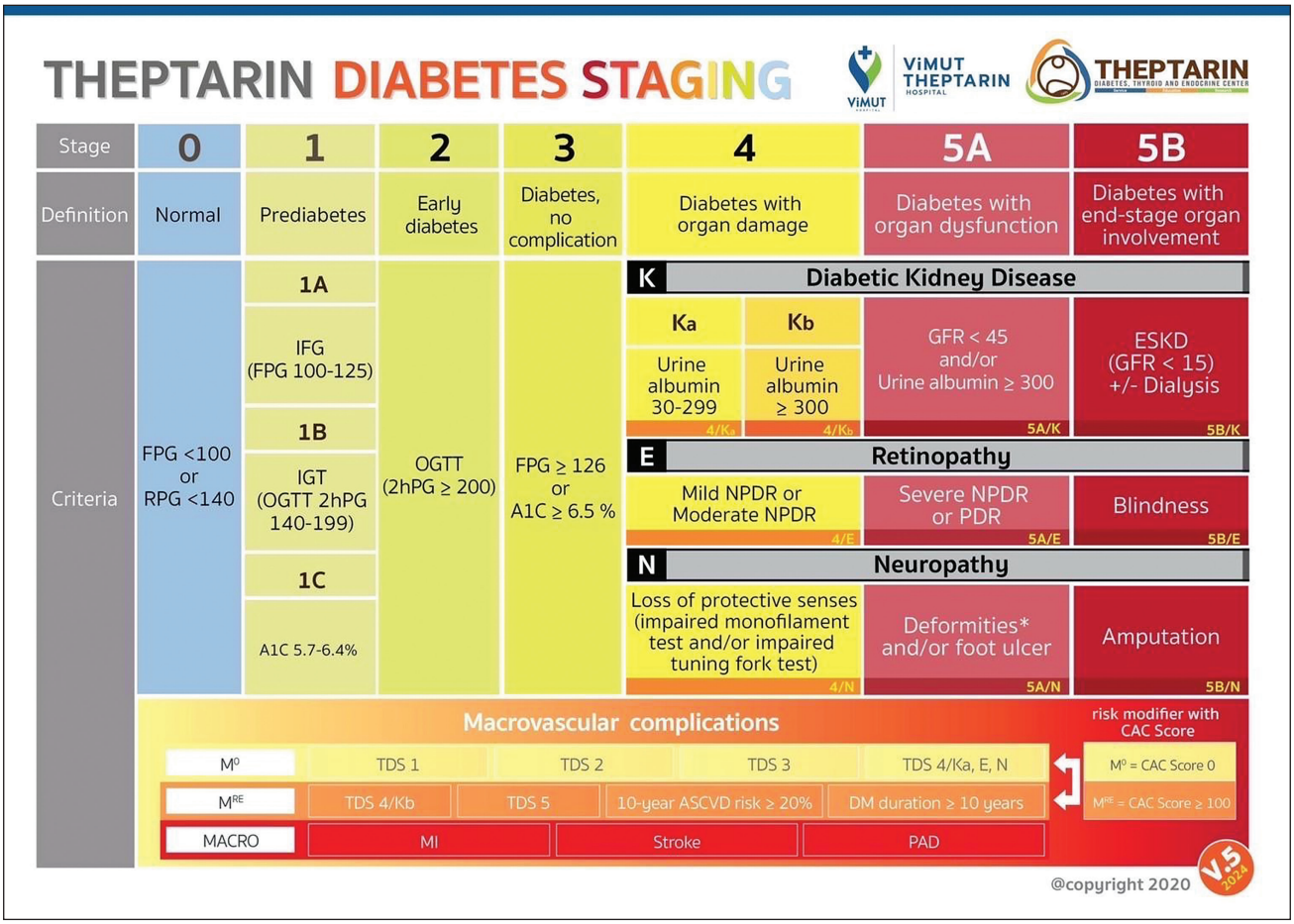
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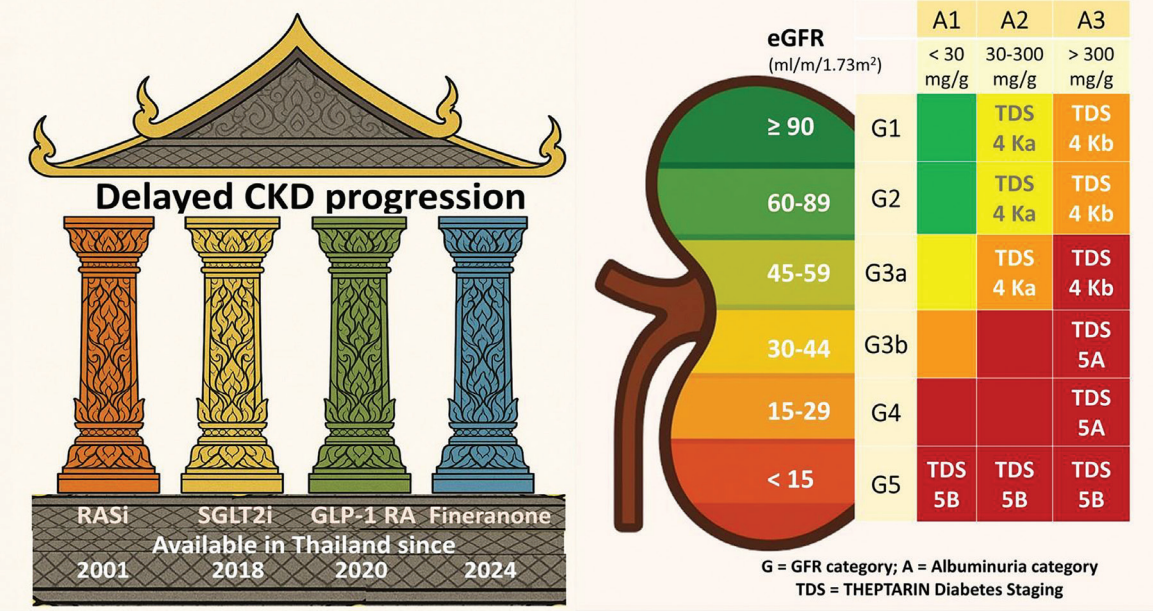
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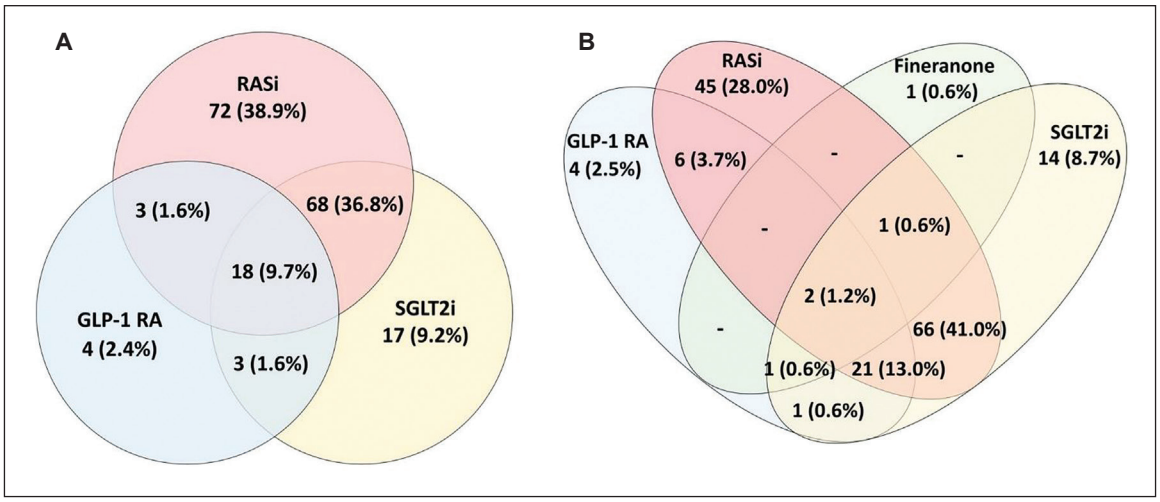
SUPPLEMENTARY FIGURES



Supplementary Figure 1. The Theptarin Diabetes Staging (TDS) system which based on pathophysiology of diabetes and progression of diabetic complications.



Supplementary Figure 2. The pillar approach for diabetic kidney disease medications involves a combination of four medication classes with proven benefits namely renin-angiotensin system inhibitors (RASi), sodium-glucose cotransporter-2 inhibitors (SGLT2i), non-steroidal mineralocorticoid receptor antagonists (nsMRA), and glucagon-like peptide-1 receptor agonists (GLP-1 RA).



Supplementary Figure 3. (A) Details of each class of guideline-directed medical therapies (GDMT) at baseline in 2021. **(B)** Details of each class of guideline-directed medical therapies (GDMT) in 2025.

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Effect of Baseline HbA1c and Inpatient Glycemic Control on Mortality and Organ Dysfunction among Patients with Diabetes Mellitus Hospitalized for COVID-19: A Multicenter Retrospective Cohort Study

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Abstract

Background. Individuals with diabetes mellitus (DM) show increased susceptibility to COVID-19 infection with higher risk for severe disease and mortality.

Objectives. We investigated whether glycemic-related factors may affect the outcomes of patients with DM hospitalized due to COVID-19.

Methodology. This is a multicenter retrospective cohort study under the initiative of the Philippine College of Endocrinology, Diabetes, and Metabolism involving eight training hospitals in the Philippines from January 2021 to January 2022. Patients with DM hospitalized due to COVID-19 were included. Univariable and multivariable analyses were done to determine whether baseline glycemic control based on glycosylated hemoglobin (HbA1c) and inpatient glycemic control based on capillary blood glucose are associated with composite poor clinical outcome of mortality and end-organ dysfunction.

Results. Among 1,093 patients, 54% had HbA1c >7%. Critical COVID-19 disease was greater in patients with poor baseline glycemic control (28.43% vs 19.72%, p = 0.001) and poor inpatient glycemic control (25.7% vs 12.64%, p <0.001). Both poor baseline glycemic (AOR 1.41, p = 0.017) and poor inpatient glycemic control (AOR 2.6, p <0.001) were associated with composite poor clinical outcome of mortality and end-organ dysfunction after adjusting for each other, but lost significance after adjusting for age, COVID-19 severity, and presence of comorbidities. COVID-19 severity had the greatest association with composite poor clinical outcome after adjusting for all other variables. HbA1c >7% increased the odds of poor inpatient control (OR = 3.10, 95% CI: 2.32–4.17, p <0.001), even after adjusting for steroid use.

Conclusion. COVID-19 severity had the greatest impact and is the only variable with a statistically significant association with composite poor clinical outcomes after adjusting for all other variables. Poor glycemic control on admission and during hospitalization were associated with more severe COVID-19, although they did not directly impact clinical outcomes. Measures to optimize glycemic control both in the long term and during hospitalization should be considered to prevent severe COVID-19, hence improving clinical outcomes and survival.

Key words: COVID-19, diabetes mellitus, glycemic control, mortality

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by San Juan et al.
Received: June 11, 2025. Accepted: August 11, 2025.
Published online first: April 27, 2026.
https://doi.org/10.15605/jafes.041.01.5089

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INTRODUCTION

Diabetes mellitus (DM) is prevalent among Coronavirus disease 2019 (COVID-19) patients who develop Acute Respiratory Distress Syndrome (ARDS) and disease progression.[1] Patients with DM were found to have a two-fold increased risk of mortality and three-fold increased risk of severe disease due to COVID-19.[2] A retrospective observational study in the United States of America (USA) revealed that patients with DM or uncontrolled hyperglycemia >180 mg/dL have a four-fold higher mortality and longer hospital stay.[3] In contrast, the CORONADO study showed that glycosylated hemoglobin (HbA1c), presence of DM complications, age, and use of glucose-lowering medications were not associated with poor outcomes.[4]

The first cases of COVID-19 in the Philippines were reported in January 2020, involving Chinese nationals who traveled from Wuhan.[5] Local community transmission was confirmed in March 2020, leading to the implementation of Enhanced Community Quarantine in Luzon and eventually nationwide.[6] By January 2022, the Philippines reported 3,242,374 cases with 52,929 deaths (1.6% mortality).[7]

The Inter-Agency Task Force for the Management of Emerging Infectious Diseases (IATF-EID) and the National Task Force against COVID-19 devised the National Action Plan Against COVID-19.[8] Case detection and management were guided by the Unified COVID-19 Algorithms that were regularly released by the Healthcare Professionals Alliance Against COVID-19.[9] Roll-out of COVID-19 vaccination started in March 2021, with a total of 55,093,313 doses administered as of January 2022, representing 64.9% of the eligible population.[7]

Recent reports describe the relationship between DM and COVID-19 to be syndemic, wherein two or more co-occurring diseases amplify each other synergistically.[10] This study aimed to investigate whether glycemic-related factors affect the prognosis of patients with DM hospitalized for COVID-19. The relationship of baseline glycemic control and inpatient glycemic control with severe disease, death from any cause, and occurrence of new or worsened organ dysfunction were investigated. Identification of risk factors contributing to life-threatening COVID-19 infection will allow us to formulate strategies to alleviate morbidity and mortality in this vulnerable population and guide us in the management of patients with DM during the pandemic and beyond.

METHODOLOGY

Study design and setting

This is a multicenter retrospective cohort study under the initiative of the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM) involving eight training hospitals in the Philippines. This study was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice, and the National Ethical Guidelines for Health and Health-Related Research 2017. The study was approved by the research ethics committee of the different institutions: University of Santo Tomas Hospital Research Ethics Committee (Manila City, Metro Manila; REC-2021-04-061-OO-CR), Makati Medical Center Institutional Review Board (Makati City, Metro Manila; MMCIRB 2021-048), St. Luke's Medical Center Quezon City Institutional Review Board (Quezon City, Metro Manila; SL-21132), The Medical City Institutional Review Board (Pasig City, Metro Manila; GCS MED 2021-059), Chinese General Hospital and Medical Center Research Ethics Review Board (Manila City, Metro Manila; RERB 2021-F-18), Chong Hua Hospital Institutional Review Board (Cebu City, Cebu; 3921-04), East Avenue Medical Center Institutional Ethics Review Board (Manila City, Metro Manila; EAMC IERB 2021-58), and St. Luke's Medical Center Global City Institutional Review Board (Taguig City, Metro Manila; SL-21187). All institutions involved are located in urban areas, with seven hospitals in the National Capitol Region and one hospital in the Central Visayas Region. Management of COVID-19 in these hospitals were guided by the latest Unified COVID-19 Algorithms.[9]

Study participants

Individuals aged 18 years or older diagnosed with either DM type 1 or DM type 2 who were hospitalized due to COVID-19 in the eight participating hospitals from January 1, 2021 to January 31, 2022 were included. Diagnosis of COVID-19 was confirmed through reverse transcriptase polymerase chain reaction (rt-PCR) test for SARS-COV2. Diagnosis of DM was defined by the presence of at least one criterion: 1) fasting blood sugar of ≥126 mg/dL, a 2-hour postprandial blood glucose of ≥200 mg/dL during a 75 g oral glucose tolerance test, or a random blood sugar ≥200 mg/dL with classic symptoms of hyperglycemia or hyperglycemic crisis[11] at any time prior to admission, 2) an HbA1c ≥6.5%[11] at any point prior to or during admission, 3) personal history of DM, and 4) history of intake of glucose-lowering medications. Patients fulfilling any of the following were excluded: 1) pregnant women with gestational or overt DM, 2) patients deemed eligible for discharge less than 24 hours from arrival but stayed in the hospital for an extended period for other reasons, 3) patients who died less than 24 hours from arrival at the hospital, and 4) individuals with unknown outcomes (including those that were still admitted or were transferred to another hospital) at the conclusion of the study. These patients were excluded to ensure that complete data on inpatient glycemic control and outcomes will be available.

Sample size

This study required a minimum sample of n = 956 to detect a small effect size (OR=1.25) with 80% power and a significance level of 0.05 (two-tailed), assuming a baseline outcome probability of 0.3 and an R^2 of 0.2. The chosen OR

corresponds to a small effect size, consistent with guidelines indicating odds ratios less than 1.5 require larger samples for detection.[12] A conservative baseline probability was selected to ensure generalizability across multiple outcomes. R^2 was set to reflect minimal variance from covariates other than glycemic control, recognizing differences in interpreting R^2 in logistic regression compared to linear regression.[13,14]

Study procedure

Study site investigators were invited to participate to facilitate data collection in eight training hospitals. Medical records were reviewed and data were extracted from hospital charts using standardized data collection forms (DCF). Data management was supervised by a biostatistician.

Definition of study variables

Baseline glycemic control was defined using the HbA1c level recorded at admission or within three months prior to admission. In accordance with the American Diabetes Association guidelines, good baseline glycemic control was defined as HbA1c ≤7%, while any HbA1c >7% was classified as poor baseline glycemic control.[15] At least three point-of-care capillary blood glucose (CBG) measurements per day were collected to calculate the following: (a) the proportion of patient-days with severe hyperglycemia (CBG ≥300 mg/dL), (b) the proportion of patient-days with hypoglycemia (CBG ≤70 mg/dL), and (c) the proportion of patient-days with mean CBG within the target range 140 to 180 mg/dL. Good inpatient glycemic control was defined as ≥85% of patient-days with mean CBG levels between 140 to 180 mg/dL, while poor inpatient glycemic control was defined as >15% of patient-days outside the target range.[15,16]

BMI was categorized according to the World Health Organization (WHO) Asia-Pacific classification.[17] Smoking history was defined as having smoked at least 100 cigarettes in their entire life. Initial vital signs, laboratory examinations, quick sequential organ failure assessment (qSOFA),[18] and all interventions administered in the hospital were collected. Potential confounders such as age, gender, pre-existing comorbidities, duration of DM, and medication intake were collected. The use of systemic corticosteroids and insulin were also analyzed to decrease confounding bias. Possible effect modifiers such as BMI and severity of COVID-19 were also considered. Severity of COVID-19 was classified according to WHO guidelines.[19]

Study outcomes

Primary outcome measure is composite poor clinical outcome, defined as the composite of death from any cause and new/worsened organ dysfunction characterized by at least one of the following: respiratory decompensation requiring non-invasive or invasive ventilation; congestive heart failure; requirement for vasopressors, inotropes, or mechanical circulatory support; ventricular tachycardia or fibrillation lasting at least 30 seconds associated with hemodynamic instability or pulseless electrical activity; resuscitated cardiac arrest; or initiation of renal replacement therapy (RRT).

Secondary outcome measures included overall and in-hospital mortality, requirement for invasive mechanical ventilation, and requirement for intensive care unit (ICU) admission.

Statistical analysis

Descriptive statistics was used to summarize demographic and clinical characteristics cohort. Frequency and proportion were used for categorical variables, while median with interquartile range (IQR) were used for non-normally distributed continuous variables. Mann-Whitney U test and Fisher's Exact/Chi-square test were applied to determine the difference of rank and frequency, respectively, between patients with poor versus good baseline glycemic control and between patients with poor versus good inpatient glycemic control.

To determine the association of baseline glycemic control and inpatient glycemic control with patient outcomes, OR and the corresponding 95% confidence interval (CI) were calculated in a univariable model using unadjusted glycemic control variables, a glycemic control model where baseline glycemic control and inpatient glycemic control variables were adjusted for each other, and a multivariable model where glycemic control variables were adjusted for each other, age, COVID-19 severity, and comorbidities. Age was considered a confounder since older patients are generally at higher risk for severe outcomes from COVID-19 and may have complex health issues affecting their glucose control. Severity of COVID-19 was also considered a confounder since it can directly impact patient outcomes such as mortality and need for intensive care. The number of comorbidities was also considered, since patients with multiple comorbidities may experience more complications and worse prognosis regardless of glycemic control.

Chi-square test was used to analyze the independence of baseline and inpatient glycemic control. All statistical tests were two-tailed tests. Shapiro-Wilk test was used to test the normality of continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 (College Station, TX, USA) and R 4.2.2 (The R Foundation) were used for data analysis.

RESULTS

A total of 1,093 patients with DM hospitalized for confirmed COVID-19 were included in the study. Sixty-three patients were excluded: 4 patients due to pregnancy, 18 patients due to unknown outcome, and 41 patients due to incomplete data.

Table 1 shows the clinical characteristics of the study population. Upon admission, 54% (n = 591) had poor baseline glycemic control (HbA1c >7%). Mean age was 60.83 years (SD ± 14.6), with 53.89% being males. There were no significant differences in BMI (median 25.59 kg/m^2, IQR: 23.3 kg/m^2 to 28.7 kg/m^2) between the subgroups. However, in terms of BMI categories, there were more patients with BMI <18.5 kg/m^2 and BMI ≥30 kg/m^2 in the good baseline glycemic control group (p = 0.003) and good inpatient glycemic control group (p = 0.001) than the poor control group.

Presence of hypertension (75.1% vs 65.48%, p = 0.001), chronic kidney disease (CKD) (12.5% vs 7.78%, p = 0.011), active malignancy (4.18% vs 1.35%, p = 0.004), diabetic retinopathy (1.79% vs 0%, p = 0.001), and cerebrovascular disease (CVD) (9.96% vs 7.11%, p = 0.09) was significantly higher among patients with good baseline glycemic control. Presence of 3 or more comorbidities were more common in the good baseline glycemic control group (p <0.001) and good inpatient glycemic control group (p = 0.009) than the poorly controlled groups.

In terms of COVID-19 severity, majority presented with moderate disease (39.98%), followed by severe (29.92%) and critical (24.43%) disease. Critical disease was greater in patients with poor baseline glycemic control (28.43% vs 19.72%, p = 0.001) and poor inpatient glycemic control (25.7% vs 12.64%, p <0.001). Likewise, the incidence of ARDS, septic shock, and ICU admission were significantly higher in those with poor baseline and poor inpatient glycemic control. qSOFA scores of 2 or higher were more common in patients with poor baseline glycemic control (7.82% vs 4.9, p <0.001) and poor inpatient glycemic control (7.06% vs 1.88%, p <0.001).

Highest FiO_2 requirements were significantly greater in those poor baseline glycemic control (median 44, IQR 28-100 vs 49, IQR 21-90, p <0.001) and poor inpatient glycemic control (median 44, IQR 28 to 100 vs 28, IQR 21 to 52, p <0.001). Initial PF ratio was significantly lower in patients with poor baseline glycemic control (median 262.43, IQR 147-366 vs 323, IQR 207- 400, p <0.001) and poor inpatient glycemic control (275, IQR 160-364 vs 357, IQR 262-414, p <0.001). Lowest PF ratio throughout admission was also significantly lower in patients with poor baseline glycemic control (median 213, IQR 100-334 vs 293, IQR 147-370, p <0.001) and poor inpatient glycemic control (median 216, IQR 100-329 vs 300, IQR 200-400, p <0.001).

Table 2 presents the interventions and medications that were administered to patients. Intravenous corticosteroid use was significantly higher in patients with poor baseline glycemic control (95.17% vs 93.94%, p <0.001) and poor inpatient glycemic control (94.36% vs 93.72%, p <0.001). Consequently, these groups also had greater episodes of steroid-induced hyperglycemia and required significantly higher levels of insulin. In addition, a higher proportion of patients with poor baseline and inpatient glycemic control were given three or more antibiotics, anticoagulants, bronchodilators, inotropes, Tocilizumab, oxygen support, and hemoperfusion as part of their COVID-19 management. There were no significant differences in the requirement for RRT, prone positioning, and convalescent plasma therapy between the subgroups.

Patient outcomes are summarized in Table 3. Composite poor clinical outcome was more common in patients with poor baseline glycemic control (39.26% vs 25.1%, p <0.001) and poor inpatient glycemic control (35.07% vs 15.99%, p <0.001). Requirement for mechanical ventilation and ICU admission were also increased in patients with poor baseline glycemic control and poor inpatient glycemic control. Overall mortality was higher in patients with poor baseline glycemic control (19.8% vs 11.55%, p <0.001) and poor inpatient glycemic control (15.66% vs 7.06%, p <0.001). A similar trend was seen for in-hospital mortality, being higher in patients with poor baseline glycemic control (16.75% vs 11.55%, p = 0.015) and poor inpatient glycemic control (14.73% vs 6.69%, p = 0.001).

Tables 4 shows the relationship between glycemic control and adverse clinical outcomes in univariable and multivariable models. Poor baseline glycemic control confers increased risk (Crude OR (COR) 1.93, 95% CI 1.49-2.51, p <0.001) for composite poor clinical outcome, remaining significant after adjusting for glycemic control (AOR 1.41, 95% CI 1.07-1.87, p = 0.017), but lost significance after adjusting for age, COVID-19 severity, and number of comorbidities (AOR 1.02, 95% CI 0.66-1.58, p = 0.934). ICU admission, mechanical ventilation, and ICU admission were significantly increased in patients with poor baseline glycemic control in the univariable model but these trends were not significant in the glycemic control model and multivariable model.

Poor inpatient glycemic control was significantly associated with increased composite poor clinical outcome (COR 2.84, 95% CI 2.00-4.11, p <0.001), overall mortality (COR 2.44, 95% CI 1.51-4.17, p <0.001), in-hospital mortality (COR 2.41, 95% CI 1.47-4.17, p<0.001), mechanical ventilation (COR 2.76, 95% CI 1.85-4.24, p<0.001), and ICU admission (COR 3.02, 95% CI 1.90-5.08, p <0.001), remaining significant after adjusting for glycemic control. All these trends became non-significant after adjusting for age, COVID-19 severity, and number of comorbidities.

The association between baseline glycemic control and in-patient glycemic control was significant (χ^2 = 58.278, p <0.001) (Supplementary Table 1). Logistic regression showed that poor baseline control increased the odds of poor inpatient control (OR = 3.10, 95% CI: 2.32–4.17, p <0.001), which remained significant after adjusting for steroid use (OR = 3.00, 95% CI: 2.23–4.06, p <0.001) (Table 5).

Supplementary Table 2 summarizes presenting symptoms and glucose-controlling medications administered. Comparison of time to reach composite poor clinical outcome

Table 1. Clinical characteristics of patients with DM hospitalized due to COVID-19

Characteristics	Total (n = 1093)	Baseline glycemic control		*P*-value	Inpatient glycemic control		*P*-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
	Frequency (%); Mean ± SD; Median (IQR)				Frequency (%); Mean ± SD; Median (IQR)		
Age, years	60.82 ± 14.6	60.85 ± 14.91	60.77 ± 14.09	0.941	61.18 ± 14.16	58.83 ± 15.31	0.084
Sex				0.429			0.943
Male	589 (53.89)	325 (54.99)	264 (52.59)		402 (53.82)	144 (53.53)	
Female	504 (46.11)	266 (45.01)	238 (47.41)		345 (46.18)	125 (46.47)	
Height, cm	162 (157 to 168)	162 (157 to 168)	162 (157 to 168)	0.762	162 (157 to 168)	162 (156 to 168)	0.450
Weight, kg	68 (60 to 77)	69 (60 to 76)	68 (59 to 79)	0.954	68 (60 to 77)	68 (59 to 79)	0.882
Body Mass Index, kg/m²	25.59 (23.3 to 28.7)	25.59 (23.4 to 28.3)	25.62 (22.9 to 29.1)	0.815	25.71 (23.4 to 28.4)	25.59 (22.9 to 29.6)	0.841
BMI category				**0.003**			**0.001**
Underweight (<18.5)	14 (1.46)	3 (0.56)	11 (2.61)		6 (0.93)	7 (2.72)	
Normal (18.5 to 24.9)	414 (43.08)	235 (43.6)	179 (42.42)		277 (43.15)	106 (41.25)	
Overweight (25 to 29.9)	366 (167)	221 (41)	145 (34.36)		262 (40.81)	83 (32.3)	
Obese (≥30)	167 (17.38)	80 (14.84)	87 (20.62)		97 (15.11)	61 (23.74)	
Smoking status				0.455			**0.036**
Never smoker	927 (84.81)	508 (85.86)	419 (83.47)		644 (86.21)	217 (80.67)	
Previous smoker	119 (10.89)	61 (10.32)	58 (11.55)		71 (9.5)	41 (15.24)	
Current smoker	47 (4.3)	22 (3.72)	25 (4.98)		43 (4.28)	11 (4.09)	
Number of pack years	1 (1 to 2)	1 (0.5 to 2)	1 (1 to 3)	0.112	3 (1 to 20)	1 (1 to 5)	**0.008**
Duration of smoking, years	20 (10 to 36)	20 (10 to 30)	21 (15 to 40)	0.195	20 (10 to 22)	20 (10 to 36)	0.625
Co-morbid condition							
Hypertension	764 (69.9)	287 (65.48)	377 (75.1)	**0.001**	519 (69.48)	195 (72.49)	0.354
Ischemic Heart Disease	118 (10.80)	61 (10.32)	57 (11.35)	0.625	85 (11.38)	28 (10.41)	0.735
Chronic Kidney Disease	109 (9.97)	46 (7.78)	63 (12.5)	**0.011**	69 (9.24)	34 (12.64)	0.126
Cerebrovascular Disease	93 (9.51)	43 (7.28)	50 (9.96)	0.128	66 (8.84)	20 (7.43)	0.525
Chronic Respiratory Disease	68 (6.22)	23 (5.75)	34 (6.77)	0.531	39 (5.22)	25 (9.29)	**0.027**
Heart Failure	40 (3.66)	25 (4.23)	15 (2.99)	0.333	28 (3.75)	7 (2.6)	0.441
Active Malignancy	29 (2.65)	8 (1.35)	21 (4.18)	**0.004**	14 (1.87)	11 (4.09)	0.063
COVID vaccination	18 (1.65)	11 (1.86)	7 (1.39)	0.637	13 (1.74)	4 (1.49)	1.000
Chronic Liver Disease	15 (1.37)	6 (1.02)	9 (1.79)	0.305	12 (1.61)	1 (0.37)	0.203
Immunodeficient State	9 (0.82)	3 (0.51)	6 (1.2)	0.315	7 (0.94)	1 (0.37)	0.689
Others[1]	148 (13.54)	70 (11.84)	78 (15.54)	0.077	82 (10.98)	58 (21.56)	**<0.001**
Number of co-morbid conditions				**<0.001**			**0.009**
None	249 (22.78)	159 (26.9)	90 (17.93)		175 (23.43)	51 (18.96)	
1 to 2	714 (65.32)	380 (64.3)	334 (66.53)		495 (66.27)	172 (63.94)	
3 or more	130 (11.89)	52 (8.8)	78 (15.54)		77 (10.31)	46 (17.1)	
Duration of diabetes, years	10 (5 to 15)	9 (5 to 14)	10 (4 to 15)	0.457	8 (4 to 12)	7 (3 to 13)	**0.002**
Type of Diabetes				0.667			0.612
Type 1 Diabetes mellitus	5 (0.46)	2 (0.34)	3 (0.60)		3 (0.4)	2 (0.75)	
Type 2 Diabetes mellitus	1085 (99.54)	587 (99.66)	498 (99.4)		744 (99.6)	265 (99.25)	
Microvascular complications of diabetes							
Diabetic nephropathy	170 (15.55)	76 (12.86)	94 (18.73)	**0.009**	120 (16.06)	37 (13.75)	0.431
Diabetic neuropathy	59 (5.4)	31 (5.25)	28 (5.58)	0.893	46 (6.16)	11 (4.09)	0.279
Diabetic retinopathy	9 (0.82)	0	9 (1.79)	**0.001**	8 (1.07)	1 (0.37)	0.459
Macrovascular complications of diabetes							
Ischemic heart disease	121 (11.07)	62 (10.49)	59 (11.75)	0.507	89 (11.91)	26 (9.67)	0.318
Cerebrovascular disease	92 (8.42)	42 (7.11)	50 (9.96)	**0.090**	66 (8.84)	21 (7.81)	0.605
Peripheral arterial disease	23 (2.1)	15 (2.54)	8 (1.59)	0.278	17 (2.28)	6 (2.23)	0.966
Severity of COVID-19				**0.001**			**<0.001**
Mild disease	73 (6.68)	28 (4.74)	45 (8.96)		35 (4.69)	38 (14.13)	
Moderate disease	426 (38.98)	226 (39.24)	200 (39.84)		278 (37.22)	133 (49.44)	
Severe disease	327 (29.92)	169 (28.6)	158 (31.47)		242 (32.4)	64 (23.79)	
Critical disease	267 (24.43)	168 (28.43)	99 (19.72)		192 (25.7)	34 (12.64)	
Incidence of hyperglycemic crisis	32 (3.11)	24 (4.06)	10 (1.99)	0.055	23 (3.08)	1 (0.37)	**0.009**
DKA	16 (66.67)	11 (64.71)	5 (71.43)	1.000	11 (64.71)	1 (100)	1.000
HHS	8 (33.33)	6 (35.29)	2 (28.57)		6 (35.29)	0	
ARDS	287 (26.26)	181 (30.63)	106 (21.12)	**<0.001**	193 (25.84)	48 (17.84)	**0.003**
Mild ARDS	33 (11.5)	14 (7.73)	19 (17.92)	**0.025**	15 (7.77)	17 (35.42)	**<0.001**
Moderate ARDS	84 (29.27)	58 (32.04)	26 (24.53)		61 (31.61)	10 (20.83)	
Severe ARDS	170 (59.23)	109 (60.22)	61 (57.55)		117 (60.62)	21 (43.75)	
Sepsis	254 (23.24)	140 (23.69)	114 (22.71)	0.702	193 (25.84)	41 (15.24)	**<0.001**
Septic Shock	163 (14.91)	112 (18.95)	51 (10.16)	**<0.001**	113 (15.13)	18 (6.69)	**<0.001**
ICU Admission	194 (17.75)	129 (21.83)	65 (12.95)	**<0.001**	146 (19.54)	20 (7.43)	**<0.001**
Vital signs on admission							
Temperature	36.8 (36.5 to 37.5)	36.8 (36.5 to 37.6)	36.8 (36.5 to 37.3)	**0.001**	36.8 (36.5 to 37.6)	36.9 (36.5 to 37.5)	0.828
O_2 saturation	96 (94 to 98)	96 (93 to 98)	96 (94 to 98)	**<0.001**	96 (94 to 98)	97 (95 to 98)	**<0.001**
Systolic blood pressure, mmHg	120 (110 to 136)	120 (110 to 137)	122.5 (110 to 133)	0.525	120 (110 to 140)	120 (110 to 130)	0.997
Diastolic blood pressure, mmHg	80 (70 to 80)	70 (70 to 80)	80 (70 to 80)	**0.042**	73 (70 to 80)	80 (70 to 80)	**0.016**

Table 1. Clinical characteristics of patients with DM hospitalized due to COVID-19 *(continued)*

Characteristics	Total (n = 1093)	Baseline glycemic control		*P*-value	Inpatient glycemic control		*P*-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
	Frequency (%); Mean ± SD; Median (IQR)				Frequency (%); Mean ± SD; Median (IQR)		
qSOFA				**<0.001**			**<0.001**
0	495 (45.92)	215 (36.56)	280 (57.14)		297 (40.3)	178 (66.92)	
1	513 (47.59)	327 (55.61)	186 (37.96)		388 (52.65)	83 (31.2)	
2	64 (5.94)	43 (7.31)	21 (4.29)		47 (6.38)	5 (1.88)	
3	6 (0.56)	3 (0.51)	3 (0.61)		5 (0.68)	0	
Heart rate, beats/minute	88 (78 to 100)	90 (80 to 105)	85 (77 to 98)	**<0.001**	88 (79 to 102)	87 (76 to 98)	**0.022**
<60	25 (2.3)	10 (1.7)	15 (3)	**<0.001**	14 (1.88)	10 (3.76)	**0.013**
60 to 100	796 (73.16)	405 (68.88)	391 (78.2)		537 (72.08)	207 (77.82)	
>100	267 (24.54)	173 (29.42)	94 (18.8)		194 (26.04)	49 (18.42)	
Respiratory rate, breaths/minute	22 (20 to 25)	23 (20 to 26)	21 (20 to 24)	**<0.001**	22 (20 to 26)	20 (20 to 22)	**<0.001**
≤30	1015 (93.12)	533 (90.19)	482 (96.59)	**<0.001**	687 (92.34)	258 (95.91)	**0.047**
>30	75 (6.88)	58 (9.81)	17 (3.41)		57 (7.66)	11 (4.09)	
Admission CBG Result	165 (121 to 230)	188 (139 to 259)	140 (111 to 189)	**<0.001**	174 (127 to 243)	139 (113 to 188)	**<0.001**
HbA1c	7.4 (6.5 to 9.5)	8.5 (7.4 to 10.7)	6.5 (5.98 to 6.89)	**<0.001**	7.6 (6.8 to 10)	6.7 (6.1 to 7.5)	**<0.001**
eGFR (ml/min)	77 (52 to 99)	78 (54 to 101)	77 (49 to 97)	0.142	77 (51 to 99)	82 (56 to 99)	0.414
eGFR category				**0.025**			0.137
<15	59 (5.72)	22 (3.85)	37 (8.04)		35 (5.05)	21 (7.98)	
15-29	52 (5.04)	26 (4.55)	26 (5.65)		37 (5.34)	11 (4.18)	
30-59	210 (20.37)	127 (22.24)	83 (18.04)		150 (21.65)	42 (15.97)	
60-89	320 (31.04)	174 (30.47)	146 (31.74)		213 (30.74)	82 (31.18)	
>90	390 (37.83)	222 (38.88)	168 (36.52)		258 (37.23)	107 (40.68)	
Hemoglobin (g/L)	13.2 (12.1 to 14.4)	13.4 (12.4 to 14.6)	13.1 (11.7 to 14.3)	**<0.001**	13.2 (12.1 to 14.4)	1.3 (12 to 14.7)	0.625
Initial troponin (n = 378)	0.025 (0.006 to 1.12)	0.031 (0.006 to 10.2)	0.024 (0.007 to 0.34)	0.113	0.03 (0.008 to 2.9)	0.011 (0.004 to 0.26)	**<0.001**
Repeat troponin (n = 21)	66.9 (15.2 to 471.3)	66.9 (21.7 to 471.3)	44.4 (0.03 to 202)	0.392	73.05 (24.35 to 336)	0.016 (0.004 to 353)	0.089
Ejection fraction (n = 134)	61 (51 to 66)	60.4 (49 to 66)	61 (55 to 66)	0.258	60 (48.5 to 66)	61.2 (56 to 66)	0.285
PaO_2/FiO_2 ratio (n = 881)	296 (170 to 385)	262.43 (147 to 366)	323 (207 to 400)	**<0.001**	275 (160 to 364)	357 (262 to 414)	**<0.001**
Highest FiO_2 requirement	40 (24 to 100)	44 (28 to 100)	49 (21 to 90)	**<0.001**	44 (28 to 100)	28 (21 to 52)	**<0.001**
Lowest PF ratio (n = 776)	270 (113 to 353)	213 (100 to 334)	293 (147 to 370)	**<0.001**	216 (100 to 329)	300 (200 to 400)	**<0.001**

Table 2. Interventions given to patients with DM hospitalized due to COVID-19

	Total (n = 1093)	Baseline glycemic control		*P*-value	Inpatient glycemic control		*P*-value
		HbA1c >7% (n = 591, 54%)	HbA1c >7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
	Frequency (%); Median (IQR)				Frequency (%); Median (IQR)		
Steroid induced hyperglycemia	832 (91.13)	491 (94.79)	341 (86.33)	**<0.001**	614 (93.6)	154 (81.05)	**<0.001**
Highest total daily insulin dose (units/kg/day) (n=782)	0.8 (0.47 to 1.2)	0.95 (0.63 to 1.3)	0.56 (0.32 to 0.89)	**<0.001**	1.11 (0.8 to 1.34)	0.4 (0.2 to 0.63)	**<0.001**
Antibiotics	935 (85.54)	543 (91.88)	392 (78.09)	**<0.001**	668 (89.42)	199 (73.98)	**<0.001**
Anticoagulants	905 (82.8)	506 (85.62)	399 (79.48)	**0.007**	637 (85.27)	201 (74.72)	**<0.001**
Antiviral	877 (80.24)	499 (84.43)	378 (75.3)	**<0.001**	592 (79.25)	220 (81.78)	0.374
Systematic corticosteroids	874 (79.96)	499 (84.43)	375 (74.7)	**<0.001**	640 (85.68)	169 (62.83)	**<0.001**
Inhaled bronchodilators	361 (33.03)	233 (39.42)	128 (25.5)	**<0.001**	265 (35.48)	58 (21.56)	**<0.001**
Tocilizumab	227 (20.77)	143 (24.2)	84 (16.73)	**0.002**	154 (20.62)	52 (19.33)	0.653
Vasopressors/Inotropes	144 (13.17)	105 (17.77)	39 (7.77)	**<0.001**	98 (13.12)	17 (6.32)	**0.003**
Anti-fungal	124 (11.34)	84 (14.21)	40 (7.97)	**0.001**	94 (12.58)	9 (3.35)	**<0.001**
Chloroquine	39 (3.57)	19 (3.21)	20 (3.98)	0.495	26 (3.48)	10 (3.72)	0.857
IV immunoglobulin	9 (0.82)	6 (1.02)	3 (0.6)	0.446	8 (1.07)	0	0.088
Oxygen support				**<0.001**			**<0.001**
None	264 (24.15)	111 (18.78)	153 (30.48)		136 (18.21)	114 (42.38)	
Nasal cannula	323 (29.55)	161 (27.24)	162 (32.27)		231 (30.92)	82 (30.48)	
Face mask	90 (8.23)	47 (7.95)	43 (8.57)		61 (8.17)	25 (9.29)	
High flow nasal cannula	236 (21.59)	151 (25.55)	85 (16.93)		190 (25.44)	31 (11.52)	
Non-invasive ventilation	9 (0.82)	6 (1.02)	3 (0.6)		8 (1.07)	1 (0.37)	
Mechanical ventilation	171 (15.65)	115 (19.46)	56 (11.16)		121 (16.2)	16 (5.95)	
Prone positioning	832 (76.12)	457 (77.33)	375 (74.7)	0.310	575 (76.97)	199 (73.98)	0.322
Renal replacement therapy	110 (10.06)	57 (9.64)	53 (10.56)	0.617	82 (10.98)	19 (7.06)	0.066
Hemoperfusion	156 (14.27)	97 (16.41)	59 (11.75)	0.028	117 (15.66)	13 (4.83)	**<0.001**
Blood Transfusion	92 (8.42)	44 (7.45)	48 (9.56)	0.209	71 (9.5)	14 (5.2)	**0.029**
Convalescent plasma therapy	41 (3.75)	24 (4.06)	17 (3.39)	0.559	24 (3.21)	11 (4.09)	0.499

Table 3. Outcome of patients with DM hospitalized due to COVID-19

	Total (n = 1093)	Baseline glycemic control		*P*-value	Inpatient glycemic control		*P*-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
	Frequency (%); Median (IQR)				Frequency (%); Median (IQR)		
Poor clinical outcome	358 (32.75)	232 (39.26)	125 (25.1)	**<0.001**	262 (35.07)	43 (15.99)	**<0.001**
Overall mortality	175 (16.01)	117 (19.8)	58 (11.55)	**<0.001**	117 (15.66)	19 (7.06)	**<0.001**
In-hospital mortality	157 (14.36)	99 (16.75)	58 (11.55)	**0.015**	110 (14.73)	18 (6.69)	**0.001**
Mechanical ventilation	260 (23.79)	164 (27.75)	96 (19.12)	**0.001**	192 (25.7)	30 (11.15)	**<0.001**
ICU admission	176 (16.1)	111 (18.78)	65 (12.95)	**0.009**	140 (18.74)	22 (8.18)	**<0.001**
Length of ICU stay, days	9 (5 to 17.5)	9 (5 to 15)	10 (5 to 19.5)	0.329	10 (6 to 18)	7 (4 to 13)	0.139
Length of hospital stay, days	10 (7 to 15)	11 (8 to 15)	10 (7 to 14)	**0.002**	11 (8 to 16)	8 (6 to 12)	**<0.001**

Table 4. Association of glycemic control with patient outcomes in univariable and multivariable models

	Univariable Model[1]		Glycemic control Model[2]		Multivariable model[3]	
	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Baseline glycemic control						
Poor clinical outcome	1.93 (1.49, 2.51)	**<0.001**	1.41 (1.07, 1.87)	**0.017**	1.02 (0.66, 1.58)	0.934
Overall mortality	1.89 (1.35, 2.67)	<0.001	1.34 (0.92, 1.97)	0.130	0.94 (0.56, 1.58)	0.816
In-hospital mortality	1.54 (1.09, 2.19)	0.015	1.19 (0.81, 1.76)	0.400	0.79 (0.47, 1.33)	0.382
Mechanical ventilation	1.62 (1.22, 2.17)	<0.001	1.21 (0.89, 1.66)	0.200	0.8 (0.51, 1.26)	0.342
ICU admission	1.88 (1.36, 2.61)	<0.001	1.38 (0.98, 1.97)	0.069	0.77 (0.46, 1.3)	0.333
Inpatient glycemic control						
Poor clinical outcome	2.84 (2.00, 4.11)	**<0.001**	2.60 (1.82, 3.78)	**<0.001**	1.36 (0.75, 2.5)	0.308
Overall mortality	2.44 (1.51, 4.17)	**<0.001**	2.26 (1.38, 3.89)	**0.002**	1.17 (0.56, 2.48)	0.680
In-hospital mortality	2.41 (1.47, 4.17)	**<0.001**	2.30 (1.38, 4.02)	**0.002**	1.23 (0.59, 2.62)	0.588
Mechanical ventilation	2.76 (1.85, 4.24)	**<0.001**	2.62 (1.74, 4.06)	**<0.001**	1.3 (0.7, 2.45)	0.417
ICU admission	3.02 (1.90, 5.08)	**<0.001**	2.77 (1.72, 4.69)	**<0.001**	1.44 (0.69, 3.02)	0.333

[1] The univariable models consider only unadjusted baseline and inpatient glycemic

[2] The glycemic control models consider only baseline and inpatient glycemic control adjusted for each other

[3] The multivariable models consider the glycemic control variables adjusted for each other and age, COVID-19 severity and comorbidities

Table 5. Logistic regression using baseline glycemic control to predict inpatient glycemic control

	Unadjusted Model 1		Steroid Use Adjusted Model 2	
	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Poor baseline glycemic control	3.10 (2.32, 4.17)	**<0.001**	3.00 (2.23, 4.06)	**<0.001**

Model 1 predicts inpatient glycemic control using baseline glycemic control.

Model 2 predicts inpatient glycemic control using baseline glycemic control adjusted for steroid use.

or discharge is summarized in Supplementary Table 3. Supplementary Table 4 presents the results of the multivariable-adjusted model predicting patient outcomes, where COVID-19 severity had the greatest association with composite poor clinical outcome (AOR 9.25, 95% CI 6.91-12.71, 95% CI), overall mortality (AOR 11.85, 95% CI 7.85-18.81, p <0.001), in-hospital mortality (AOR 11.13, 95% CI 7.36-17.75, p <0.001), mechanical ventilation (AOR 8.29, 95% CI 6.17-11.4, p <0.001), and ICU admission (AOR 15.33, 95% CI 10.33-23.68, p <0.001) after adjusting for all other variables. Presence of three or more comorbidities was significantly associated with composite poor clinical outcome (AOR 1.5, 95% CI 1.02-2.19, p = 0.038) and mechanical ventilation (AOR 1.62, 95% CI 1.1-2.41, p <0.015) after adjusting for all other variables.

DISCUSSION

Baseline HbA1c, BMI, and comorbidities

There was greater occurrence of BMI <18.5kg/m^2 and BMI ≥30 kg/m^2 in patients with good baseline glycemic control in this cohort. Data from the National Health and Nutrition Examination Survey 2017–2018 showed that each 1kg/m2 increase in BMI resulted in 0.015% increase in HbA1c (95% CI 0.011-0.018; p <0.001) in patients without DM, but was non-significantly associated with a 0.01% decrease in HbA1c in patients with DM (95% CI −0.04-0.03; p = 0.68).[20] The loss of significance of BMI as a predictor of glycemic control in patients with known DM may be due to the type of glucose-lowering medication administered and the complex mechanisms involved in DM.

Surprisingly, pre-existing hypertension, CKD, and CVD were more common in patients with HbA1c <7%. A possible explanation may be better health-seeking behavior in patients who were able to achieve good baseline glycemic control, leading to more frequent physician visits and earlier diagnosis of co-morbidities.[21,22] Recent studies suggest that HbA1c variability may be a more powerful predictor of microvascular and macrovascular complications in patients with DM. Greater HbA1c variability based on HbA1c-standard deviation, HbA1c-coefficient of variance, and HbA1c variability score were associated with increased

risks of all-cause mortality, cardiovascular events, progression to chronic kidney disease, amputation, and peripheral neuropathy.[23] A longitudinal review of HbA1c and glycemic control over the past two to three years prior to admission may provide more information on these unexpected findings.

HbA1c is an accurate and reliable measure of long-term glycemic control, but it may be affected by hemoglobinopathies and conditions that modify erythrocyte turnover.[24] In this study, hemoglobin levels were significantly lower in patients with HbA1c <7% (13.1 g/L vs 13.4 g/L p <0.001). Patients with CKD with eGFR <30 ml/min per 1.73 m^2 may have lower HbA1c due to shortened erythrocyte survival from anemia, blood transfusions, erythropoiesis-stimulating agents, or iron-replacement therapies.[25] Other possible causes of lower hemoglobin levels in patients with HbA1c <7% were not documented in this study.

Glycemic control and COVID-19 severity

Poor baseline glycemic control is significantly associated with more severe COVID-19. In the present study, patients with DM with HbA1c >7% exhibited higher rates of critical illness, ICU admission, and invasive mechanical ventilation. This dose-dependent relationship between HbA1c and risk of severe COVID-19 was also seen in a study in Indonesia, where HbA1c level ≥8% was associated with a 3.55-fold increased risk of severe illness (95% CI 1.68–7.52; p = 0.001).[26] Similarly, analysis of the Kaiser-Permanente database in the USA showed a linear relationship between HbA1c levels and COVID-19 severity, with OR of 2.32 (95% CI 1.90–2.84) for HbA1c 7-8.9% and 2.61 (95% CI 1.94–3.52) for HbA1c ≥9%.[27] Poor inpatient glycemic control was significantly associated with more severe COVID-19. This is consistent with a report that hyperglycemia even in patients without DM was associated with a lower likelihood of non-severe COVID-19 (p <0.02).[28]

Patients with poor baseline and inpatient glycemic control required more aggressive management involving corticosteroids, antibiotics, bronchodilators, anticoagulants, and inotropes. This finding is consistent with previous studies where patients with poor glycemic control are more likely to need invasive interventions.[29–33] One study found that every 1% increase in longitudinal HbA1c over the two to three years prior to COVID-19 infection was associated with a 12% increased risk of ICU admission.[34]

The widespread use of corticosteroids, a standard treatment in severe COVID-19 cases, further complicates glycemic control. Hyperglycemia induced by corticosteroids can lead to higher insulin dose requirement and increased risk of hyperglycemic crises. In this study, there was a significant association between poor inpatient glycemic control and hyperglycemic crisis. This concurs with another study where patients with uncontrolled DM developed DKA more often (18.18% vs 3.45%, p = 0.0257).[35] SARS-CoV-2-mediated hyperglycemic emergencies may be due to binding of the virus to ACE2 receptors on pancreatic islets, leading to immune-mediated destruction of beta cells or beta cell death induced by inflammatory cytokines like TNF-α and IFNγ.[36]

Risk of mortality and composite poor clinical outcome

Mortality was higher in patients with poor baseline and inpatient glycemic control in the univariable and glycemic control models. Lombardi et al., reported that patients with uncontrolled DM had a 54% higher risk of dying during COVID-19 hospitalization compared to those with normoglycemia.[37] In a center in Colorado, USA, odds of death and/or intubation within 7 days of admission increased by 19% for every 1 unit increase in HbA1c (OR 1.19, 95% CI 1.01 to 1.43; p = 0.04).[32] HbA1c has been included as a variable in a predictive model for COVID-19 that had an area under the curve of 0.889 for predicting hospitalization and 0.967 for predicting mortality.[38]

Uncontrolled hyperglycemia contributes to systemic inflammation and increases the risk of multi-organ failure. Hyperglycemia in critically ill patients, regardless of pre-existing DM, is linked to increased mortality, prolonged ICU stay, and higher resource utilization. Patients with secondary hyperglycemia and COVID-19 had a significantly higher risk of death, ICU admission, and mechanical ventilation (OR 5.47, 95% CI 1.51–19.82, p = 0.010).[39]

Good inpatient glycemic control lowers the risk for composite poor clinical outcome. In a matched propensity analysis, good inpatient glycemic control had adjusted HR of 0.47 (95% CI, 0.27–0.83, p = 0.009) for ARDS, adjusted HR of 0.24 (95% CI, 0.08–0.71, p = 0.010) for acute heart injury, adjusted HR of 0.12 (95% CI, 0.01–0.96, p = 0.046) for acute kidney injury, and adjusted HR of 0.14 (95% CI, 0.03 - 0.60, p = 0.008) for 28-day mortality compared with poor inpatient glycemic control.[29] A study in Brazil used glycemic variability as a measure for glycemic control and found that overall mortality is increased at standard deviation ≥44.7 mg/dL (3.7% vs 12.6%, p <0.001) and coefficient of variation ≥27.5% (29.7% vs 12.3%, p <0.001).[40]

Inpatient glycemic control demonstrated a stronger association with adverse outcomes control in the univariable and glycemic control models. The syndemic relationship between DM and COVID-19 may explain why poor inpatient glycemic control has greater effect on mortality and composite primary outcome than poor baseline glycemic control. Hyperglycemia activates inflammatory pathways and increases oxidative damage, leading to increased susceptibility to COVID-19 infection with an exaggerated cytokine response, eventually leading to organ failure wherever ACE2 receptors are located.[41] In turn, COVID-19 can directly decrease beta-cell insulin secretion and induce beta-cell apoptosis[42] while corticosteroids given as part of COVID-19 treatment worsen insulin resistance, thereby further worsening hyperglycemia.

After adjusting for age, COVID-19 severity, and number of comorbidities, neither baseline glycemic control nor inpatient glycemic control were significantly associated with any patient outcome. COVID-19 severity appears to have a central role in patient prognosis, with number of comorbidities having a less significant effect. This is similar to the findings of the CORONADO study, where multivariable analysis showed that the presence of microvascular (OR 2.14, 95% CI 1.16–3.94) and macrovascular (OR 2.54, 95% CI 1.44–4.50) complications were associated with seven-day mortality, while HbA1c was not significantly associated with any outcome.[4] This suggests that baseline glycemic control and inpatient glycemic control do not directly influence patient outcomes, but contribute indirectly via their significant effect on COVID-19 severity and comorbidities.

The strong relationship between poor baseline glycemic control and poor inpatient glycemic control, even after adjusting for corticosteroid use, suggests that adequate long-term control of DM will mitigate glycemic excursions during admission for COVID-19, hence reducing COVID severity, occurrence of end-organ dysfunction, and mortality.

Since only patients hospitalized for at least 24 hours were included, this study may be affected by selection bias. Mild COVID-19 cases may have been managed as outpatients, while the most critical cases may have expired less than 24 hours after admission. HbA1c should always be interpreted with caution since it may not be reflective of glycemic control in certain populations, such as those with CKD, anemia, and hemoglobinopathies. Longitudinal HbA1c may be a more reliable measure of long-term baseline glycemic control.

During the data collection period of this study (January 1, 2021 to January 31, 2022), the Philippines faced successive surges in COVID-19 cases linked to the emergence of COVID-19 variants. The Alpha variant (B.1.1.7) was initially detected in January 2021.[43] The more aggressive Delta variant (B.1.617.2) drove a major wave of moderate to severe infections from July to August 2021.[44] By late December 2021, Omicron subvariants (BA.1 and BA.2) triggered another spike in infections, with daily cases peaking in early January 2022.[45] The differences in transmissibility and disease severity of these variants may have affected the findings in our study, but were not included in our data collection since results of genome sequencing were not routinely done on all samples. Similarly, data on vaccination status were not available for some patients.

Management of COVID-19 across eight institutions were guided by the Unified COVID-19 Algorithms, which was developed by the Healthcare Professionals Alliance Against COVID-19. These algorithms were revised throughout the duration of data collection to reflect most recent evidence and policy updates: Version 1 was released on November 7, 2020,[46] Version 2 was released on June 21, 2021, and Version 4 was released on February 21, 2022.[9] New antiviral medications and other strategies introduced in later versions of the algorithms may have affected clinical outcomes, but this cannot be avoided due to continuous developments in COVID-19 management.

Results of this study may be applicable primarily to adult patients of Asian descent with DM with confirmed COVID-19. Differences in age, ethnicity, and underlying health conditions in other populations may limit generalizability. Variability in treatment protocols, healthcare resources, and glucose control measurement practices across regions could further impact the applicability of the results. Lastly, the temporal context of the study, reflecting a specific wave of the pandemic, raises questions about the relevance of the findings as the virus evolves, COVID-19 vaccination becomes routine, and treatment strategies change. Thus, while our findings offer valuable insights, caution is warranted in generalizing these results to diverse populations or future contexts.

CONCLUSION

COVID-19 severity had the greatest impact and is the only variable with a statistically significant association with composite poor clinical outcomes after adjusting for all other variables. Similar to other studies, poor glycemic control on admission and during hospitalization were associated with more severe COVID-19, although they did not directly impact clinical outcomes. Inpatient glycemic control had a stronger influence on clinical course, while HbA1c >7% was predictive of poor inpatient glycemic control. Strategies to optimize glycemic control both in the long term and during hospitalization should be considered to prevent severe COVID-19, hence improving clinical outcomes and survival.

Acknowledgments
We would like to thank the Philippine College of Endocrinology, Diabetes, and Metabolism for their support.

Statement of Authorship
All authors claim fulfillment of ICMJE authorship criteria.

CRediT Author Statement
MDSJ, JLN, JPMB, MS: Conceptualization, Investigation, Data curation, Resources, Writing – original draft, Writing – reviewing and editing, Visualization; **JC, RC, DE, MKAT:** Conceptualization, Investigation, Data curation, Resources, Writing – original draft; **EPP:** Conceptualization, Methodology, Writing – reviewing and editing, Visualization; **SMP:** Conceptualization, Methodology, Validation; **CC, CDP, KF, MPK, EM, CCT:** Supervision.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
EPP is the JAFES Editor-in-Chief.

Funding Source

The authors received a grant from the Philippine College of Endocrinology, Diabetes and Metabolism.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Baseline vs inpatient glycemic control contingency table

Baseline glycemic control	Inpatient glycemic control		Total
	Good	Poor	
Good	182	301	483
Poor	87	446	533
Total	269	747	1016

Chi-square test: 58.278 (1 degree of freedom), p-value <0.001

Supplementary Table 2. Other Clinical Characteristics of the Cohort

	Total (n = 1093)	Baseline glycemic control		*P*-value	Inpatient glycemic control		*P*-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
	Frequency (%); Median (IQR)				Frequency (%); Median (IQR)		
Presenting Symptoms							
Cough	809 (74.02)	442 (74.79)	367 (73.11)	0.534	554 (74.16)	191 (71)	0.335
Fever at home	647 (59.19)	348 (58.88)	299 (59.56)	0.853	438 (58.63)	166 (61.71)	0.386
Shortness of breath	571 (52.24)	341 (57.7)	230 (45.82)	**<0.001**	402 (53.82)	113 (42.01)	**0.001**
Fatigue	407 (37.24)	249 (42.13)	158 (31.47)	**<0.001**	304 (40.7)	72 (26.77)	**<0.001**
Sputum production	217 (19.85)	103 (17.43)	114 (22.71)	**0.033**	152 (20.35)	52 (19.33)	0.790
Difficulty breathing	205 (18.76)	138 (23.35)	67 (13.35)	**<0.001**	156 (20.88)	26 (9.67)	**<0.001**
Anosmia	133 (12.17)	100 (16.92)	33 (6.57)	**<0.001**	108 (14.46)	5 (1.86)	**<0.001**
Myalgia or arthralgia	125 (11.44)	76 (12.86)	49 (9.76)	0.127	76 (10.17)	41 (15.24)	**0.034**
Sore throat	123 (11.25)	70 (11.84)	53 (10.56)	0.565	76 (10.17)	33 (12.27)	0.358
Diarrhea	117 (10.7)	65 (11)	52 (10.36)	0.769	93 (12.45)	19 (7.06)	**0.017**
Nasal congestion or colds	112 (10.25)	58 (9.81)	54 (10.76)	0.618	79 (10.58)	27 (10.04)	0.907
Anorexia	84 (7.69)	59 (9.98)	25 (4.98)	**0.002**	71 (9.5)	9 (3.35)	**0.001**
Chills	64 (5.86)	46 (7.78)	18 (3.59)	**0.004**	59 (7.9)	0	**<0.001**
Headache	53 (4.85)	34 (5.75)	19 (3.78)	0.158	38 (5.09)	14 (5.2)	1.000
Nausea and vomiting	32 (2.93)	16 (2.71)	16 (3.19)	0.720	24 (3.21)	8 (2.97)	1.000
Desaturation	27 (2.47)	18 (3.05)	9 (1.79)	0.241	18 (2.41)	9 (3.35)	0.386
Dysgeusia	24 (2.2)	17 (2.88)	7 (1.39)	0.102	19 (2.54)	3 (1.12)	0.224
Others	159 (14.55)	78 (13.2)	81 (16.14)	0.170	100 (13.39)	49 (18.22)	0.055
Glucose-controlling Medications during Admission							
DPP4 Inhibitors	747 (68.34)	444 (75.13)	303 (60.36)	**<0.001**	543 (72.69)	157 (58.36)	**<0.001**
Basal Bolus	690 (63.13)	429 (72.59)	261 (51.99)	**<0.001**	547 (73.23)	97 (36.06)	**<0.001**
Metformin	303 (27.72)	170 (28.76)	133 (26.49)	0.416	194 (25.97)	95 (35.32)	**0.004**
PRN short/ rapid acting insulin	186 (17.02)	76 (12.86)	110 (21.91)	**<0.001**	107 (14.32)	67 (24.91)	**<0.001**
Sulfonylurea	77 (7.04)	39 (6.6)	38 (7.57)	0.555	53 (7.1)	23 (8.55)	0.421
IV Insulin drip	71 (6.5)	55 (9.31)	16 (3.19)	**<0.001**	58 (7.76)	2 (0.74)	**<0.001**
Basal only	60 (5.49)	37 (6.26)	23 (4.58)	0.234	35 (4.69)	23 (8.55)	**0.031**
Premixed	60 (5.49)	48 (8.12)	12 (2.39)	**<0.001**	54 (7.23)	0	**<0.001**
SGLT2 Inhibitors	38 (3.48)	17 (2.88)	21 (4.18)	0.251	21 (2.81)	12 (4.46)	0.227
Basal plus	16 (1.46)	10 (1.69)	6 (1.2)	0.616	8 (1.07)	8 (2.97)	**0.043**
Thiazolidinediones	13 (1.19)	3 (0.51)	10 (1.99)	**0.027**	8 (1.07)	5 (1.86)	0.346
GLP 1 RA	8 (0.73)	4 (0.68)	4 (0.8)	1.000	5 (0.67)	3 (1.12)	0.443
Others	11 (1.01)	5 (0.85)	6 (1.2)	0.763	9 (1.2)	2 (0.74)	0.737

Supplementary Table 3. Comparison of time to reach primary composite outcome, death, or discharge between patients with poor and good glycemic control

	Baseline glycemic control		*P*-value	Inpatient glycemic control		*P*-value
	HbA1c >7%	HbA1c ≤7%		Poor control	Good control	
Time to first occurrence of either death from any cause or new/worsened organ dysfunction, days, median (IQR)	14 (9)	13 (14)	0.407	15 (12)	11 (9)	**0.019**
Time to discharge, days, median (IQR)	11 (7)	10 (7)	**0.002**	11 (7)	8 (6)	**<0.001**

Supplementary Table 4. Multivariable-adjusted model predicting patient outcomes

Characteristic	Poor clinical outcome		Overall mortality		In-hospital mortality		Mechanical ventilation		ICU admission	
	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Baseline glycemic control	1.02 (0.66, 1.58)	0.934	0.94 (0.56, 1.58)	0.816	0.79 (0.47, 1.33)	0.382	0.8 (0.51, 1.26)	0.342	0.77 (0.46, 1.3)	0.333
Inpatient glycemic control	1.36 (0.75, 2.5)	0.308	1.17 (0.56, 2.48)	0.680	1.23 (0.59, 2.62)	0.588	1.3 (0.7, 2.45)	0.417	1.44 (0.69, 3.02)	0.333
Age	0.99 (0.98, 1.01)	0.424	1.02 (1, 1.04)	0.063	1.02 (1, 1.04)	0.077	1 (0.98, 1.02)	0.909	1 (0.98, 1.02)	0.782
COVID-19 severity	9.25 (6.91, 12.71)	**<0.001**	11.85 (7.85, 18.81)	**<0.001**	11.13 (7.36, 17.75)	**<0.001**	8.29 (6.17, 11.4)	**<0.001**	15.33 (10.33, 23.68)	**<0.001**
Comorbidities	1.5 (1.02, 2.19)	**0.038**	1 (0.65, 1.55)	0.988	1.03 (0.67, 1.59)	0.897	1.62 (1.1, 2.41)	**<0.015**	0.92 (0.59, 1.42)	0.696

P-values computed using likelihood ratio test

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

COVID-19 Infection and Gut Microbial Dysbiosis Among Filipinos with Type 2 Diabetes Mellitus

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Abstract

Background. Both type 2 diabetes mellitus (T2DM) and COVID-19 are associated with gut microbial alterations. It remains unclear whether COVID-19 causes further gut dysbiosis among individuals with T2DM.

Objective. This study aimed to characterize the gut microbiome of Filipinos with T2DM who had COVID-19.

Methodology. 101 Filipinos, aged 30–59, residing in the Greater Manila Area, were recruited into one of four groups: non-COVID/non-T2DM (A), COVID-recovered/non-T2DM (B), non-COVID/T2DM (C), and COVID-recovered/T2DM (D). Gut microbial composition was characterized through 16S rRNA gene profiling of stool samples using Illumina MiSeq-next-generation Sequencing. These sequences were subjected to mothur and PICRUSt2 for taxonomic and functional analyses.

Results. Gut microbial analysis revealed potential disease biomarkers, as *Roseburia* is more abundant among participants with COVID-19 history, while *Parabacteroides* is more abundant among participants with T2DM. Principal coordinate analysis (PCOA) revealed that participants with T2DM clustered together, while participants without T2DM displayed significantly different clustering.

Conclusion. These findings suggest that COVID-19 does not cause further gut dysbiosis among individuals with T2DM and that T2DM exerts a stronger influence on the gut microbiome compared to COVID-19. These findings are useful for clinicians to better understand the COVID-19 risk to T2DM.

Key words: gut microbiome, COVID-19, type 2 diabetes mellitus, 16S rDNA

INTRODUCTION

The gut microbiome impacts host physiology significantly. It is integral to host digestion and nutrition, polysaccharide breakdown, nutrient absorption, inflammatory responses, gut permeability and bile acid modification.[1] Diversity is integral to a healthy gut microbiome as it permits redundancy, defined as multiple communities of microbes performing similar functions. On the other hand, dysbiosis presents health risks to the host. This is defined as an imbalance in microbial populations and has been associated with a variety of diseases including malnutrition, inflammatory bowel diseases, neurological disorders, cancer, obesity and Type 2 Diabetes Mellitus (T2DM).[2] Specifically, among individuals with T2DM, gut microbial alterations previously documented include: (1) a decrease in relative abundance among *Bifidobacterium*, *Akkermansia* and *Faecalibacterium prausnitzii,* microbial communities either known to produce butyrate or up-regulate butyrate production, which is associated with insulin-resistance, and (2) an increase in relative abundance of *Dorea* which is associated with a reduction of the above-mentioned butyrate-producing bacteria.[2-4]

Gut microbial composition is also found to be associated with COVID-19 disease outcome and duration. Gut dysbiosis is suggested to be contributory to the course and severity of COVID-19 disease.[5] Gut dysbiosis is characterized by the following: (1) relative decrease in symbiotic microorganisms; (2) relative increase in potentially harmful microorganisms; and (3) overall reduction in microbial diversity.[6] In a recently concluded study among Filipinos with active COVID-19 infection of varying severity, it was shown that some gut microbial alterations are found for severe COVID-19 infections but not for asymptomatic and mild disease. It was shown that *Enterococcus* and *Streptococcus*, recognized to be opportunistic pathogens, are enriched among those who suffer from severe COVID-19 infections. This further suggests a possible contribution of the gut microbiome to the pathophysiology of severe COVID-19. This enrichment is also found to be accompanied by a reduction in *Bifidobacterium*, *Collinsella*, *Roseburia*,

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Velasco and Dalmacio.
Received: November 24, 2025. Accepted: January 15, 2026.
Published online first: April 30, 2026.
https://doi.org/10.15605/jafes.041.01.6343

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Dorea, *Megamonas* and *Coprococcus*, which have established immunomodulatory roles.[7] Furthermore, the composition of the gut microbiome also appears to be influenced by COVID-19 infection, and the alterations may also persist up to 6 months after infection.[8] Chen et al., monitored the gut microbial composition of participants longitudinally at three different time-points: acute (at the time of illness onset), convalescence (2 weeks after hospital discharge) and post-convalescence (6 months after discharge). They found that the gut microbial richness is reduced significantly at the acute phase among COVID-19 patients compared with uninfected controls. Interestingly, they also found that the microbiota richness seemingly increased but was not restored to normal levels 6-months after recovery.[8] While this study was done on a small sample size, it suggests that COVID-19 infection alters gut microbial composition 6 months after recovery. This time frame coincides with the duration of time at which post-COVID symptoms may still continue to persist.

The COVID-19 pandemic puts individuals with Type 2 Diabetes Mellitus patients at a greater risk than the general population. Epidemiologic analysis of clinical and demographic data done early in the pandemic reveals that individuals with Type 2 Diabetes Mellitus are about three-times as likely to die from COVID-19, relative to the general population.[9] The gut dysbiosis among individuals with Type 2 Diabetes Mellitus is suggested to play a role in this apparent increased risk of severe disease and mortality.[5] *Clostridiales* was previously found to be dominant among Filipinos with T2DM, and *Lactobacillus* and *Bifidobacterium* were found to be dominant among Filipinos with T2DM and obesity.[10] Currently, there is limited knowledge on whether COVID-19 infection adds further alterations to the already dysbiotic gut microbiome among individuals with T2DM.

COVID-19 appears to be associated with alterations on the gut microbiome after recovery. Individuals with T2DM known to be at risk for developing gut microbial dysbiosis might be at risk for developing further gut microbial alterations after COVID-19 infection. This study aimed to characterize how COVID-19 alters the gut microbiome among individuals with and without Type 2 Diabetes Mellitus, three to twelve months after recovery. Specifically, this study sought to (1) compare gut microbial composition of Filipinos with and without COVID-19 history among those with and without T2DM; (2) predict gut microbial function of Filipinos with and without COVID-19 history among those with and without T2DM and (3) determine an association between gut microbial composition with T2DM status and COVID-19 history.

METHODOLOGY

Study design

This cross-sectional study involves a descriptive and observational approach to compare gut microbiome profiles among individuals with and without Type 2 Diabetes Mellitus among those with and without COVID-19 history in the past three to twelve months. Demographic, anthropometric, diet and clinical data were collected upon enrollment of the participants to the study. All collected information was documented with an individual case report form and a food frequency questionnaire. Stool samples were collected from all the participants of the study.

The study was implemented in the Greater Manila Area. Participants of the study are 30 to 59 years old. One hundred and one individuals were recruited via convenience sampling. Recruitment was done primarily from responses from advertisements posted on social media, snowball referrals from participants as well as referrals from colleagues. After satisfying the eligibility criteria, twenty-four (24) were assigned to group A: without T2DM, without COVID-19 history. Twenty-five (25) were assigned to group B: without T2DM with COVID-19 history. Twenty-seven (27) were assigned to group C: with T2DM, without COVID-19 history. Twenty-five (25) were assigned to group D: with T2DM, with COVID-19 history.

Sample size computation for this study was based on a calculator using the Dirichlet-multinomial model for hypothesis testing and power calculation for taxonomic-based human microbiome data based on a study by La Rosa et al.[11] This considers prior knowledge of certain parameters such as the most abundant or least abundant operational taxonomic units (OTUs) and their relative change in abundance among the cases. Parameters considered in this sample-size computation were based on the work of Li et al. (2020), characterizing the gut microbiome profiles of T2DM patients in China.[3] It was shown that a sample size of n=24 participants at $\alpha \leq 0.01$ or $\alpha \leq 0.05$ would attain 95% statistical power (Figure 1). Thus, each study group, as well as the control group, was set at a minimum of twenty four (24) participants.

Participant eligibility criteria

All participants recruited are Filipino, resident of the Greater Manila Area and aged 30 to 59 years old. Additional inclusion criteria include: hemoglobin A_{1c} <6.5 % for sub-groups without T2DM; hemoglobin A_{1c} ≥6.5 % or physician-diagnosed T2DM for sub-groups with T2DM; never had a positive result for COVID-19 RT PCR test or antigen test for sub-groups without COVID-19 history; diagnosed with COVID-19 confirmed with proof of COVID-19 RT-PCR test result in the previous 3 to 12 months for sub-groups with COVID-19 history.[12]

While history of antibiotic intake during the past 180 days can affect the composition of the gut microbiome, excluding them would be difficult to achieve as some participants to be recruited conceivably have had to receive antibiotics for concomitant bacterial infections while being managed for COVID-19. Hence, the history of antibiotic intake was shortened to the past 60 days for participants

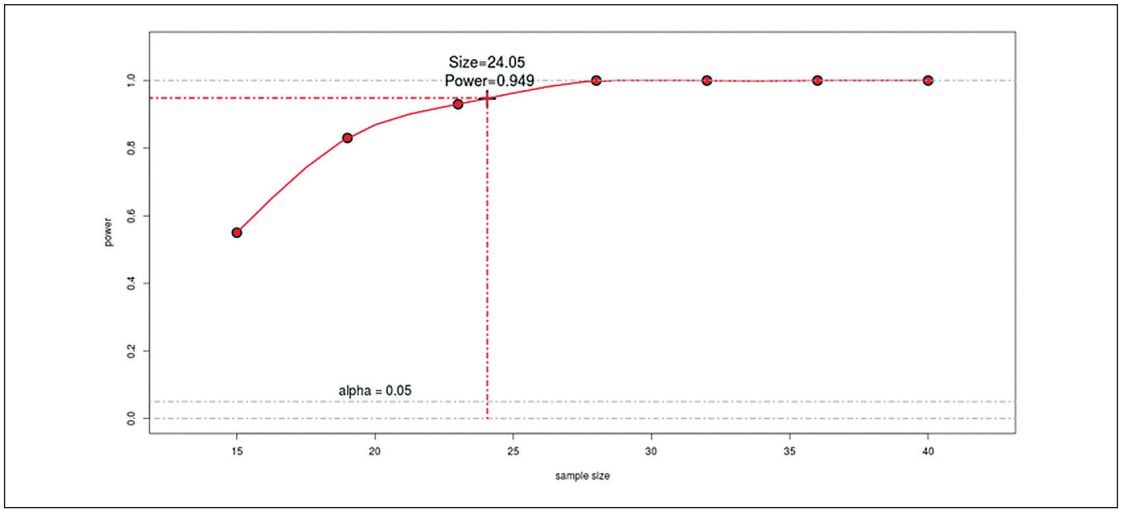


Figure 1. Curve showing statistical power per calculated sample size for stool gut microbiome studies.
This figure was generated using https://fedematt.shinyapps.io/shinyMB/

to be excluded from the study. A meta-analysis performed by Elvers et al., found that after cessation of common antibiotic therapy, gut bacteria recovers to their baseline within a few weeks.[13] Other considerations for exclusion were pregnancy, breastfeeding, history of gastrointestinal surgery and being physically unable to provide viable and uncontaminated stool samples. Further exclusion criteria include the use of the following medications: proton-pump inhibitors, H2-receptor antagonist, tricyclic antidepressants, narcotics, anticholinergics, laxatives and non-steroidal anti-inflammatory drugs in the past 30 days.

Sample collection

After consent has been successfully secured from the participant, the investigator facilitated sample collection in the same visit. Two specimens were collected: (1) blood and (2) stool. For the blood collection, the investigator used a 3-cc syringe to extract 1 to 2-cc of venous blood from the median cubital vein of the participant. The extracted blood was subjected to hemoglobin A_{1c} determination. For the stool collection, the investigator gave verbal and printed instructions, as well as a stool collection kit for the participant. Stool samples were kept in a 50-cc conical tube with DNA/RNA Shield (ZymoResearch™) viral inactivation buffer.

DNA isolation

DNA was obtained from the 0.25 grams of stool samples acquired from the study participants through protocols and reagents described in a commercially available DNA Isolation Kit (QIAmp PowerFecal Pro DNA Kit). DNA concentration was determined using the Promega QuantusTM Fluorometer (France) using QuantiFluor(r) Dye Systems.

Next generation sequencing

DNA isolates with a concentration of more than 20 ng/mL were sent to Macrogen Inc. (Republic of Korea) for 16S rRNA gene V3-V4 amplicon sequencing. The DNA Library preparation and Illumina MiSeq-based next-generation sequencing was performed by Macrogen Inc. with the DNA library constructed using the Nextera XT DNA Library Preparation Kit. The fastq files derived from NGS were processed on a Galaxy server with the latest version of *mothur* (c. 1.48.0) for downstream analysis. Based on the protocol previously published by Schloss et al. (2020), the paired end reads of all 16S rRNA gene sequences were consolidated in a singular dataset.[14] This dataset was subjected to the bioinformatics pipeline illustrated in Figure 2.

Bioinformatics analysis

Downstream analysis was performed on MicrobiomeAnalyst (https://dev.microbiomeanalyst.ca/MicrobiomeAnalyst/home.xhtml, accessed December 2023), a web-based and R-based graphical interface platform enabling statistical analysis of the microbiome data. Alpha diversity analysis was estimated using the following indices: Observed OTUs, Shannon and Faith pd. Beta diversity, on the other hand, was determined using Principal Coordinate Analysis (PCoA). MicrobiomeAnalyst uses Microbiome Multivariable Associations with Linear Models (MaAsLin 2) to assess multivariable association of microbial community features with complex metadata in population-scale observational studies. Differentially abundant taxa were evaluated both in their raw counts, as well as their log-2 transformed counts. Kruskal-Wallis rank-sum test was performed to detect the significant differences between study groups with respect to these counts, a p-value of <0.05 as well as a False Discovery Rate (FDR) value of <0.05 was considered significant to minimize spurious correlations. Although log-2 transformation is useful in

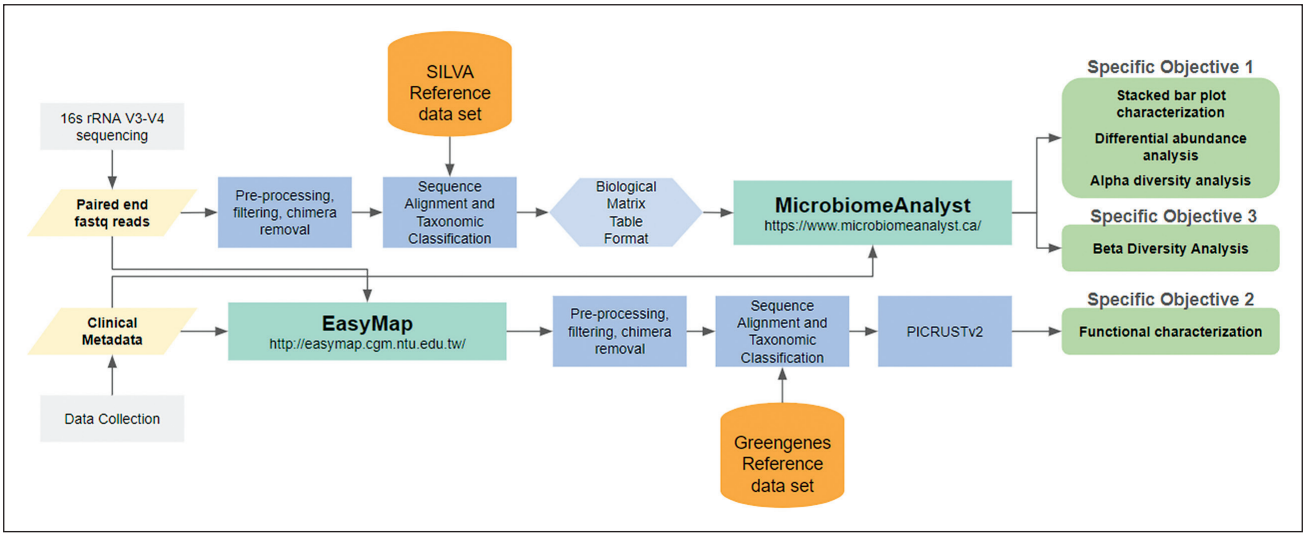


Figure 2. Bioinformatics pipeline used in this study.

This figure was created using Microsoft Powerpoint.

addressing variance, one limitation of this study is the lack of compositional transformation analysis. Functional inferences of the microbial communities were done using the Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2 (PICRUSt2) (v2.2.0-b). This was done on EasyMAP (https://easymap.cgm.ntu.edu.tw/, accessed December 2023), a web-based interface enabling 16S Microbiome analysis. In this analysis, the Greengenes V3-4 classifier was used as the reference database. This step integrates LEfSe and PICRUSt to predict functions of microbes that are significantly different between groups. PICRUSt2 predictions were based on the following gene families: Enzyme Classification numbers and Kyoto Encyclopedia of Genes and Genomes (KEGG) orthologs (KO) (v77.1) Alpha value for Kruskal-Wallis test was set at 0.05, while threshold on logarithmic LDA score for discriminative features was set at 2.

Statistical analysis

Bioinformatics analysis incorporating MaAsLin 2 was conducted for the microbiome outcomes of this study. Traditional parametric tests were used for the comparison of dietary consumption of participants. All collected data except for dietary consumption were incorporated in the bioinformatics analysis. To assess for statistical differences in the collected clinical, anthropometric, demographic and dietary data, the following statistical tests were used: (1) Chi-square or Fischer's exact test for nominal variables; (2) ANOVA or t-test for continuous variables. For the dietary consumption of participants, ANOVA was subsequently followed-up by FDR test using two-stage linear step-up procedure of Benjamini, Krieger and Yekutiel. Microbiome These calculations were performed on GraphPad Prism 8.0.1. To assess for statistical differences in relative abundance of identified taxa, Kruskal-wallis rank sum test and Linear Discriminant Analysis (LDA) were performed. To calculate the statistical significance in observed relationships in the principal coordinate analysis (PCOA), PERMANOVA was performed. These calculations were performed on MicrobiomeAnalyst and EasyMap.

Research ethics oversight

The protocol of this study was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) for evaluation (UPMREB 2022-0046-01). Participant recruitment, data and stool specimen collection commenced only after the approval of the UPMREB Review Panel was secured. All principles of Bioethics in the conduct of scientific research, as well as national laws and regulations, were upheld throughout the study.

RESULTS

Characterization of the study participants

The clinical, sociodemographic and anthropometric data collected from each participant is summarized below (Table 1). ANOVA or unpaired t-test were performed to detect significant differences for continuous variables while Chi-square or Fischer's exact test were performed to detect significant differences for categorical variables.

Dietary composition of participants

Participants across all study groups have similar diets in terms of overall calories, carbohydrates, fats and dietary fibers consumed per day. However, the non-COVID/non-T2DM group (A) was reported to consume significantly more protein compared to the rest of the groups (Figure 3). Table 2 summarizes the p-values from ANOVA and the q-values from FDR testing in the statistical analyses of dietary consumption.

Table 1. Clinical, sociodemographic and anthropometric characteristics of participants

	A No COVID / No T2DM	B COVID / No T2DM	C No COVID / T2DM	D COVID / T2DM	*P*-values
N	24	25	27	25	
Sex (M/F)	(11/13)	(12/13)	(10/17)	(14/11)	0.5923
mean age (years) ± sd	39.29 ± 8.65	34.44 ± 4.39	48.363 ± 8.51	43.76 ± 8.51	<0.0001
mean weight (kg) ± sd	65.06 ± 12.29	70.20 ± 14.69	69.93 ± 21.00	76.52 ± 16.61	0.1241
mean BMI (kg/m2) ± sd	25.35 ± 4.18	26.35 ± 4.18	26.75 ± 7.61	28.81 ± 6.08	0.1990
mean HbA1c (%) ± sd	5.600 ± 0.34	5.496 ± 0.31	8.248 ± 1.79	7.808 ± 2.05	<0.0001
Proportion of fully vaccinated (%)	95.83%	100%	96.30%	96%	0.7948
mean days since COVID infection ± sd	-	191.2 ± 66.84	-	234.7 ± 87.99	0.0549
Number of individuals with following COVID severity classification at the time of COVID infection					
Asymptomatic	-	6	-	0	
Mild	-	9	-	0	
Moderate	-	10	-	24	
Severe	-	0	-	1	
Critical	-	0	-	0	
Proportion with the following comorbidities (%)					
Hypertension	12.5%	20%	51.85%	56%	0.0012
CKD	-	-	-	4%	0.3809
Bronchial asthma	8.33%	8%	-	4%	0.2519
COPD	4.17%	4%	-	-	0.5385
CVD	-	4%	3.7%	8%	0.5463
Thyroid disease	4.17%	-	-	-	0.3560
Hyperuricemia	-	4%	7.41%	4%	0.6077
Hyperlipidemia	-	4%	18.52%	16%	0.0750
Allergic rhinitis	-	4%	-	-	0.3809
PCOS	-	4%	-	-	0.3809
PTB history	-	-	3.7%	-	0.3809
Liver disease	-	-	3.7%	-	0.3809
Proportion taking the following anti-diabetes medications (%)					
Metformin	-	-	55.56%	64%	0.5822
Thiazolidinedione	-	-	3.7%	-	0.9999
Sulfonylurea	-	-	22.22%	16%	0.7289
Insulin	-	-	11.11%	12%	0.9999
SGLT2 Inhibitor	-	-	11.11%	16%	0.6983
GLP1 Analogue	-	-	-	4%	0.9999
DPP4 Inhibitor	-	-	14.81%	20%	0.7224

P-values were determined using one-way ANOVA for continuous variables, and Chi-square or Fischer's exact test for categorical variables.

Table 2. ANOVA and FDR testing results for dietary consumption of participants

	Total Calories	Carbohydrate	Fat	Protein	Dietary Fiber
ANOVA (p-values)	0.1148	0.5526	0.6106	0.0053*	0.0954
FDR test (q-values)					
A vs B	0.1462	0.7109	0.6413	0.0041	0.1009
A vs C	0.1638	0.7109	0.6413	0.0118	0.3740
A vs D	0.1462	0.7109	0.6413	0.0041	0.1971
B vs C	0.9240	0.9970	0.9996	0.4004	0.4274
B vs D	0.9240	0.9970	0.9996	0.4368	0.6435
C vs D	0.9240	0.9970	0.9996	0.4057	0.6435

P-values were determined using one-way ANOVA for continuous variables, *q*-values were determined using FDR approach using two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli.

Identification of microbial biomarkers

Identification of microbial biomarkers from all groups through linear discriminant analysis with effect size (LEfSe) revealed *Parabacteroides* (LDA score 4.6) to be significantly more abundant for the T2DM groups for both with and without history of COVID-19 (groups C and D) (Figure 4). Furthermore, *Roseburia* (LDA score 5.38) was revealed to be significantly more abundant for the COVID-19 recovered groups for both with and without T2DM (groups B and D) (Figure 4).

Alpha and beta diversity analyses

The alpha diversity observed across all study groups is not significantly different (Figure 5A). Beta diversity analysis, however, revealed statistically significant clustering (p -value <0.05) demonstrated by the Principal Coordinate Analysis plot (Figure 5B). The non-COVID/ non-T2DM group (A) had clustering overlap with the COVID-recovered/non-T2DM group (B).

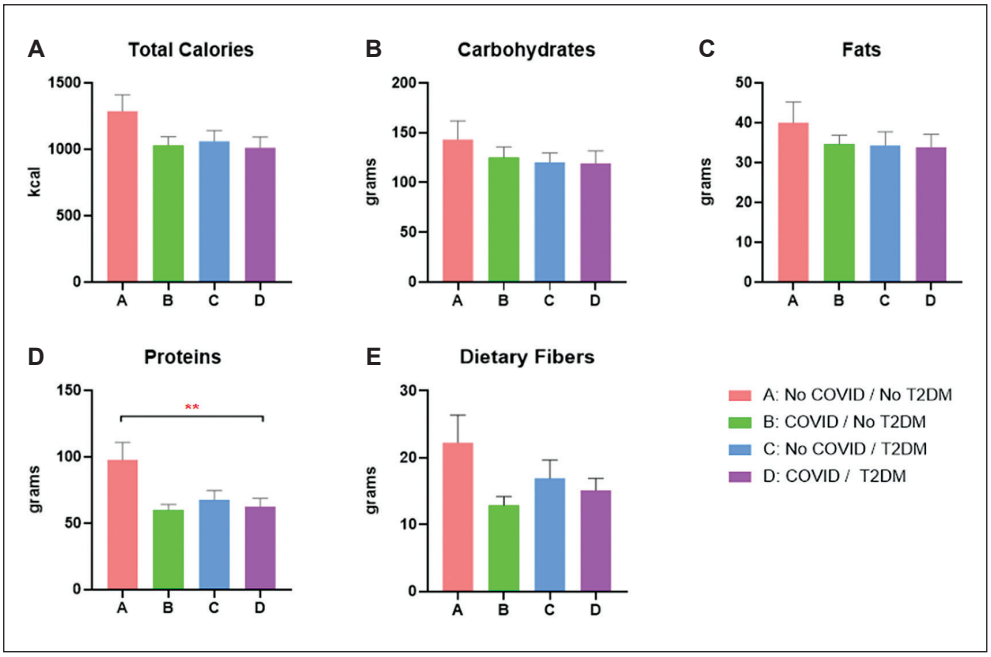
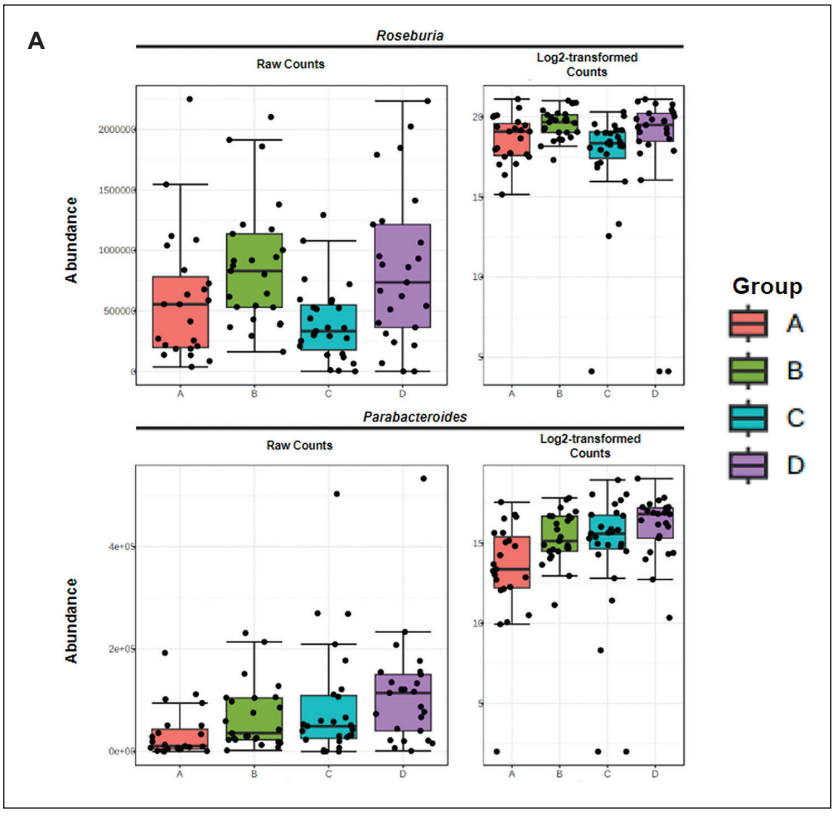


Figure 3. Dietary composition of the study participants. The bars represent the mean dietary intake per group while the error bars represent standard error of the mean. ANOVA was used to calculate significant differences between the groups, total calories *p*-value: 0.1148, carbohydrates *p*-value: 0.5526, fats *p*-value: 0.6106, proteins *p*-value: 0.0053 and dietary fibers *p*-value: 0.0965.

This figure was generated using GraphPad Prism 8.0.1



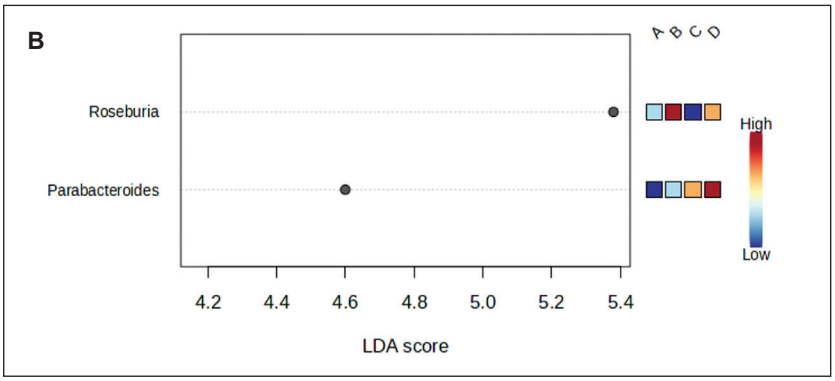


Figure 4. (A) Differentially abundant OTUs across all four groups. *Roseburia*, *p*-value: 0.0014513, FDR: 0.058891. *Parabacteroides*, *p*-value: 0.0017369, FDR: 0.058782. Kruskal-Wallis rank sum test was performed to evaluate differentially abundant taxa. **(B)** Dot plot showing Linear Discriminant Analysis Effect Size (LEfSe) to evaluate differentially abundant taxa across all four groups. *Roseburia* LDA score 5.38, *Parabacteroides* LDA score 4.6. Kruskal-wallis rank sum test followed by LDA to evaluate relevance or effect size of differential abundant taxa.

This figure was generated using Microbiome Analyst.

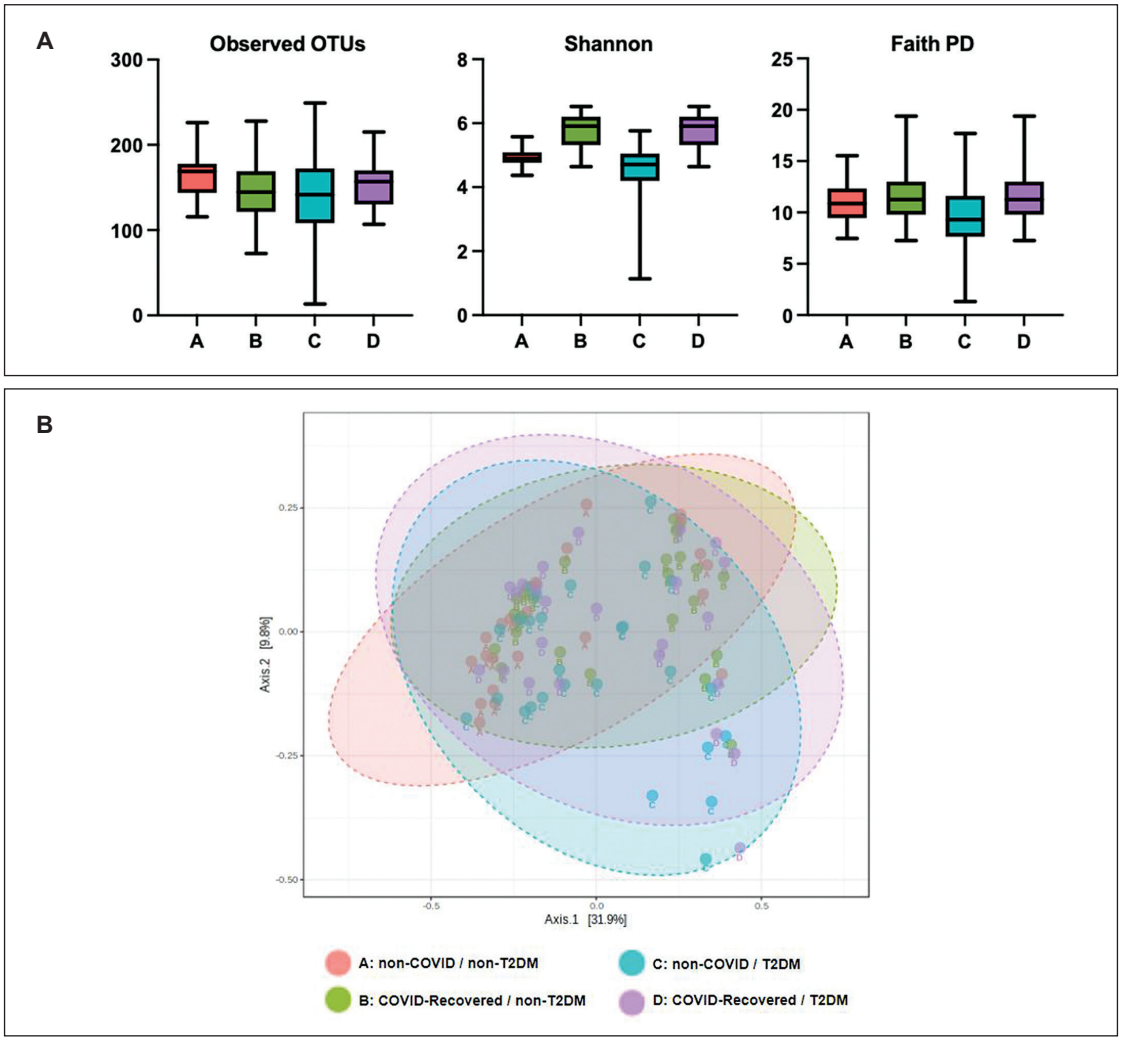


Figure 5. (A) Alpha diversity indices of the fecal microbiota among study groups. All four study groups show no significant differences in terms of their alpha diversity indices. Non-COVID/non-T2DM (A), COVID-recovered/non-T2DM (B), non-COVID/T2DM (C) and COVID-recovered/T2DM (D). **(B)** Principal coordinate analysis to differentiate among study groups. PERMANOVA analysis revealed *p*-value: 0.009, R-squared: 0.05403 and F-value: 1.8277. Non-COVID/non-T2DM (A), COVID-recovered/non-T2DM (B), non-COVID/T2DM (C) and COVID-recovered/T2DM (D).

This figure was generated using Microbiome Analyst.

Functional characterization of the gut microbiome

PICRUSt2 analysis between the non-COVID/non-T2DM group (A) and the COVID-recovered/non-T2DM group (B) revealed several differentially active pathways (Figure 6A). Glycan biosynthesis and metabolism was found to be more active for the gut microbiome of non-COVID/non-T2DM group (A), while amino acid metabolism, membrane transport and environmental adaptation were found to be more active for the gut microbiome of COVID-recovered/T2DM group (B).

PICRUSt2 analysis between the non-COVID/T2DM group (C) and the COVID-recovered/T2DM group (D) revealed several differentially active pathways (Figure 6B). Mismatch repair, folate biosynthesis and propanoate metabolism were predicted to be more active for the gut microbiome of group C, while bacterial chemotaxis and glycerophospholipid metabolism were found to be more active for the gut microbiome of group D.

DISCUSSION

Diet

Diet is a strong modifier of the gut microbiome composition. It is involved with the host immune system directly via bacterial cellular molecules or indirectly via the production of soluble bioactive compounds, such as SCFAs.[15-17] Furthermore, it has been shown that short-term alteration of diet would reproducibly alter the human gut microbial composition.[18] The only macronutrient found to be significantly different for dietary consumption is protein. This may contribute to the observed differentially abundant taxa, as protein consumption is positively associated with overall microbial diversity, and depending

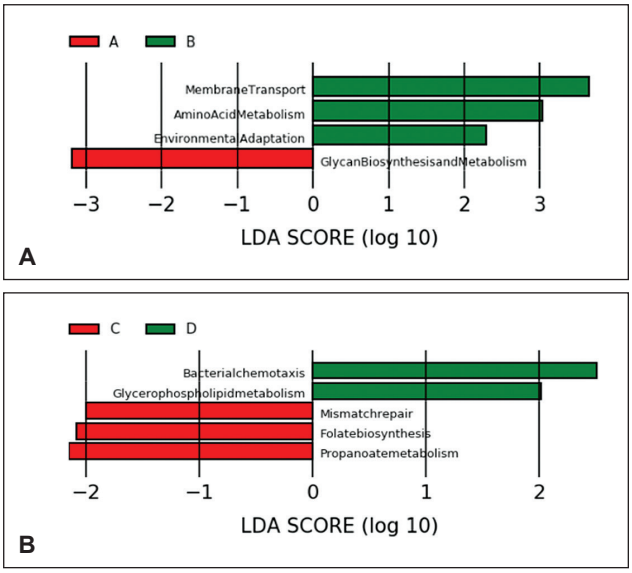


Figure 6. (A) PICRUSt2 results at KEGG metabolic pathway analysis level 2 for study groups A and B. Linear discriminant analysis (LDA) combined with effect size measurements (LEfSe) showing predicted functions for the gut microbiome of study groups A and B. **(B)** PICRUSt results at KEGG metabolic pathway analysis level 3 for study groups C and D. Linear discriminant analysis (LDA) combined with effect size measurements (LEfSe) showing predicted functions for the gut microbiome of study groups C and D. A *p*-value of <0.05 and 2.0 or higher LDA score were considered significant in Kruskal–Wallis.

This figure was generated using EasyMAP.

on the source of protein, some microbial taxa may be enhanced or reduced.[19]

Age

This study purposely used an age range of 30 to 59 in the effort to control the effect of age on the gut microbiome. The rationale for this range is that the T2DM population starts to increase in the 30s.[10] Furthermore, the adult-type gut microbiome remains stable and only starts to decay after the 60s.[10] While there is significant differences in age across the study groups (Table 1), all participants included are in the same age category, minimizing the effect of age on the results.

Identified potential biomarkers

Parabacteroides belongs to the phylum Bacteroides, and it has been described to break down branched amino acids. Previous studies have also characterized the genus *Parabacteroides* as inversely correlated with insulin resistance, and was shown to be relatively reduced among T2DM individuals when compared with non-T2DM controls.[20,21] Given these, the fact that *Parabacteroides* was found to be significantly enriched for the non-COVID/T2DM (C) and COVID-recovered/T2DM (D) is intriguing. This may be explained by the fact that metformin intake is associated with enrichment of *Parabacteroides*.[22] In addition to this, metformin intake has also been reported to be associated with enrichment of *Akkermansia, Bacteroides, Phascolarctobacterium* and *Coriobacterium* and reduction of *Bifidobacterium*, *Clostridium* and *Dorea*.[22-24] Taking these observations into account, COVID-19 may still have some influence over the gut microbial composition especially for the COVID-recovered/non-T2DM group (B). It can be deduced, however, that COVID-19 may not have pushed the T2DM group D into further dysbiosis.

Roseburia belongs to the phylum Firmicutes. It is described to be short-chain fatty acid producers impacting colonic motility, immunity and anti-inflammation.[25,26] Both *Roseburia* and *Parabacteroides* were previously identified as biomarkers for COVID-19 severity. De Jesus and Dalmacio found that both *Roseburia* and *Lachnospiraceae* to be reduced among individuals with active severe COVID-19 and is relatively enriched for individuals with only active asymptomatic, mild and moderate COVID-19.[7] It is important to note that almost all of the participants recruited in this study had asymptomatic, mild and moderate COVID-19. The fact that *Roseburia* and *Lachnospiraceae* are found to be enriched among the COVID-recovered/non-T2DM (B) and COVID-recovered/T2DM (D) may have been a protective factor during the COVID-19 infection, protecting these individuals from severe COVID-19.

Alpha and beta diversity

Alpha diversity indices across all four groups were not found to be significantly different (Figure 5A). While a different alpha diversity is suggestive of an altered gut microbial profile, a similar alpha diversity does not always reflect a similar gut microbial profile. Similar alpha diversity suggests similar species diversity within the study groups.

Beta diversity, on the other hand, aims to characterize how similar or different groups or communities are. The Principal Coordinate Analysis plot (Figure 5B) revealed significant clustering between the non-T2DM groups and the T2DM groups. This supports the notion that the COVID-recovered/non-T2DM group (B) have a gut microbial structure that resembles that of the non-COVID/non-T2DM group (A), and that these two groups have considerable non-overlapping areas with the two T2DM groups C and D. This reflects the different gut microbial structure present for the two T2DM groups. This observation is consistent with the widely known gut microbial differences attributed to T2DM. While subtle differences may still be appreciated, it is evident that between the two variables, T2DM has a stronger influence on the gut microbiome compared with a history of COVID-19 infection. Findings from this study do not support the hypothesis that COVID-19 causes further dysbiosis among individuals with T2DM. This observation should take into consideration that most of the participants of this study only had mild disease of COVID-19 and at the time of recruitment, none of the participants exhibited Post-Acute COVID-19 syndrome. There is literature to support that having a more severe

clinical course of COVID-19 or the presence of post-acute-COVID-19 syndrome symptoms would potentially have a pronounced influence on the gut microbial structure that may persist months after the acute COVID-19 infection.[27-29]

Gut microbial function

Metabolic pathways predicted to be differentially active between the gut microbiome of groups A and B, are illustrated in Figure 6A. Glycans are building blocks of mucins, which are the main structural component of mucus and play a critical role in the interaction between microbes and epithelial surfaces.[30] Certain members of the gut microbiome interact with the host by metabolizing mucins, activating immunity by mucin degradation.[31] Likewise, amino acid metabolism, found to be more active for the gut microbiome of the COVID-recovered/non-T2DM group (B) can have either positive or negative effects on the host.[32] Some members of the gut microbiome are recognized as amino-acid fermenters, including *Clostridium*, *Bacillus-Lactobacillus-Streptococcus* groups and *Proteobacteria*. These bacteria are likely to contribute to protein digestion and subsequent absorption in the GI tract.

Metabolic pathways predicted to be differentially active between the gut microbiome of groups C and D, are illustrated in Figure 6B. Notably, glycerophospholipid metabolism is more active for the gut microbiome of the COVID-recovered/T2DM group (D). This pathway has been previously associated with depression, by modulating the gut-brain axis.[33,34] This is an interesting finding considering that there are reports linking Post-COVID-19 with depression.[35] On the other hand, folate synthesis and propanoate metabolism are found to be more active for the gut microbiome of the non-COVID/T2DM group (C). Folate is important for several metabolic processes including one-carbon transfer, methylation metabolism and the biosynthesis of thymidylate, purines and several amino acids.[36] Bacterial folate has previously been suggested as a potential nutrition source for the host.[37] The gut microbiota ferments dietary non-digestible carbohydrates into short-chain fatty acids (SCFA), examples of which are propionate, butyrate and acetate.[38] SCFAs improve gut health through several local effects, including maintenance of intestinal barrier integrity, mucus production, and protection against inflammation.

While PICRUST analysis provides valuable insights into gut microbial function, it should be emphasized that this approach has limitations. These results must be treated as predictions and would benefit from further tests for validation.

CONCLUSION

This study aimed to characterize how COVID-19 is associated with the gut microbiome among Filipino adults with and without T2DM. *Parabacteroides* and *Roseburia* have been identified as potential biomarkers. *Parabacteroides* is found to be significantly more abundant for the T2DM groups for both with and without history of COVID-19. Furthemore, *Roseburia* is found to be differentially enriched for those with COVID-19 history, for both the T2DM and the non-T2DM groups. This may be generalized only for those who recovered from asymptomatic, mild or moderate COVID-19, and for those who do not suffer from Post-Acute COVID-19. This suggests a possible protective role of *Roseburia* for COVID-19 recovered individuals who encountered only mild COVID-19 diseases. Between COVID-19 and T2DM, principal coordinate analysis reveals that T2DM exerts a stronger influence on the gut microbiome as shown at close clustering together found for the non-COVID/T2DM (C) and COVID-recovered/T2DM (D) group. The findings from this study does not support that COVID-19 causes further gut microbial dysbiosis among individuals with T2DM.

Gut microbiome functional analysis reveals several differentially active pathways. For the non-T2DM groups, glycan biosynthesis and metabolism are found to be more active for the non-COVID/non-T2DM group (A), while amino acid metabolism, membrane transport and environmental adaptation are found to be more active for the COVID-recovered/T2DM group (B). For the T2DM groups, glycerophospholipid metabolism is more active for the COVID-recovered/T2DM group (D). On the other hand, folate synthesis and propanoate metabolism are found to be more active for the non-COVID/T2DM group (C). While these findings are insightful, PICRUST results are predictive in nature, and further studies may be pursued to validate them.

Acknowledgments
The authors thank Dr. Federico De Jesus for technical assistance in the bioinformatics analysis performed in this study.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
ADV: Conceptualization, Validation, Formal Analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **LMD:** Conceptualization, Methodology, Validation, Formal Analysis, Resources, Writing – review and editing, Supervision.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
The authors declare no conflict of interest.

Funding Source
This project is funded by the Department of Science and Technology through the Philippine Council of Health Research and Development.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Prevalence and Impact of Hypothyroidism on Glycaemic Control in Indian Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Abstract

Objectives. This study aimed to determine the prevalence of hypothyroidism in Indian patients with T2DM and explore its impact on glycemic control and comorbidities.

Methodology. This cross-sectional study involved 218 patients with T2DM attending a tertiary care centre. Patient demographics, comorbidities, and blood samples were collected to measure glycosylated haemoglobin (HbA1c) and thyroid-stimulating hormone (TSH) levels. Patients were classified as euthyroid, hyperthyroid, or hypothyroid based on TSH levels. A sub-analysis compared demographic and biochemical parameters between euthyroid and hypothyroid groups.

Results. The study included 218 patients with T2DM with a mean age of 57.6 ± 11.1 years, and a female predominance (54.1%). The prevalence of hypothyroidism was 58.7%, higher among females. No significant differences in comorbidities or HbA1c levels were observed between euthyroid and hypothyroid patients. Among patients with HbA1c ≥6.4%, women showed a higher prevalence of hypothyroidism.

Conclusion. The high prevalence of hypothyroidism among patients with T2DM, particularly in females, underscores the need for routine thyroid function screening in this population. Despite the lack of significant differences in comorbidities or glycaemic control between euthyroid and hypothyroid patients seen in this study, the potential impact of thyroid dysfunction on diabetes management warrants further investigation.

Key words: type 2 diabetes mellitus, hypothyroidism, thyroid dysfunction, glycaemic control, comorbidities

INTRODUCTION

The burden of type 2 diabetes mellitus (T2DM) in India is escalating, with projections estimating 134 million cases by 2045, highlighting a significant public health challenge.[1] Contributing factors include demographic shifts such as urbanization and an aging population, alongside lifestyle changes characterized by increased prevalence of obesity, physical inactivity, and poor dietary habits.[2] Current prevalence rates indicate a concerning trend, with diabetes distress affecting approximately 33% of patients with T2DM, which complicates management and adherence to treatment.[1] Additionally, the rise in gestational diabetes mellitus (GDM) from 0.53% to 0.80% between 2015-2021 suggests a growing risk for future onset of T2DM in mothers and their offspring.[3]

The relationship between type 2 diabetes mellitus and thyroid dysfunction, particularly hypothyroidism, is well-documented, with hypothyroidism being the most prevalent thyroid disorder among patients with diabetes. Studies indicate that individuals with T2DM exhibit a higher prevalence of thyroid disorders compared to the general population, with subclinical hypothyroidism being notably common, affecting approximately 12-15% of patients with diabetes.[4,5] Metabolic disturbances inherent in diabetes, along with poor glycemic control, have been linked to an increased risk of thyroid dysfunction.[4,5] Specifically, elevated thyroid-stimulating hormone (TSH) levels correlate with poor metabolic control, suggesting that thyroid dysfunction may exacerbate diabetic complications.[6] Furthermore, the interplay between insulin and thyroid hormones indicates that metabolic syndrome may predispose individuals to thyroid disorders, highlighting the importance of screening for thyroid dysfunction in patients with T2DM to optimize management and improve outcomes.[6,7]

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Rawat and Rawat.
Received: january 9, 2025. Accepted: March 11, 2025.
Published online first: April 26, 2026.
https://doi.org/10.15605/jafes.041.01.4989

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Identifying hypothyroidism in patients with diabetes is crucial due to the significant impact on glycemic control and cardiovascular risk. Hypothyroidism, found in 6-20% of patients with type 2 diabetes mellitus, exacerbates metabolic complications, including increased rates of retinopathy (13.8%), nephropathy (19.04%), and neuropathy (25%) in individuals with hypothyroidism compared to their non-hypothyroid counterparts.[5] The prevalence of hypothyroidism in patients with T2DM varies globally, with studies indicating rates of 14% in Indian populations.[8] However, discrepancies exist, as some studies report lower prevalence rates, highlighting the need for region-specific research to understand local variations better.[9] Furthermore, hypothyroidism is associated with metabolic syndrome and increased cardiovascular risks, thus necessitating routine screening for thyroid dysfunction in patients with diabetes to facilitate early intervention.[8-10]

Studying the prevalence of hypothyroidism in Indian patients with T2DM is essential due to the significant impact on diabetes management and outcomes. Despite global evidence of a strong link between T2DM and hypothyroidism, large-scale studies in India are lacking, and existing data show inconsistent findings. Identifying hypothyroidism in patients with diabetes could lead to tailored treatment strategies and better management of comorbidities. This study aims to determine the prevalence of hypothyroidism in Indian patients with diabetes and the relationship of hypothyroidism with diabetes-related complications, co-morbidities and health outcomes.

METHODOLOGY

Study design and population

This cross-sectional study was conducted among patients with T2DM who attended a primary care centre in India. Participants were included if they had a confirmed diagnosis of T2DM and were aged 18 years or older, irrespective of their pregnancy status. Patients with type 1 diabetes, those on thyroid hormone therapy, and those with a history of thyroid surgery or radiotherapy were excluded from the study. Individuals meeting the inclusion criteria were continuously recruited from June 2021 to April 2024. Only individuals with complete data were included in the study. The study was conducted in accordance with the Declaration of Helsinki. All the patients were oriented about the study, informed oral consent was obtained, and institutional approval for using the data for the current study was received.

Sample size estimation

Considering the prevalence of thyroid disorders in 60% of individuals with T2DM at 95% CI and with a finite sample size of 200, we estimated a margin of error in the range of 7%. The sample size was then estimated to be 189. To account for a 10% drop out rate, 208 was considered for the enrolment.

Data collection

Data on patient demographics, including age and gender, were collected. Information on comorbidities such as hypertension, dyslipidaemia, coronary artery disease, chronic kidney disease, and other conditions was also recorded. Potential confounders such as the duration of diabetes and a family history of thyroid disorders were also noted. Blood samples were collected after an overnight fast to measure glycosylated haemoglobin (HbA1c) and thyroid-stimulating hormone (TSH) levels. HbA1c levels were used to assess glycaemic control, and TSH levels were measured to evaluate thyroid function.

Classification and grouping

The primary outcome of the current study was to determine the prevalence of hypothyroidism in Indian patients with T2DM. The secondary outcome was to determine factors associated with the incidence of hypothyroidism in T2DM. Patients were classified into euthyroid, hyperthyroid, and hypothyroid groups based on TSH levels. Hypothyroidism was defined as TSH level >4.5 mU/L, while hyperthyroidism was defined as TSH level <0.4 mU/L. Euthyroid status was defined as TSH level within the normal reference range (0.4-4.5 mU/L).

Sub-analysis

A sub-analysis was conducted to compare demographic and biochemical parameters between euthyroid and hypothyroid patients. Gender distribution, age, family history, co-morbidities, and HbA1c levels were analyzed. Further comparisons were made between euthyroid and hypothyroid patients with HbA1c ≥6.4%.

Statistical analysis

Data were presented as mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Distributions of variables were assessed. The chi-square test was used to compare categorical variables, and the independent t-test was used for continuous variables. Analyses were performed using available-case data for each variable. A p-value <0.05 was considered statistically significant.

RESULTS

The current study included 218 patients with T2DM (Table 1), with a mean age of 57.6 ± 11.1 years and M:F ratio of 0.85:1. HbA1c data were available for 208 of 218 patients. For subgroup analyses, hyperthyroid patients (n = 5) were excluded. Among the remaining patients, HbA1c values were available for 203 individuals. Majority had a diabetes duration of 1-5 years. Comorbidities were present in 145 (66.5%) patients, of which hypertension was the most common, found in 84/145 (57.9%) patients, followed by dyslipidaemia in 36/145 (24.8%) patients and coronary

artery disease in 28/145 (19.3%) patients. The average HbA1c level was 7.8 ± 1.5%, with 87.5% of patients having HbA1c >6.4%, indicating a high proportion of patients with poor glycaemic control.

A family history of thyroid disorders was observed in 89 (40.8%) patients. The prevalence of hypothyroidism among our cohort was 58.7%. Following this, a sub-analysis was conducted to compare the demographic and biochemical parameters between euthyroid and hypothyroid patients (Table 2). The prevalence of hypothyroidism was higher among females compared to males with T2DM. No significant differences were observed in the comorbidity profile or HbA1c levels between euthyroid and hypothyroid patients (Table 2; Supplement Table 1).

Among patients with HbA1c ≥6.4%, females demonstrated a higher prevalence of hypothyroidism. Additionally, five out of six patients with a history of coronary artery bypass surgery were hypothyroid.

Table 1. Demographic and clinical profile of the study population

Total population (N)	218
Age	57.6 ± 11.1
Age [Median IQR]	58.0 [50.0, 66.0]
Age distribution (in year)	
18-30 – Young adults	4 (1.8%)
31-50 – Middle-aged adults	51 (23.4%)
51-70 – Older adults	140 (64.2%)
>70 – Elderly	23 (10.6%)
Gender distribution	
Male	100 (45.9%)
Female	118 (54.1%)
Family history of thyroid disorders	89 (40.8%)
Duration of T2DM	6.3 ± 6.8
Duration of T2DM	
<1 year	32 (14.7%)
1-5 years	102 (46.8%)
>5 years	82 (37.6%)
Number of comorbidities	
Zero comorbidities	73 (33.5%)
Single comorbidities	45 (20.6%)
Double comorbidities	81 (37.2%)
Triple comorbidities	19 (8.7%)
Number of individuals with comorbidities	145
Comorbid conditions	
Hypertension	84/145 (57.9%)
Dyslipidaemia	36/145 (24.8%)
Coronary artery disease	28/145 (19.3%)
Chronic kidney disease	23/145 (15.9%)
Anaemia	22/145 (15.2%)
Bronchial asthma	1/145 (0.7%)
Irritable bowel syndrome	1/145 (0.7%)
Osteoarthritis	1/145 (0.7%)
Insulin Resistance	2/145 (1.4%)
Benign Prostatic Hyperplasia in men	64/100 (64%)
Coronary artery bypass graft surgery	8 (3.7%)
N	208
HbA1c (in %)	7.8 ± 1.5
HbA1c [Median IQR]	7.4 [6.7, 8.4]
HbA1c Distribution	
<5.7% – Non-diabetic	4 (1.9%)
5.7% to 6.4% – Prediabetes	22 (10.6%)
>6.4% – Diabetes	182 (87.5%)
N	218
TSH (in mU/L)	4.1 ± 2.5
TSH [Medin IQR]	3.3 [2.4, 5.1]
Euthyroid	85 (39.0%)
Hyperthyroid	5 (2.3%)
Hypothyroid	128 (58.7%)
FT3	3.4 ± 1.0
FT4	1.4 ± 0.5

HbA1c – Haemoglobin A1c; TSH – Thyroid Stimulating Hormone

Table 2. Comparison of demographics and biochemical parameters between euthyroid and hypothyroidism patients with T2DM

	Euthyroid	**Hypothyroid**	***P*-values**
Total population (N)	85	128	
Age	58.3 ± 11.3	57.1 ± 11.1	0.443#
Age [Median IQR]	60.0 [51.5, 66.5]	57.0 [50.0, 65.0]	
Age distribution (in year)			
18-30 – Young adults	1 (1.2%)	3 (2.3%)	0.820*
31-50 – Middle-aged adults	18 (21.2%)	32 (25.0%)	
51-70 – Older adults	57 (67.1%)	79 (61.7%)	
>70 – Elderly	9 (10.6%)	14 (10.9%)	
Gender distribution			
Male	54 (63.5%)	45 (35.2%)	<0.001*
Female	31 (36.5%)	83 (64.8%)	
Family history of thyroid disorders	35 (41.2%)	51 (39.8%)	0.194*
Comorbidities			
No comorbidities	34 (40.0%)	40 (31.3%)	0.190*
Hypertension	28 (32.9%)	53 (41.4%)	0.211*
Benign prostatic hyperplasia	21 (24.7%)	43 (33.6%)	0.164*
Dyslipidemia	10 (11.8%)	25 (19.5%)	0.133*
Coronary artery disease	12 (14.1%)	15 (11.7%)	0.603*
Chronic kidney disease	9 (10.6%)	14 (10.9%)	0.936*
Anaemia	8 (9.4%)	13 (10.2%)	0.857*
Bronchial asthma	0 (0.0%)	0 (0.0%)	-
Irritable bowel syndrome	1 (1.2%)	0 (0.0%)	-
Osteoarthritis	0 (0.0%)	1 (0.8%)	-
Insulin Resistance	0 (0.0%)	2 (1.6%)	-
Coronary artery bypass graft surgery (N = 6)	2 (33.3%)	4 (66.7%)	0.250*
Other comorbid conditions			
Zero comorbidities	34 (40.0%)	38 (29.7%)	0.329*
Single comorbidities	19 (22.4%)	26 (20.3%)	
Double comorbidities	26 (30.6%)	52 (40.6%)	
Triple comorbidities	6 (7.1%)	12 (9.4%)	
N	83	120	
HbA1c (in percentage)	7.8 ± 1.6	7.7 ± 1.5	0.650#
HbA1c [Median IQR]	7.4 [6.8, 8.9]	7.3 [6.7, 8.4]	
N	83	120	
HbA1c (in percentage)			
<5.7% – Non-diabetic	2 (2.4%)	2 (1.7%)	0.846*
5.7% to 6.4% – Prediabetes	8 (9.6%)	14 (11.7%)	
>6.4% – Diabetes	73 (88.0%)	104 (86.7%)	

HbA1c – Haemoglobin A1c; TSH – Thyroid Stimulating Hormone, * Chi-square test; # Students t-test

DISCUSSION

The current study highlights the burden of thyroid disorders among Indian patients with T2DM. Majority of patients (~64%) in the study were within 50 to 70 years of age with a slight female predominance (M:F ratio – 0.85: 1.0). This age distribution aligns with the general epidemiology of T2DM, where the risk of thyroid disorders increases with age, particularly among individuals over 50.[8] The slight female predominance is consistent with previous studies, which have also reported higher rates of thyroid dysfunction among females with T2DM (31.4%) due to the autoimmune nature of thyroid disease, which is more common in females.[10]

Hypertension was the most common comorbidity (in 58%), followed by dyslipidaemia (24.8%) and coronary artery disease (19.3%) (Table 1). Hypertension and dyslipidemia are common comorbidities in patients with T2DM and contribute significantly to cardiovascular risk.[11-13] These conditions are interrelated, as both hypertension and dyslipidemia are modifiable risk factors that exacerbate cardiovascular disease (CVD) risk in patients with T2DM.[14]

A family history of thyroid disorders was observed in 89 (40.8%) patients. The prevalence of hypothyroidism in our study population was 58.7%. In India, the reported prevalence of hypothyroidism in the adult population is about 10.8% and increases to about 13% in the older population.[8] Another study reported a 28% prevalence of hypothyroidism among individuals with metabolic syndrome, indicating a higher burden in this subgroup.[14] Due to the practical and logistical constraints associated with recruitment and resource availability, a target population of approximately 200 individuals was deemed to be feasible. Therefore, the sample size estimation was performed within this limit to ensure that the study remains achievable within the given time frame and setting. While this may limit the statistical power to detect smaller effect sizes, it can still yield meaningful preliminary insights for exploratory or pilot studies within specific or limited populations. A study reported that individuals with a family history of thyroid disorders had a nine-fold risk of developing hypothyroidism.[15] This reflects a well-established risk factor for hypothyroidism due to shared genetic predispositions and lifestyle factors.[15]

About 88% of our study participants had poor glycemic control. This finding aligns with prior studies that also report elevated HbA1c levels [HbA1c ≥7% (OR = 4.3, p = 0.025)][9,16] and poor glycemic control (ranged between 45.2% and 93%)[17] in a significant proportion of patients with T2DM, often exacerbated by co-existing conditions such as hypothyroidism. This highlights the potential role of hypothyroidism in complicating glycemic control, as thyroid dysfunction can adversely affect glucose metabolism and insulin sensitivity.[7,18]

In a sub-analysis conducted to compare the demographic variables between euthyroid and hypothyroid patients, the prevalence of hypothyroidism was higher among females compared to males (Table 2). Furthermore, among patients with uncontrolled HbA1c ≥6.4%, females demonstrated a higher prevalence of hypothyroidism (Supp. Table 1). This aligns with existing research that shows a gender disparity in thyroid disorders, with higher rates of hypothyroidism in females.[10]

The observation that no significant differences were observed in the comorbidity profile or HbA1c levels between euthyroid and hypothyroid patients is consistent with previous findings that indicate females with diabetes are at increased risk for thyroid dysfunction, particularly when glycemic control is poor.[10,17] The finding of about 83% (5/6) of patients with a history of CABG surgery afflicted with hypothyroidism is consistent with research linking hypothyroidism to increased cardiovascular risk, including the likelihood of undergoing coronary artery bypass grafting.[19]

Screening for thyroid disorders using a symptom-based approach is cost-effective. However, given that thyroid dysfunction may be asymptomatic, and with thyroid screening becoming more cost-effective in India, it is important for physicians to implement routine thyroid screening among patients with T2DM. The limitations of the current study include a single center study design and lack of long-term follow-up among patients. Future multi-centric large scale longitudinal studies may shed light on the causal relationships between thyroid dysfunction and diabetes outcomes among Indian patients with diabetes.

Limitations

The study findings are limited by relatively small sample size and absence of long-term follow-up due to feasibility constraints and resource availability. Additionally, potential confounding factors such as medication use, duration of diabetes, and lifestyle parameters were not extensively explored. This is a single center study, which may limit the generalizability of the results to broader populations across different regions of India.

CONCLUSION

This study highlights the significant prevalence of hypothyroidism among patients with T2DM in India, particularly among females, consistent with global trends of higher thyroid dysfunction rates in females. Although no significant differences were observed in glycemic control or comorbidity profiles between euthyroid and hypothyroid patients, the high prevalence of hypothyroidism, especially in those with uncontrolled hyperglycemia, underscores the need for routine thyroid screening in patients with T2DM. This approach could facilitate early intervention, optimizing diabetes management and potentially reducing the risk of diabetes-related complications. The findings also

emphasize the importance of gender-specific strategies in managing T2DM and associated comorbidities.

Acknowledgments
The authors would like to thank Rawat Medicare Center for their assistance in publishing this data.

Statement of Authorship
All authors fulfilled ICMJE authorship criteria.

CRediT Author Statement
JR: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft preparation, Writing – review and editing; **AR:** Methodology, Formal analysis, Data curation, Writing – original draft preparation, Writing – review and editing.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Prevalence and Factors Associated with Diabetes Related Emotional Distress (DRED) Among Filipino Adult Patients with Type 2 Diabetes Mellitus Using A Validated Filipino Version of the Diabetes Distress Scale (DDS)

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Abstract

Background. Diabetes related emotional distress (DRED) is important in diabetes management. There are limited studies involving diabetes distress and its association with glycemic control and other clinicodemographic factors among Filipinos.

Objective. This study aimed to translate the Diabetes Distress Scale (DDS) into Filipino and validate this version among Filipino adult patients with type 2 DM and assess the prevalence of DRED and its association with glycemic control and other factors.

Methodology. A Filipino DDS was constructed through forward and backward translation of the English version and was validated. A subsequent cross-sectional study was conducted among 186 individuals with type 2 diabetes in a single-center tertiary hospital. The prevalence of DRED and its association with HbA1c level and other related factors were assessed.

Results. The overall prevalence of DRED for this study was 34.41% with a mean overall score for the DDS of 2.02. Age (AOR 0.95, 95% CI 0.93–0.98; p = 0.002), higher medication burden, (AOR 1.33, 95% CI 1.01–1.77; p = 0.043) and peripheral artery disease (AOR 6.03, 95% CI 1.79–23.29; p = 0.005) were predictors of DRED.

Conclusion. This Filipino version of the DDS showed that it is a valid instrument in the assessment of diabetes related distress among Filipino patients with type 2 diabetes. Diabetes distress scores were not associated with glycemic control. A younger age of diagnosis of diabetes, a history of PAD, and higher medication burden were found to be associated with development of DRED.

Key words: Diabetes Distress Scale, Filipino, validity, type 2 diabetes, diabetes-related distress

INTRODUCTION

Living with diabetes can be influenced by psychosocial factors that may affect both clinical outcomes and psychological well-being. Adjusting to the demands of diabetes management involving lifelong adherence to medications, dietary modifications, regular exercise, glucose monitoring, surveillance for complications, and medical follow-up may place a significant psychological burden on individuals.[1] This burden is reflected in the high prevalence of depressive symptoms among patients with diabetes which may occur in 1 out of 4 patients with diabetes, but only 10-15% are diagnosed with clinical depression.[2] In a local study in the Philippines, the prevalence of depression among patients with type 2 diabetes mellitus was 19.9%.[3] Patients with diabetes who already had depression were found to have worse glycemic control, and have two times higher risk of mortality compared to those without depression.[4]

While depression is an important comorbidity, literature differentiates it from a distinct condition termed as diabetes related emotional distress (DRED) or diabetes distress (DD). Diabetes related emotional distress refers to the significant negative psychological reactions related to the emotional burdens and worries specific to an individual's experience in the daily self-management, social stigma, financial implications, and the prospect of long-term complications involved in diabetes. It pertains to symptoms that overlap with depression but does not meet the criteria for major depressive disorder and is regarded as a separate construct which requires different assessment and management strategies.[5-7]

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Mirano et al.
Received: August 15, 2025. Accepted: October 11, 2025.
Published online first: April 30, 2026.
https://doi.org/10.15605/jafes.041.01.6243

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The reported prevalence of DRED is approximately 36% among people with type 2 diabetes. Higher rates were observed among populations with a greater proportion of women and those with comorbid depressive conditions.[8,9] Increased prevalence has also been reported among patients with diabetic complications, poor glycemic control, younger age, lack of partners, and non-white ethnicity.[9,10] A cross-sectional study done locally showed a higher prevalence of 42.6% with a majority of the study population being young, pre-obese, and a having a diabetes duration of approximately 5 years.[11]

Multiple sociodemographic, clinical, and behavioral factors have been linked to DRED, including early life and environmental exposures, lower socioeconomic status, living alone, limited social support, and lower educational attainment.[2,12,13] Behavioral factors such as smoking and alcohol use, along with female sex, higher HbA1c, elevated triglycerides, more diabetes-related complications, and higher BMI, also increase risk.[13–15] Overall, patients with greater clinical burden and extensive self-management demands are at higher risk for developing DRED.

High levels of DRED have been associated with poorer self-management behaviors, including suboptimal medication adherence, unhealthy dietary patterns, and reduced physical activity which may result to a higher A1C and lower self-efficacy. Elevated DRED was linked with higher HbA1c values, higher depression scores, and heightened concerns regarding eating, body shape, and weight concerns as well as poorer psychological well-being, especially among younger patients.[12,15,16] Although one local study revealed no significant association between DRED with diabetes self-care behavior or level of glycated hemoglobin, a trend toward higher HbA1c values was observed among participants reporting diabetes distress, suggesting a potential indirect effect on glycemic outcomes.[11]

The American Diabetes Association recommends the routine monitoring for the presence of diabetes distress using person-based diabetes-specific validated measures.[17] The two most widely used scales are the Problem Areas in Diabetes (PAID) Scale and Diabetes Distress Scale (DDS). The PAID scale is a 20 – item instrument focused on diabetes related emotional concerns and has been found to have a high sensitivity and specificity.[18] The DDS scale on the other hand is comprised of 17 questions, which are separated into four different subscales: 1) regimen-related distress; 2) physician-related distress; 3) emotional burden; and 4) interpersonal distress. It is a brief self-reporting measure of diabetes-related emotional distress that identifies a diabetic patient's concerns about disease management, emotional burden, social support, and health care accessibility.[5] A study found that while the PAID Scale emphasizes emotional concerns and correlates more with dysfunctional coping, quality of life, and depressive symptoms, the DDS focuses on physician-related factors and self-management distress and is more strongly associated with diabetes self-care and metabolic outcomes.[19]

In the Philippines, there has been no locally adapted scale to screen for diabetes distress among patients with type 2 DM. Local data on the association between DRED and glycemic outcomes and other related factors remain limited. This study therefore aimed to translate the DDS to Filipino and determine the association of DDS with metabolic outcomes among Filipinos with type 2 diabetes mellitus.

OBJECTIVES

As a general objective, this study aims to determine the prevalence of diabetes related emotional distress and its association with glycemic control and other related factors of adult Filipinos with type 2 Diabetes Mellitus at St Luke's Medical Center, Quezon City using a validated Filipino version of the Diabetes Distress Scale. Specifically, it aims: 1) to determine the association between diabetes distress status and glycemic control (HbA1c) as well as clinicodemographic factors such as age, sex, level of education, BMI, duration of diabetes, DM medications, and presence of macrovascular or microvascular complications using a Filipino version of the Diabetes Distress Scale; 2) to determine the prevalence of diabetes-related emotional distress overall and across DDS subdomains including, emotional burden, physician-related distress, regimen-related distress, and interpersonal distress; 3) to translate and validate the clinimetric properties of the Diabetic Distress Scale, specifically its content validity, face validity, cross-cultural validity, and its reliability.

METHODOLOGY

Phase I: Translation and validation of the Diabetes Distress Scale

The English version of the questionnaire was forward translated to Filipino by two separate individuals: one professor from the University of the Philippines Department of Linguistics and one physician expert in the medical field particularly in diabetes who is fluent in both English and Tagalog. The two versions of the forward translated questionnaires were then synthesized by the research team. Any edits were incorporated into the questionnaire. The synthesized forward translated questionnaire was then back translated to English. Similarly, two translators were assigned to generate two separate back translations. The first translator was a professional translator who is fluent in both English and Filipino from the UP College of Linguistics and who has not read the original questionnaire. The second translator was again another physician who was bilingual (proficient in English and Filipino). The two versions of the back translated questionnaires were once again synthesized by the research team and qualitatively checked against the original questionnaire. Further revisions were done to the translated scale.

Method of validation of translated Filipino Diabetes Distress Scale

A minimum of 3 experts but ideally 8-12 experts was required to assess the content validity index of the translated questionnaire.[20] To fully assess for content validity, questions were asked from the expert panel, based on the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) criteria for content validity (Appendix A).

A minimum of 10 patients with type 2 diabetes mellitus was required for this study to assess the face validity of the translated scale.[21] They were asked to evaluate the translated scale with the following guide questions:[22]

A. Description of the survey questionnaire: Are the title and instructions clear and easy to follow?
B. For each item: The respondents will be asked the following questions, using the "think aloud testing" technique:
   i. Do you have difficulty answering each question?
   ii. If yes, how will you restate them?
   iii. Are the responses difficult to understand?
   iv. If yes, how will you restate them?
   v. Are the questions relevant to your condition?
   vi. Are the questions offensive/upsetting to you?
   vii. If yes, how will you restate them?

Feedback was organized according to themes. Major remarks regarding face validity were noted. The translated scale was reevaluated using the feedback pertaining to content, grammar, cultural differences and was further modified to obtain the final translated version of the DDS (Appendix B).

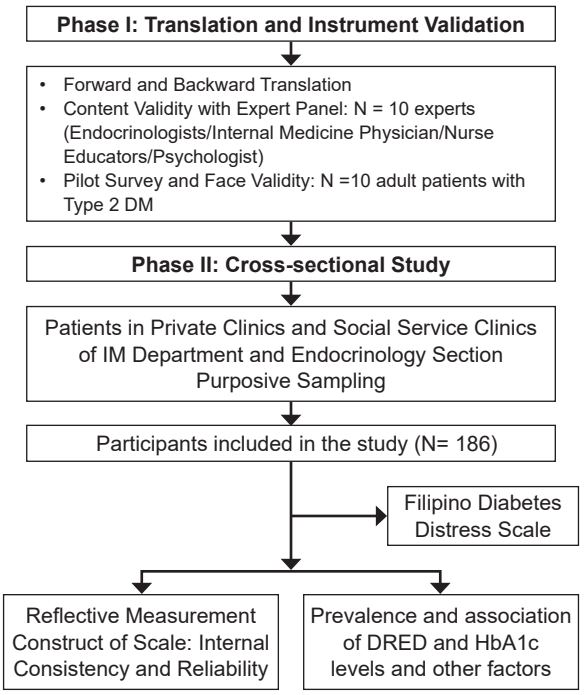


Figure 1. Flowchart of study design.

Phase II: Cross-sectional study

The final version of the scale was used in a cross-sectional, analytical study on the Association of Diabetes Related Emotional Distress with Glycemic Control Among Filipino Adult Patients with Type 2 Diabetes Mellitus in St. Luke's Medical Center (Figure 1). Sample size was computed using two approaches to ensure adequate power for both reliability and association analyses. For the logistic regression analysis assessing associations, a minimum of 115 participants was calculated using a 5% significance level, 80% power, and an assumed odds ratio of 3.0, representing a large effect size with the following equation:

Sample Size based on odds ratio: [23]

$$n \geq \frac{\left(z_{1-\alpha/2}+z_{1-\beta}\right)^2}{P(1-P)E^2}$$

where $P = \frac{OR}{1+OR}$ and $E = ln(OR)\left(\frac{\sqrt{3}}{\pi}\right)$

Legend:
$z_{1-\alpha/2}$ = 1.96
$z_{1-\beta}$ = 0.842 or 1.282
OR = 3.00 (assuming that this will have large effect)[24]

For the internal consistency analysis, a minimum of 104 participants was required, based on a 5% significance level, 80% power, and an assumed Cronbach's α of 0.8, which is within the acceptable reliability range using the following equation: [25]

$$n \geq \frac{2k}{k-1} \times \frac{\left(Z_{\alpha/2}+Z_{\beta}\right)^2}{ln(\delta)^2} + 2$$

where $\delta = \frac{1-c}{1-p_k}$

Legend:
k = number of items = 17
c = lowest acceptable Cronbach alpha = 0.7
p_k = expected Cronbach alpha = 0.8
$z_{\alpha/2}$ = standard normal distribution corresponding to the specified size of the critical region (5%) = 1.960
z_{β} = standard normal distribution corresponding to the chosen level of power (80%) = 0.842

The larger of the two estimates was adopted to ensure sufficient power for all planned analyses.

Study participants who were recruited included private and social service patients seen face-to-face at the outpatient department of Internal Medicine and Endocrinology of the St. Luke's Medical Center in the year 2022 who were

diagnosed with type 2 diabetes mellitus and met the inclusion criteria. A member of the investigator team from the Department of Internal Medicine recruited patients with diabetes mellitus. Once recruited, the investigators obtained the subject's consent using a form approved by the IERC prior to participation in the study.

The inclusion criteria for the study consisted of Filipino adults 18 years old and above who were diagnosed with type 2 diabetes mellitus, with good comprehension (able to read and write) of the Filipino language, and submitted the signed Informed Consent Form (ICF). Those who were unable to understand Filipino language, critically ill and with presence of psychiatric illness were excluded from the study.

Informed consent and ethical considerations

The study protocol and informed consent form were reviewed and approved by the Institutional Review Board of St. Luke's Medical Center prior to study initiation. Eligible patients from the Internal Medicine and Endocrinology outpatient private and social service clinics were approached for participation. All participants underwent an informed consent process wherein the nature, procedures, and potential risks of the study were fully explained, and written informed consent was obtained prior to participation. The study was conducted in accordance with local and international ethical standards, including the principles of the Declaration of Helsinki, World Health Organization guidelines, International Conference on Harmonization, Good Clinical Practice, the Data Privacy Act of 2012 and the National Ethics Guidelines for Health Research (2017). Participant confidentiality was strictly maintained throughout the study. All data were de-identified and assigned code numbers, with the master list linking identifiers stored separately and accessible only to the research team. Physical and electronic records were securely stored and will be retained for five years before secure destruction. No personally identifiable information was disclosed outside the research team. Participants were informed of their right to withdraw at any time without penalty. No monetary compensation was provided. The study was self-funded by the authors, and no conflicts of interest were declared.

Materials and methods

Baseline characteristics of the patients were determined including age, gender, BMI, personal and social history, duration of diabetes, medications for diabetes, presence of macro/microvascular complications through an interview and cross referenced with existing clinical records. The level of DRED was measured using the Filipino Diabetes Distress Scale (Filipino-DDS), a self-administered 17-item Likert scale with each item scored from 1 (no distress) to 6 (serious distress) and the mean item score was computed by summing all item scores and dividing by the total number of items. The participants were given 5-15 minutes to answer the questionnaire by themselves. Participants who required more time were given the opportunity to complete the questionnaire at their own pace to ensure thoughtful and accurate responses. The corresponding questionnaires were then tabulated. A mean item score of <2.0 was classified as little to no distress, 2.0 – 2.9 was considered 'moderate distress,' and a mean item score >3.0 considered 'high distress.'[26] The latest HbA1c (within 3 months) was obtained from medical records. All questionnaires and clinical data were complete at the time of collection, and no missing or implausible values were identified. Completeness was verified by cross-checking patient responses with clinical records, and as such, no imputation or replacement methods were required.

Description of outcome measures

The outcome of interest was the Diabetes Distress Scale (DDS) total score measured with the validated Filipino DDS. The association of the score with clinicodemographic and metabolic factors including age, sex, level of education, BMI, duration of diabetes, DM medications, and presence of macrovascular or microvascular complications were reported as odds ratios with 95% confidence intervals.

Secondary outcomes included DDS subscale scores and the prevalence of moderate or high distress based on prespecified cut points. The clinimetric properties of the Filipino DDS were evaluated, including the content validity index, face validity, cross-cultural validity, and reliability.

Data analysis

Content validity was measured using item-level content validity index (I-CVI); the proportion of experts who agree that the item is either quite or highly relevant; items with higher than I-CVI 0.80 were accepted, while those lower were subject to discussion by the expert panel and the investigators.

The reliability of the scale was obtained using the internal consistency reliability using Cronbach's α coefficient. A Cronbach's α coefficient value less than 0.40 is considered unreliable, a value between 0.40 and 0.59 is less reliable, between 0.60 and 0.79 is reliable, and between 0.80 and 1.00 is extremely reliable. Item-total correlations, and Cronbach's alpha if item is deleted were used to conduct item analysis for the instrument. An item-total correlation is acceptable with a value no less than 0.40, as estimated by Pearson's correlation coefficient.

Descriptive statistics was used for categorical variables were frequency and percentage. Shapiro-Wilk test was used to determine the normality distribution. Continuous quantitative data that meet normality assumption were summarized using mean and standard deviation (SD), while those that do not were described using median and interquartile range. For group comparisons by diabetes-related distress [moderate to high (with distress) vs none/

low (no distress)], all variables were analyzed in categorical form, and comparisons used chi-square or Fisher's exact tests as deemed appropriate. No inferential tests on continuous outcomes were conducted.

Logistic regression was used to determine the association of clinicodemographic and metabolic factors with moderate to high diabetes-related distress (vs none/low). Crude and adjusted odds ratios with 95% confidence intervals were reported. For the multivariable analysis, all variables were entered as candidate covariates; the final model was derived using backward stepwise selection based on the Akaike information criterion. Null hypothesis was rejected at 0.05α-level of significance. Stata version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

Phase I: Translation and validation of Diabetes Distress Scale

A total of 10 experts were requested to review the translated questionnaire to assess the content validity index.[17] This pool included 5 Endocrinologists, 2 Internal Medicine Physicians, 2 Nurse educators and 1 Psychologist. All the items had high item relevance, with eight items receiving a perfect rating of 100%. The ratings ranged from highly relevant to quite relevant. There were no comments regarding the comprehensiveness of the questionnaire. Comments regarding the comprehensibility of items were about the translation. Other comments regarding the tool expressed concerns regarding the tone of the items. It was suggested to change the tone from negative to positive or neutral. It was also noted that no item mentioned specific complications of the condition.

Meanwhile, ten patients were recruited for face validity. Some of the items were perceived to have some level of difficulty (1;10%). However, all items were perceived to be important. It was mentioned that items 2 and 5 were difficult to answer due to its sensitivity with regards to patient-doctor relationship.

Phase II: Cross-sectional study

A total of 186 patients with type 2 diabetes mellitus was recruited for the study with the following characteristics (Table 1). The patients had a median age of 60 years (51-66), and majority were female (65%). Most patients had completed college education (69.35%) and were married (79.03%). The majority of patients (90.86%) were treated with oral medications. Diabetic retinopathy (30.65%), MI/CAD (24.73%), and diabetic nephropathy (21.51%) were the most common macro/microvascular complications. The majority of patients were nonsmokers (87.63%) and had a BMI in the normal range (43.01% with BMI 18.5-24.9 kg/m^2). The median HbA1c was 7.2% with a median diabetes duration of 84 months (36-135).

Internal consistency reliability of the Filipino DDS was assessed among 186 participants. Cronbach's alpha values for the four subscales ranged from 0.81 to 0.85, and the overall Cronbach's alpha for the 17 items was 0.922, demonstrating excellent internal consistency.

Table 1. Characteristics of patients with T2DM recruited (n = 186)

Continuous clinicodemographic factors	Median (IQR)
Age	60 (51-66)
Duration of diabetes, months	84 (36-135)
Systolic blood pressure (mmHg)	120 (120-130)
Diastolic blood pressure (mmHg)	80 (78-80)
Heart rate, bpm	78 (71-83)
Respiratory rate, cpm	18 (16-19)
Temperature, degrees Celsius	36.5 (36.1-36.8)
HbA1c	7.2 (6.5-8.7)
Categorical Clinicodemographic Factors	**Frequency (%)**
Sex	
Male	65 (34.95)
Female	121 (65.05)
Highest educational attainment	
Elementary	11 (5.91)
Highschool	38 (20.43)
College	129 (69.35)
Post-grad	8 (4.3)
Civil status	
Single	21 (11.29)
Married	147 (79.03)
Widowed	17 (9.14)
Separated/Divorced	1 (0.54)
DM medications	
Oral medications	169 (90.86)
Injectable medications	11 (5.91)
Insulin	69 (37.10)
Total number of DM medications	3 (2-3)
Macro/Microvascular complications	
Diabetic retinopathy	57 (30.65)
Diabetic nephropathy	40 (21.51)
Diabetic neuropathy	24 (12.9)
History of TIA/Stroke	13 (6.99)
History of MI/CAD	46 (24.73)
History of PAD	15 (8.06)
Comorbidities	
Hypertension	143 (76.88)
Dyslipidemia	149 (80.11)
Thyroid disease	33 (17.74)
Chronic lung disease	4 (2.15)
Heart failure	17 (9.14)
Liver disease	30 (16.13)
Bone/Mineral disorder	33 (17.74)
Malignancy	35 (18.82)
Smoking status	
Nonsmoker	163 (87.63)
Current	17 (9.14)
Previous	6 (3.23)
Alcoholic beverage drinker	34 (18.28)
BMI (kg/m^2)	
<18.5	1 (0.54)
18.5-22.9	50 (26.88)
23.0-24.9	30 (16.13)
≥25	105 (56.45)

Table 2. Diabetes distress as measured by DDS17 among patients with T2DM (n = 186)

	Mean score Mean ± SD	Moderate Distress	High Distress
		Frequency and prevalence % [95% CI]	
Overall	2.02 ± 0.73	64 (34.41) [27.61-41.71]	21 (11.29) [7.13-16.74]
Emotional Burden Domain	2.33 ± 0.95	74 (39.78) [32.70-47.20]	45 (24.19) [18.23-31.00]
Physician related Distress Domain	1.42 ± 0.71	21 (11.29) [7.13-16.74]	11 (5.91) [2.99-10.34]
Regimen related Distress Domain	2.34 ± 0.89	84 (45.16) [37.87-52.61]	43 (23.12) [17.26-29.85]
Interpersonal Distress Domain	1.79 ± 0.91	52 (27.96) [21.63-34.99]	20 (10.75) [6.69-16.12]

The overall prevalence of DRED for this study was 34.41% [95% CI: 27.61-41.71] (Table 2). Specifically, the prevalence of moderate distress was highest for regimen-related distress at 45.16% [95% CI: 37.87-52.61], followed by emotional-related distress at 39.78% [95% CI: 32.70-47.20]. The lowest prevalence of moderate distress was found in the physician-related distress domain at 11.29% [95% CI: 7.13-16.74]. For high distress, emotional burden had the highest prevalence at 24.19% [95% CI: 18.23-31.00], followed by regimen at 23.12% [95% CI: 17.26-29.85]. Physician domain had the lowest prevalence of high distress at 5.91% [95% CI: 2.99-10.34]. There is a higher proportion of DRED among patients with shorter duration of diabetes and with history of peripheral artery disease (Table 3).

In terms of distress scores, the mean overall DDS score was 2.02 (SD = 0.73). Regimen-related distress had the highest mean score at 2.34 (SD = 0.89), closely followed by emotional distress at 2.33 (SD = 0.95). Interpersonal distress and physician-related distress had lower mean scores of 1.79 (SD = 0.91) and 1.42 (SD = 0.71), respectively.

Age was found to be a significant predictor of diabetes distress, with the odds decreasing for every one-year increase in age (OR 0.97, 95% CI 0.95–1.00), starting from the median study age of 60 years (range 27–86). The HbA1c level showed no significant association with developing diabetes distress including other factors such as sex, duration of diabetes, presence of DM complications, having extensive DM regimen, smoking status, alcohol consumption status, BMI, lack of family or social support, and level of education (Table 4).

In the adjusted model for moderate to high distress versus none/low, age was still associated with lower odds for every year increase in age (AOR 0.95, 95% CI 0.93–0.98; $p = 0.002$). A higher medication burden increased odds (per additional diabetes medication: AOR 1.33, 95% CI 1.01–1.77; $p = 0.043$). Peripheral artery disease (PAD) was a strong predictor of diabetes distress (AOR 6.03, 95% CI 1.79–23.29; $p = 0.005$), while prior TIA or stroke showed a nonsignificant trend (AOR 3.20, 95% CI 0.98–11.50; $p = 0.059$). Injectable therapy and systolic blood pressure were not significantly associated with diabetes distress (injectable therapy: AOR 0.29, 95% CI 0.06–1.23; $p = 0.108$; systolic blood pressure per mmHg: AOR 0.98, 95% CI 0.94–1.01; $p = 0.141$) (Table 5).

DISCUSSION

This study was able to systematically translate the English DDS into the Filipino language and evaluate its psychometric properties. Overall results show that for both content and face validity, all items in the Filipino-DDS were relevant, easy to comprehend, and important. The process of translation and cultural adaptation of a questionnaire is complex and requires evidence of the semantic equivalence of the items, cultural fit of the instrument and adequate psychometric properties. The Filipino-DDS was able to maintain the 17 items of the original English DDS as in the translation done in Mexico.[27] In contrast, other translations including those in Thailand and China, have modified or reduced items and domains.[28,29] Experts have commented that the translation of the scale can also be improved by switching the phrasing to a positive or neutral tone. Some respondents have expressed discomfort when responding to items, particularly in the physician related domain. This feedback highlights the importance of cultural and contextual adaptation in instrument development, ensuring that respondents can answer honestly without fear of affecting their relationship with healthcare providers. Nonetheless, this research has demonstrated that the Filipino-DDS is a valid and reliable instrument in the assessment of diabetes related distress among Filipino patients with diabetes.

One of the limitations of the translation and validation process of this study is that the Filipino-DDS was not compared with other DM-related health or psychological indicators as such criterion validity was not assessed. Comparison of the Filipino-DDS with other measures of diabetes distress or self-care behaviors would be warranted in future studies. In addition, the Filipino-DDS was only used for validation among patients with type 2 diabetes mellitus, while the original DDS17 was validated for patients with type 1 DM as well. A validation of this scale among patients with type 1 diabetes would be of interest in further studies.

More than a third of the study population had reported moderate level of diabetes distress which coincided with the global prevalence estimates at 34% but was much lower when compared with the local study done (42.6%), and in another southeast Asian country that is Malaysia (49.2%).[30] Factors that may lead to a lower prevalence in this study include the sample size, health care setting, current health condition of the study population, and other

Table 3. Proportion of patients with and without diabetes distress

	With distress N, %	No distress N, %	*P*-value
Age, years			
<60	42 (47.2%)	47 (52.8%)	0.183
≥60	36 (37.1%)	61 (62.9%)	
Sex			
Male	23 (35.4%)	42 (64.6%)	0.214
Female	55 (45.5%)	66 (54.5%)	
Highest educational attainment			
Elementary	4 (36.4%)	7 (63.6%)	0.654
Highschool	15 (39.5%)	23 (60.5%)	
College	54 (41.9%)	75 (58.1%)	
Post-grad	5 (62.5%)	3 (37.5%)	
Civil status			
Single	12 (57.1%)	9 (42.9%)	0.175
Married	61 (41.5%)	86 (58.5%)	
Widowed/Separated	5 (27.8%)	13 (72.2%)	
Duration of diabetes, months			
<12	17 (63%)	10 (37%)	0.002*
12-36	16 (61.5%)	10 (38.5%)	
37-60	4 (16%)	21 (84%)	
61-120	22 (39.3%)	34 (60.7%)	
>120	19 (36.5%)	33 (63.5%)	
DM medications			
Oral medications	71 (42%)	98 (58%)	0.947
Injectable medications	4 (36.4%)	7 (63.6%)	0.764
Insulin	32 (46.4%)	37 (53.6%)	0.360
OAD+Insulin	25 (48.1%)	27 (51.9%)	0.323
OAD + injectable	0	0	-
OAD+Injectable+Insulin	2 (40%)	3 (60%)	0.929
Insulin + Injectable	2 (33.3%)	4 (66.7%)	0.504
Total number of DM medications			
<3	32 (36.8%)	55 (63.2%)	0.233
≥3	46 (46.5%)	53 (53.5%)	
Macro/Microvascular complications			
Diabetic retinopathy	22 (38.6%)	35 (61.4%)	0.629
Diabetic nephropathy	16 (40%)	24 (60%)	0.857
Diabetic neuropathy	11 (45.8%)	13 (54.2%)	0.825
History of TIA/Stroke	8 (61.5%)	5 (38.5%)	0.155
History of MI/CAD	20 (43.5%)	26 (56.5%)	0.864
History of PAD	10 (66.7%)	5 (33.3%)	0.043*
Comorbidities			
Hypertension	57 (39.9%)	86 (60.1%)	0.378
Dyslipidemia	59 (39.6%)	90 (60.4%)	0.200
Thyroid disease	11 (33.3%)	22 (66.7%)	0.332
Chronic lung disease	2 (50%)	2 (50%)	1.000
Heart failure	9 (52.9%)	8 (47.1%)	0.440
Liver disease	13 (43.3%)	17 (56.7%)	0.865
Bone/Mineral disorder	16 (48.5%)	17 (51.5%)	0.440
Malignancy	11 (31.4%)	24 (68.6%)	0.186
Smoking status			
Nonsmoker	69 (42.3%)	94 (57.7%)	0.906
Current	2 (33.3%)	4 (66.7%)	
Previous	7 (41.2%)	10 (58.8%)	
Alcoholic beverage drinker	13 (38.2%)	21 (61.8%)	0.703
BMI, kg/m²			
18.5-24.9	28 (34.6%)	53 (65.4%)	0.039*
25.0-29.9	28 (41.2%)	40 (58.8%)	
≥30	22 (59.5%)	15 (40.5%)	
HbA1c			
<7%	25 (35.7%)	45 (64.3%)	0.165
≥7%	51 (46.8%)	58 (53.2%)	

Table 4. Predictors of diabetes distress (n = 186)

	Odds Ratio [95% CI]	*p*-value
Age	0.97 [0.95 – 1.00]	0.040
Sex		
Male	Reference	
Female	1.43 [0.77 – 2.63]	0.254
Highest educational attainment		
Elementary	Reference	
Highschool	1.58 [0.39 – 6.28]	0.520
College	1.43 [0.40 – 5.12]	0.583
Post-grad	2.92 [0.44 – 19.23]	0.266
Civil status		
Single	Reference	
Married	0.65 [0.26 – 1.62]	0.353
Widowed	0.31 [0.08 – 1.21]	0.092
Duration of diabetes, months	1.00 [1.00 – 1.00]	0.330
DM medications		
Oral medications	1.22 [0.45 – 3.37]	0.695
Injectable medications	0.66 [0.19 – 2.35]	0.524
Insulin	1.26 [0.69 – 2.28]	0.452
Total number of DM medications	1.16 [0.90 – 1.49]	0.241
Macro/Microvascular complications		
Diabetic retinopathy	0.66 [0.35 – 1.24]	0.197
Diabetic nephropathy	0.96 [0.48 – 1.95]	0.920
Diabetic neuropathy	1.22 [0.52 – 2.88]	0.651
History of TIA/Stroke	1.99 [0.63 – 6.34]	0.242
History of MI/CAD	1.12 [0.57 – 2.18]	0.739
History of PAD	2.56 [0.84 – 7.81]	0.099
Comorbidities		
Hypertension	0.67 [0.34 – 1.32]	0.244
Dyslipidemia	0.58 [0.28 – 1.19]	0.134
Thyroid disease	0.63 [0.29 – 1.36]	0.238
Chronic lung disease	1.19 [0.16 – 8.65]	0.862
Heart failure	1.38 [0.51 – 3.74]	0.531
Liver disease	0.89 [0.41 – 1.96]	0.776
Bone/Mineral disorder	1.15 [0.54 – 2.43]	0.723
Malignancy	0.75 [0.36 – 1.59]	0.453
Smoking status		
Nonsmoker	Reference	
Current	1.04 [0.38 – 2.84]	0.934
Previous	0.59 [0.10 – 3.29]	0.545
Alcoholic beverage drinker	0.80 [0.38 – 1.70]	0.559
BMI, kg/m²		
18.5-24.9	Reference	
25.0-29.9	1.06 [0.55 – 2.04]	0.864
≥30	2.09 [0.95 – 4.62]	0.069
Systolic blood pressure, mmHg	0.99 [0.96 – 1.02]	0.619
Diastolic blood pressure, mmHg	1.03 [0.98 – 1.08]	0.291
Heart rate, bpm	0.99 [0.96 – 1.03]	0.739
Respiratory rate, cpm	0.94 [0.79 – 1.12]	0.486
HbA1c	1.00 [1.00 – 1.00]	0.538

Table 5. Predictors of diabetes distress – multivariate analysis

	Adjusted Odds Ratio [95% CI]	*p*-value
Age	0.95 [0.93 – 0.98]	**0.002**
DM medications		
Injectable medications	0.29 [0.06 – 1.23]	0.108
Total number of DM medications	1.33 [1.01 – 1.77]	**0.043**
Macro/Microvascular complications		
History of TIA/Stroke	3.20 [0.98 – 11.50]	0.059
History of PAD	6.03 [1.79 – 23.29]	**0.005**
Systolic blood pressure, mmHg	0.98 [0.94 – 1.01]	0.141

sociodemographic factors. In this study, the participants were recruited from a tertiary hospital and majority of the patients enrolled were from Endocrine specialty clinics who had an older mean age, and lower mean HbA1c levels. The discrepancy may also result from better family support and social support in Filipino culture and the increased trust in healthcare providers in Philippines with lower levels of diabetes scale scores in the interpersonal -related distress domains and physician -related stress domains.

Glycemic control was not associated with DRED which is similar to Totesora et al. Other factors such as gender, education level, marital status, duration of diabetes, presence of DM complications and other comorbidities, as well body mass index were not associated with diabetes-related distress.

A younger age was significantly associated with DRED. The research showed that for every year increase in age above a median age of 60 years old, the odds of DRED decrease by 5%. This was in congruence with a study showing that a younger age was significantly more associated with DRED and depressive symptoms.[31] Previous studies have shown that societal judgment, blame, and stigma expressed toward people living with type 2 diabetes can become more internalized, resulting in self-blame and self-judgment.[31,32] These may be more prominent among younger people since having diabetes at a younger age is less common.

The presence of PAD was also found to be significantly associated with diabetes distress. While no studies were found that directly measured diabetes distress in PAD patients, several studies show that PAD is correlated with depression, which was mentioned to have overlapping symptoms with DRED. It was also correlated with anxiety, pain, mobility limitations, and impaired quality of life which are known contributors to psychosocial burden in diabetes.[33] In another study, patients with PAD and T2DM have reduced physical function and are more sedentary, which may increase emotional burden of these patients.[34] There may be some indirect evidence that PAD is associated with higher diabetes distress in our sample. The association of diabetes distress with PAD may also reflect the psychological impact of more advanced or symptomatic vascular complications, which are often linked to chronic pain, mobility limitation, and fear of amputation.

A higher medication burden was also significantly associated with increased DRED. Studies have demonstrated that multiple concurrent medications are associated with greater psychological burden and worse health-related quality of life in people with diabetes.[35] It may also reflect a more advanced or multimorbid disease, signaling greater perceived disease severity and fear of complications, both of which can contribute to developing DRED. In a separate study, patients who have high levels of diabetes distress had lower odds of adhering to their medications. Consequently, the treatment burden is included along with negative emotions about living with diabetes, dietary concerns, and dissatisfaction with external support as areas of distress by patients with type 2 DM.[36] Our findings thus align with reports that polypharmacy and perceived treatment burden are important psychosocial determinants in diabetes and DRED.

The findings of this study differed from reports in Southwest Ethiopia, India, Saudi Arabia, and Vietnam, where HbA1c, BMI, treatment regimen, and physical activity were significant predictors of diabetes distress, although younger age was a consistent determinant across studies.[13,37-40] Compared with these populations, our cohort was older, had longer diabetes duration, lower mean HbA1c levels, higher educational attainment, and was predominantly treated with oral hypoglycemic agents, which may partly explain the observed differences. Variations in sociodemographic characteristics, healthcare access, and treatment patterns, as well as cultural factors such as strong family support, collectivist values, optimism, religiosity, and acceptance, may further mitigate emotional distress among Filipino patients.[41-44] These findings further give importance of interpreting diabetes distress within its cultural context and support the need for culturally tailored interventions.

This study is able to examine a wide range of clinico-demographic factors and diabetes-specific characteristics that may be associated with diabetes distress and resulting glycemic control. This allows for additional evidence to support screening for patients with type 2 DM for DRED especially those who develop this condition at a younger age. Targeted interventions for specific domains and a holistic approach to diabetes management should be adopted among patients with moderate to high level of distress. Diabetes self-management education and support (DSMEs) among these patients are important to provide help and empowerment and assist them on how to navigate self-management decisions and activities.

The lack of association between HbA1c and diabetes distress may reflect the limitation of HbA1c in effectively capturing short-term fluctuations, glycemic variability, or episodes of hypoglycemia, which may have a stronger impact on emotional distress. Psychosocial factors such as coping mechanisms, perceived support, and self-efficacy may also influence distress independently of glycemic control. Future longitudinal studies using continuous glucose monitoring or incorporating measures of hypoglycemia could provide a clearer understanding of this relationship. The psychometric properties, such as sensitivity to change and predictive validity, as well as the temporal change of glycemic control and other factors and how it correlated with presence of diabetes distress were not assessed in this study. Other prospective studies can be conducted to assess if the Filipino-DDS can assess diabetes distress dynamically over time especially among patients undergoing specific interventions in relation to their diabetes related distress.

Another limitation of the study includes the fact that it had a smaller sample size as compared to other cross-sectional

studies done to determine the association of diabetes distress and glycemic control. It was only done in one tertiary hospital and may not be representative of the whole Filipino population. The population pool was only mainly from IM and Endocrinology specialty clinics and might not be exhaustive since other patients with diabetes from other General Medicine practice and other subspecialty clinics were not included. Furthermore, the study population largely did not have diabetic kidney disease, and nearly 70% were college graduates, which may limit generalizability to the broader Filipino population with differing clinical and sociodemographic profiles. It may be prudent to conduct further validation studies in a larger multicenter population among Filipino patients with type 2 diabetes mellitus.

CONCLUSION

This study demonstrated that the Filipino-DDS is a valid instrument in the assessment of diabetes related distress among Filipino patients with type 2 diabetes mellitus. Diabetes related distress has a significant prevalence among type 2 DM patients and requires special attention by healthcare providers in order to prevent it. Diabetes distress scores were not associated with glycemic control. Age, history of peripheral artery disease, and a higher medication burden were found to be a significant predictors for developing diabetes distress with a younger age being associated with the development of diabetes distress.

Acknowledgments
The authors extend their deepest gratitude to Siena Placino, a medical student, for her assistance in the writing and synthesis of the discussion section of this paper. The authors also thank their consultants and the nurse from St. Luke's Medical Center, Quezon City, for generously sharing their expertise during the process of translating the Diabetes Distress Scale into Filipino.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CMM: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **HCT:** Conceptualization, Methodology, Validation, Formal Analysis, Data curation, Investigation, Writing – review and editing, **OAD:** Conceptualization, Methodology, Supervision; Validation, Data curation, Visualization, Writing – review and editing.

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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APPENDICES

Appendix A. Cosmin criteria for content validity

Content validity

Date: _____
Name: _____
Position: _____

Dear experts,

We are currently developing a questionnaire that aims to determine the association of diabetes-related emotional distress with glycemic control and other related factors of adult Filipinos with type 2 diabetes mellitus at St. Luke's Medical Center, QC using a Filipino Diabetes Distress Scale. We intend to test the content validity of the questionnaire based on the following research elements.

Population: Filipino Adults 18 years old and above diagnosed with Type 2 Diabetes Mellitus
Exposure: Glycemic control
Outcome: Diabetes Related Emotional Distress

Instruction: We need your expert judgment on the degree of relevance of each item to the construct of interest and how the translated items are conceptually equivalent. Please be as objective and constructive as possible in your review and use the following as guide questions.

Relevance:
1. Are the items relevant for the construct of interest?
2. Are the items relevant for the target population of interest?
3. Are the items relevant for the context of use of interest?
4. Are the response options appropriate? _____
5. Are there other issues that need to be addressed? _____

For relevance kindly encircle the number depending on the following:

Degree of Relevance:
1 – the item is not relevant to the measured domain
2 – the item is somewhat relevant to the measured domain
3 – the item is quite relevant to the measured domain
4 – the item is highly relevant to the measured domain

Comprehensiveness:
6. Are there any missing key concepts on motivations and barriers for this research paper? _____
_____

Comprehensibility:
7. Are the instructions clear and understandable? _____
8. Are the questions clear and understood as intended? _____
9. Are the items appropriately worded (i.e., neutral and non-offensive)? _____
10. Do the response options match the questions? _____

Other comments: _____
_____
_____

Filipino Translation	Relevance (1-lowest, 4-highest)				English DDS	Conceptually equivalent (Y/N)	Comments
1. Pakiramdam ko ay kinukuha ng diabetes ang marami sa aking mental at pisikal na lakas araw-araw.	1	2	3	4	Feeling that diabetes is taking up too much of my mental and physical energy every day.		
2. Pakiramdam ko ay hindi sapat ang kaalaman ng aking doktor tungkol sa diabetes at pangangalaga sa diabetes.	1	2	3	4	Feeling that my doctor doesn't know enough about diabetes and diabetes care.		
3. Pakiramdam ko ay hindi ako kampante sa aking pang-araw-araw na kakayahan para mapangalagaan ang diabetes.	1	2	3	4	Not feeling confident in my day-to day ability to manage diabetes.		
4. Nakakaramdam ako ng galit, takot, at/o matinding lungkot kapag naiisip ko ang pamumuhay na may diabetes.	1	2	3	4	Feeling angry, scared and/or depressed when I think about living with diabetes.		
5. Pakiramdam ko ay hindi ako nabibigyan ng aking doktor ng malinaw na tuntunin kung paano pangangalagaan ang aking diabetes.	1	2	3	4	Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.		
6. Pakiramdam ko ay hindi ko nasusuri nang madalas ang aking asukal sa dugo.	1	2	3	4	Feeling that I am not testing my blood sugars frequently enough.		
7. Pakiramdam ko ay magkakaroon ako ng seryosong pangmatagalang komplikasyon, kahit na ano ang gawin ko.	1	2	3	4	Feeling that I will end up with serious long-term complications, no matter what I do.		
8. Pakiramdam ko ay madalas na hindi ako nakakasunod sa aking pang-araw araw na gawain ng may diabetes.	1	2	3	4	Feeling that I am often failing with my diabetes routine.		
9. Pakiramdam ko ay hindi ako sinusuportahan ng aking mga kaibigan o pamilya sa mga pagsisikap kong maalagaan ang aking sarili (hal., nagpaplano sila ng mga aktibidad na hindi tugma sa aking iskedyul, hinihikayat akong kumain ng mga “bawal” na pagkain).	1	2	3	4	Feeling that friends or family are not supportive enough of self-care efforts (e.g. planning activities that conflict with my schedule, encouraging me to eat the "wrong" foods).		
10. Pakiramdam ko ay kinokontrol ng diabetes ang aking buhay.	1	2	3	4	Feeling that diabetes controls my life.		
11. Pakiramdam ko ay hindi sineseryoso ng aking doktor ang aking mga alalahanin.	1	2	3	4	Feeling that my doctor doesn't tak my concerns seriously enough.		
12. Pakiramdam ko ay hindi ako nakakasunod sa maayos na meal plan o plano sa pagkain.	1	2	3	4	Feeling that I am not sticking closely enough to a good meal plan.		
13. Pakiramdam ko ay hindi nakikita ng aking mga kaibigan o pamilya kung gaano kahirap mabuhay na may diabetes.	1	2	3	4	Feeling that friends or family don' appreciate how difficult living with diabetes can be.		
14. Pakiramdam ko ay nabibigatan ako sa mga dapat gawin ng taong nabubuhay na may diabetes.	1	2	3	4	Feeling overwhelmed by the demands of living with diabetes.		
15. Pakiramdam ko ay wala akong doktor na regular kong mapupuntahan tungkol sa aking diabetes.	1	2	3	4	Feeling that I don't have a doctor who I can see regularly enough about my diabetes.		
16. Hindi ako nakakaramdam ng motibasyon para mapanatili ko ang aking pangangalaga sa sarili ng may diabetes.	1	2	3	4	Not feeling motivated to keep up my diabetes self management.		
17. Pakiramdam ko ay hindi ako binibigyan ng aking mga kaibigan o pamilya ng ninanais kong emosyonal na suporta.	1	2	3	4	Feeling that friends or family don't give me the emotional support that I would like.		

Appendix B. Filipino Diabetes Distress Scale (DDS-17)

Panuto: Mahirap minsan ang mabuhay nang may diabetes. Maraming problema at abala kaugnay ng diabetes at maaaring mag-iba ang antas ng kalubhaan nito. Ang mga problema ay maaaring mga maliliit na abala lamang hanggang sa malalaking kahirapan sa buhay. Nakalista sa ibaba ang 17 potensyal na mga problem areas o lugar ng problema na maaaring maranasan ng mga taong may diabetes. Isaalang-alang ang antas kung saan ang bawat isa sa mga 17 item ay maaaring nagdulot ng pagkabahala o nakaabala sa inyo SA NAKARAANG BUWAN at bilugan ang angkop na numero.

Paalala lang na nais naming ipakita ninyo ang antas kung saan ang bawat item ay maaaring nakakaabala sa inyong buhay, at HINDI lamang kung totoo ang bawat item sa inyo. Kung sa tingin ninyo ay hindi nakakaabala ang isang partikular na item sa inyo o hindi ito problema para sa inyo, bilugan ang 1. Kung talagang nakakaabala ito sa inyo, maaaring bilugan ang 6.

	Hindi problema	Maliit na problema	Katamtamang problema	Medyo seryosong problema	Seryosong problema	Napakaseryosong problema
1. Pakiramdam ko ay kinukuha ng diabetes ang marami sa aking pag-iisip at pisikal na lakas araw-araw.	1	2	3	4	5	6
2. Pakiramdam ko ay hindi sapat ang kaalaman ng aking doktor tungkol sa diabetes at pangangalaga sa diabetes.	1	2	3	4	5	6
3. Pakiramdam ko ay hindi ako kampante sa aking pang-araw-araw na kakayahan para mapangalagaan ang diabetes.	1	2	3	4	5	6
4. Nakakaramdam ako ng galit, takot, at/o matinding lungkot kapag naiisip ko ang pamumuhay na may diabetes.	1	2	3	4	5	6
5. Pakiramdam ko ay hindi ako nabibigyan ng aking doktor ng malinaw na patakaran kung paano pangangalagaan ang aking diabetes.	1	2	3	4	5	6
6. Pakiramdam ko ay hindi ko nasusukat nang madalas ang aking asukal sa dugo.	1	2	3	4	5	6
7. Pakiramdam ko ay magkakaroon ako ng seryosong pangmatagalang komplikasyon, kahit na ano ang gawin ko.	1	2	3	4	5	6
8. Pakiramdam ko ay madalas na hindi ako nakakasunod sa aking pang-araw araw na gawain ng may diabetes.	1	2	3	4	5	6
9. Pakiramdam ko ay hindi ako sinusuportahan ng aking mga kaibigan o pamilya sa mga pagsisikap kong maalagaan ang aking sarili (hal., nagpaplano sila ng mga aktibidad na hindi tugma sa aking iskedyul, hinihikayat akong kumain ng mga “bawal” na pagkain).	1	2	3	4	5	6
10. Pakiramdam ko ay kinokontrol ng diabetes ang aking buhay.	1	2	3	4	5	6
11. Pakiramdam ko ay hindi sineseryoso ng aking doktor ang aking mga alalahanin.	1	2	3	4	5	6
12. Pakiramdam ko ay hindi ako nakakasunod sa tama or wastong pagkain	1	2	3	4	5	6
13. Pakiramdam ko ay hindi nauunawaan ng aking mga kaibigan o pamilya kung gaano kahirap mabuhay na may diabetes.	1	2	3	4	5	6
14. Pakiramdam ko ay nabibigatan ako sa mga dapat gawin ng taong may diabetes.	1	2	3	4	5	6
15. Pakiramdam ko ay wala akong doktor na regular kong mapupuntahan para sa aking diabetes.	1	2	3	4	5	6
16. Hindi ako nakakaramdam ng motibasyon o gana para sa pangangalaga ng aking diabetes.	1	2	3	4	5	6
17. Pakiramdam ko ay hindi ako binibigyan ng aking mga kaibigan o pamilya ng ninanais kong emosyonal na suporta.	1	2	3	4	5	6

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

The Association of Ramadan Fasting on Relative Leukocyte Telomere Length in Type 2 Diabetes Mellitus

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Abstract

Background. Leukocyte telomere length (LTL) is considered a biomarker of cellular senescence. Previous studies have reported the associations between shortened telomere length and type 2 diabetes mellitus (T2DM). However, the role of underlying factors remained unclear. While Ramadan fasting has consistently been shown to improve anthropometric and metabolic parameters in T2DM, its effect on cellular senescence has scarcely been reported.

Objective. We sought to determine whether Ramadan Fasting affects leukocyte telomere length in persons with T2DM.

Methodology. An interventional before-and-after study was conducted on 40 to 60-year-old subjects with T2DM consecutively recruited before Ramadan fasting (May 2018 and May 2019) from the Internal Medicine Outpatient Clinic at Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. Relative LTL was compared between 48 subjects before Ramadan fasting and after at least 14 days of fasting and then adjusted with key clinical and biochemical parameters.

Results. The relative rLTL in subjects with T2DM was comparable between before and after at least 14 days of Ramadan fasting. (0.391 [0.021–1.515] vs 1.117 [0.528–1.741], $p = 0.112$).

Conclusion. No significant difference was found in relative leukocyte telomere length among subjects with type 2 diabetes who have undergone Ramadan fasting for at least 14 days. However, this study showed a tendency to have an increase in relative LTL.

Key words: Ramadan fasting, relative leukocyte telomere length, type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a degenerative disease with a growing prevalence each year. According to the International Diabetic Federation (IDF), the global prevalence of diabetes mellitus in 2019 reached 9.3% or approximately 463 million cases, with a mortality of 4.2 million.[1] Type 2 diabetes mellitus is related to the risk of age-related comorbidities through an acceleration of biological ageing, called cellular senescence. An increased turnover and chronic activation of inflammatory cells in T2DM contribute to the cellular oxidative stress that elicits the deletion of telomeres.[2,3] Telomeres are the tandem repeats of TTAGGG of the deoxyribonucleic acid (DNA) sequence required for DNA replication. During DNA replication, telomeres progressively get shorter, and once a critical limit is reached, cells undergo senescence and apoptosis. The G triplet of telomere is very susceptible to oxidative stress that potentially breaks the telomeric double-strands, resulting in shortened telomere length.[4,5]

The relationship between shortened relative leukocyte telomere length (rLTL) and T2DM has been reported in previous studies. The first study to report this finding was by Jeanclos E et al.,[6] in 1998, where they noted that T2DM is mediated via an immunologic process, hence patient's

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Hardika et al.
Received: December 15, 2025. Accepted: February 8, 2026.
Published online first: April 26, 2026.
https://doi.org/10.15605/jafes.041.01.5071

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white blood cells (WBCs) profile might differ from those in the non-diabetic population. The accelerated telomere attrition rate is thought to play a significant role because it will result in premature senescence of leukocytes and an exhausted patient's immune system. A meta-analysis by Zhao et al.,[7] which extracted telomere length from 9 population cohorts and pooled eligible studies resulted in a significant association between T2DM and telomere length (OR 1.291; 95% CI 1.112 - 1.498; p <0.001), the risk is even more visible in high-quality studies (OR 1.452; 95% CI 1.204 – 1.753; p = 0.005). This risk was also adjusted for several factors, such as body mass index (BMI) and age. Interestingly, they also discovered that baseline rLTL was an independent predictor for the risk of cerebrovascular disease (CVD) in T2DM patients.

Inflammation and oxidative stress could accelerate telomere shortening. The relationship between telomere length and cardiometabolic factors has been reported in previous studies. A more recent cohort study by Cheng et al.,[8] found that in 5,349 patients, rLTL was inversely correlated with age, diabetes duration, blood pressure, HbA1c, and urine albumin-to-creatinine ratio (uACR). The association of other clinical parameters, such as anthropometric measurements, calorie intake, physical activity, and lipid profile, with rLTL are points of research interest. Furthermore, any intervention addressing inflammatory improvement might benefit cellular senescence prevention.[9-13] Particular emphasis was placed on calorie restriction, which has been hugely reported to improve inflammatory and metabolic parameters in T2DM.

Ramadan fasting (RF) is one calorie restriction model, particularly an intermittent or time-restricted feeding model. The benefit of RF on metabolic and anthropometric measures in T2DM has been reported in previous studies. However, the benefits of RF on cellular senescence in T2DM must be elaborated more. Therefore, this study aims to evaluate the effect of Ramadan fasting on rejuvenating cellular senescence in T2DM by examining the changes in the level of relative telomere length before and after at least 14 days of Ramadan fasting.

METHODOLOGY

Study design

This is an interventional before-and-after study without control (pre-and-post-study design) that analyzes the effect of Ramadan fasting on rLTL in persons with T2DM as a part of a larger study entitled, "Fasting in Type 2 Diabetes Mellitus Patients and Its Implications for Various Aspects: Glucose and Lipid Metabolism, Hemodynamic, Anthropometry and Body Composition, Nutrition, Cognitive System, Aging and Inflammation," conducted by the Division of Endocrinology and Metabolism, Internal Medicine Department, Faculty of Medicine, Universitas Indonesia (FMUI), Jakarta, Indonesia. Before Ramadan month in 2018 and 2019, we consecutively recruited persons with T2DM aged 40 to 60 who planned to fast during Ramadan. The diagnosis of T2DM was based on a previous diagnosis of T2DM from a physician or the presence of A1c level of ≥6.5%. Those who had chronic kidney disease, severe liver disease, chronic gastrointestinal disease, cardiovascular disease, and autoimmune disease, who were pregnant or breastfeeding, and had a history of non-steroidal anti-inflammatory drug use, steroid consumption, or antibiotic consumption within the last month were excluded from this study. Patients considered to be at very high risk of fasting during Ramadan, according to International Diabetes Federation—Diabetes and Ramadan International Alliance (IDF-DAR) guidelines, were excluded. After the screening, eligible participants signed the study consent form. The visits were arranged 1-2 weeks before Ramadan (T0), at least 14 days during Ramadan (T1) of 1439 – 1440 Hijri, corresponding to about 16th May to 14th June 2018, and 5th May to 14th June 2019. For this current study, we selected subjects with complete data on age, body mass index, calorie intake, and blood parameters (fasting blood glucose, HbA1c, lipid profile). We compared rLTL data subjects with T2DM before and after fasting. This study was approved by the Ethical Health Research Committee of the Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo National General Hospital, with ethical approval no. 0550/UN2.FI/ETIK/2018.

Telomeric length measurement

Whole blood samples of 25 mL were stored at a temperature of -80 °C in the Metabolic Disorder, Cardiovascular and Aging Cluster (MVA), Indonesia Medical Education and Research Institute (IMERI), FMUI, Jakarta, and then examined in October 2020. DNA was extracted from the peripheral blood leukocytes in MVA IMERI. The telomere length of the isolated DNA was measured using quantitative real-time PCR (RT-PCR) (Applied Biosystems 7900 HT) as a T/S ratio in the integrated laboratory of the FMUI. The T/S ratio compares telomeric DNA (T) with the level of single-copy (S) reference gene using quantitative real-time polymerase chain reaction (PCR). Cycling conditions for telomeres were 20-60 seconds at 95 °C, followed by at 95 °C for 15 seconds and 60 °C for 30-60 seconds. The P19-2-001, a single-copy gene, served as a reference gene in the conventional qPCR technique to measure telomeres.

Anthropometry measurement

The body weight (BW) and body composition measurements were conducted using Tanita MC780MA bioelectrical impedance analysis (BIA), while a portable stadiometer (GEA Medical, SH-2A High Meter 2 M) was used to measure height. Waist circumference was measured using an ergonomic circumference measuring tape based on WHO standard protocol as the middle point between the last palpable costae and the top of the iliac crest. The blood pressure measurement was done in a sitting position after resting for 10–15 minutes using GEA Medical® type SH-2A High Meter 2 M.

Nutritional intake measurement

The nutritional intake data were attained using a 3-day non-consecutive food record, of which all subjects were asked to write their food and drink consumption for two days during the weekday and one day during the weekend. The food record data were then verified by a certified nutritionist when the continuous glucose monitors (CGMs) sensor was disconnected. Nutritional analysis was then performed using the Nutrisurvey® program. The final nutritional data was obtained after calculating each average parameter value, and these data were displayed on the table.

Physical activity measurement

The physical activity data were assessed using different questionnaires, where, in 2018, the Global Physical Activity Questionnaire (GPAQ) was used, and in 2019, Bouchard was used, and the examinations were performed at home. With the GPAQ questionnaire, subjects were asked to answer 16 questions. After converting the data into total physical activity Metabolic Equivalents (METs) in minutes/week, it was categorized as light, moderate or vigorous activity. The Bouchard questionnaire captured the activity of each subject every 15 minutes for 24 hours, resulting in 96 periods, and was also performed for two days during the weekday and one day during the weekend for each visit. For each 15 minutes, the subjects were instructed to fill it up with a number ranging from 1–9 according to the intensity of the predominant activity during that period. The questionnaire results were quantified to yield energy expenditure, depicted by METs in kcal/kg. The final energy expenditure data were obtained by counting the average of METs every 3 hours during the 3-day courses. The data were further transferred into a graph representing 24-hour METs during and after Ramadan fasting, which was then also stratified as light, moderate, or vigorous activity.

Data analysis

Normally distributed data were presented as the mean with standard deviation, whereas non-normally distributed data were displayed ~~in~~ as the median with interquartile range. A normality test was conducted using the Shapiro-Wilk test. The paired T-test or Wilcoxon test was used to compare differences before and after fasting.

The sample size of 48 subjects with T2DM who had RF was calculated based on a hypothesis test on the difference between the means of two dependent groups at 80% desired power, a two-tailed alpha level of 0.05 and effect size or expected mean of the difference and standard deviation of the change in outcome of 0.27 and 0.49, respectively.[14] Those null hypotheses were rejected at the 0.05 alpha level of significance. Data analysis was carried out using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

This study compared rLTL before and after at least 14 days of RF in 48 subjects with T2DM, with a mean age of 50 ± 5 years, 66.7% were females, whereas the mean BMI was 27.59 ± 4.69 kg/m^2. For the glycemic profiles, the median FBG was 147.00 (115.00 – 204.00) mg/dl; meanwhile, the median HbA1c profile was 8.00 (7.00 – 10.50)%. Baseline characteristics are shown in Table 1.

In individuals with T2DM, the median rLTL measured before fasting (T0) was 0.391 (0.024 – 1.515), while after fasting (T1), it increased to 1.117 (0.540 – 1.729). Figure 1 displays the boxplots comparing rLTL at T0 and T1. Nevertheless, the Wilcoxon test results show that there is no significant statistical difference in rLTL levels before and after fasting (p = 0.112).

Table 1. Baseline characteristics of subjects with T2DM who have undergone at least 14 days of Ramadan fasting

Characteristics	T2DM subjects (n = 48)
Age, year (mean [SD])	50 (5)
41 – 50 years old, n (%)	22 (45.83)
51 – 60 years old, n (%)	26 (54.17)
Gender	
Male, n (%)	16 (33.30)
Female, n (%)	32 (66.70)
Duration of DM, year (median [IQR])	5 (5 – 8)
History of DM medication	
Metformin, n (%)	33 (68.80)
Sulfonylurea, n (%)	23 (47.90)
Pioglitazone, n (%)	1 (2.10)
Acarbose, n (%)	4 (8.30)
Insulin, n (%)	5 (10.40)
Physical activity	
Light, n (%)	18 (37.50)
Moderate, n (%)	18 (37.50)
Vigorous, n (%)	1 (2.10)
Calorie intake, kcal (median [IQR])	1263.55 (1057.08–1556.03)
Carbohydrate, g (median [IQR])	170.00 (41.89)
Protein, g (median [IQR])	45.88 (38.67–76.18)
Protein g/kg BW(mean [SD])	0.50 (0.242)
Fat, g (median [IQR])	49.90 (34.77–59.93)
Smoking	
Never smoke, n (%)	34 (70.80)
Former smokers, n (%)	5 (10.40)
Current smokers, n (%)	9 (18.80)
Waist circumference, cm (mean [SD])	91.19 (11.69)
Female	89.44 (9.97)
Male	94.66 (14.27)
Body mass index, kg/m^2 (mean [SD])	27.59 (4.69)
Systolic blood pressure, mmHg (mean [SD])	130.55 (18.03)
Diastolic blood pressure, mmHg (median [IQR])	80 (70–80)
Fasting blood glucose, mg/dl (median [IQR])	147.00 (115.00–204.00)
HbA1c, % (median [IQR])	8.00 (7.00–10.50)
Total cholesterol, mg/dl (median [IQR])	199.00 (177.50–229.00)
HDL, mg/dl (median [IQR])	50.00 (43.755–57.75)
LDL, mg/dl (mean [SD])	129.05 (43.66)
Triglyceride, mg/dl (median [IQR])	172.50 (123.00–264.75)

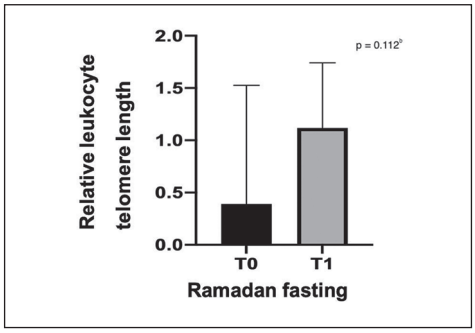


Figure 1. Boxplot of rLTL in T2DM subjects before and after Ramadan fasting.
Note: [b] Wilcoxon test, significant *p*-value <0.05

Furthermore, this study analysed the effects of fasting on total calorie intake, metabolic profile, and anthropometric parameters in subjects with T2DM. Ramadan fasting significantly lowered total calorie intake, carbohydrate, protein in grams, protein in grams per body weight, and fat consumption (p <0.001, p = 0.002, p = 0.002, p = 0.001 and p = 0.002, respectively) (Figure 3). Fasting also significantly decreased anthropometric parameters, including body weight, BMI, and waist circumference. (Figure 2).

Systolic blood pressure, fasting blood glucose, HbA1c profile, and lipid profile, including total cholesterol, HDL, LDL, and triglyceride levels, were also significantly reduced after at least 14 days of Ramadan fasting (p <0.001, p = 0.001, p = 0.010, p = 0.015, p = 0.049, p = 0.002, and p <0.001 respectively) (Figure 3).

DISCUSSION

This study aims to evaluate the association of rLTL before and after at least 14 days of RF among subjects with T2DM. Our study showed that longer telomeres were found in subjects with T2DM who had undergone fasting for at least 14 days (T0 0.391 (0.024 – 1.515) vs T1 1.117 (0.540 – 1.729), p = 0.112), despite not being statistically significant. A study conducted by Asghar et al.,[15] also showed a similar pattern in post-acute malarial infection. It is hypothesized that in post-infection patients, there is a decline in expression of CDKN2A which is responsible for suppressing telomerase enzyme activity during the infection process. Two distinct mechanisms regulate telomere length. Telomere shortening occurs with each round of DNA replication. When telomere length reaches its critical limit, cells undergo senescence.[16,17] In contrast, telomere elongation is modulated by the telomerase enzyme by adding a third telomeric G-rich strand, which results in telomere elongation and cell viability and rejuvenation.[18,19] Currently, there are no studies evaluating the effect of time-restricted feeding such as Ramadan fasting in telomerase enzyme activity and whether dynamic telomere elongation in our study results from telomerase activity or other unknown factors.

There is another explanation regarding inhibition of telomere shortening after fasting. In our study, there was a significant decrease in total calorie intake after fasting, which may affect increasing rLTL. As discussed previously, chronic inflammation is often seen in adipose tissue, exerting senescence-associated secretory phenotype (SASP) in patients with T2DM. SASP triggers age-related degenerative

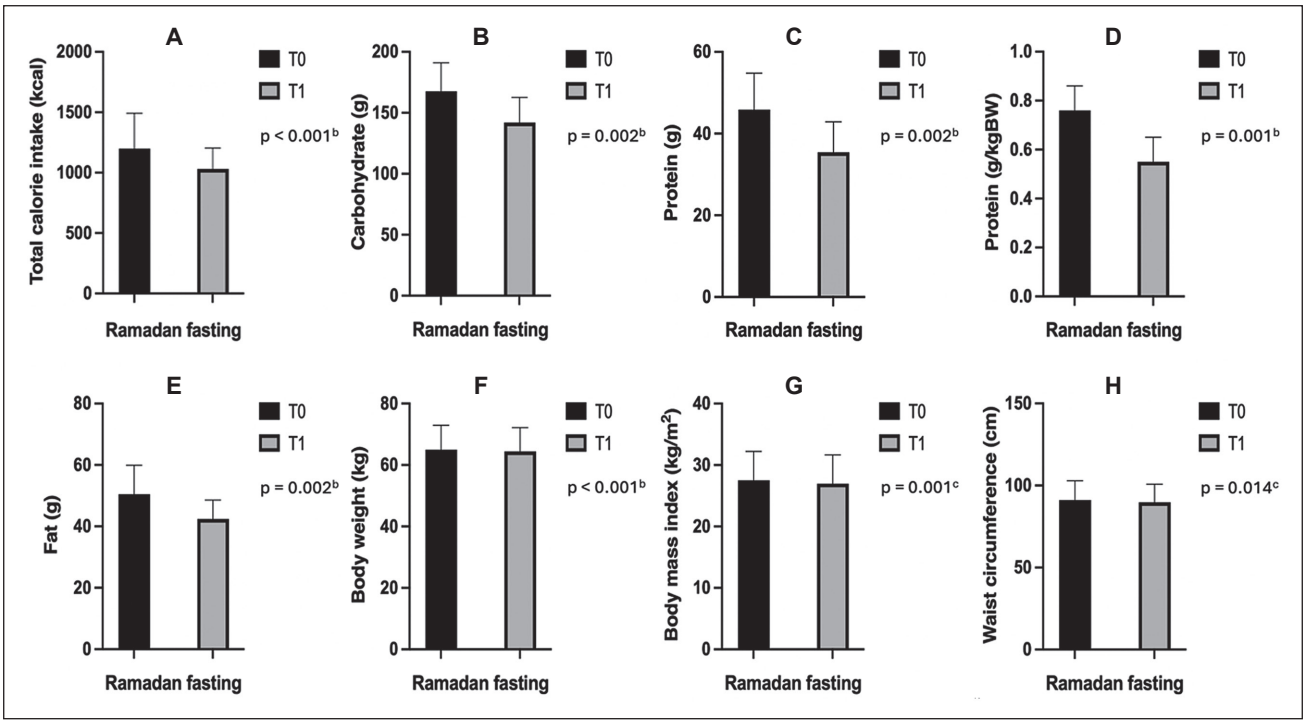


Figure 2. Changes in calorie intake and anthropometric measures after fasting; **(A)** total calorie intake, kcal (median [IQR]), **(B)** carbohydrate, g (median [IQR]), **(C)** protein, g (median [IQR]), **(D)** protein, g/kgBW (median [IQR]), **(E)** fat, g (median [IQR]), **(F)** body weight, kg (median [IQR]), **(G)** body mass index, kg/m^2 (mean [SD]), **(H)** waist circumference, cm (mean [SD]).
Note: [b] Wilcoxon test, [c] Paired t-test, significant *p*-value <0.05

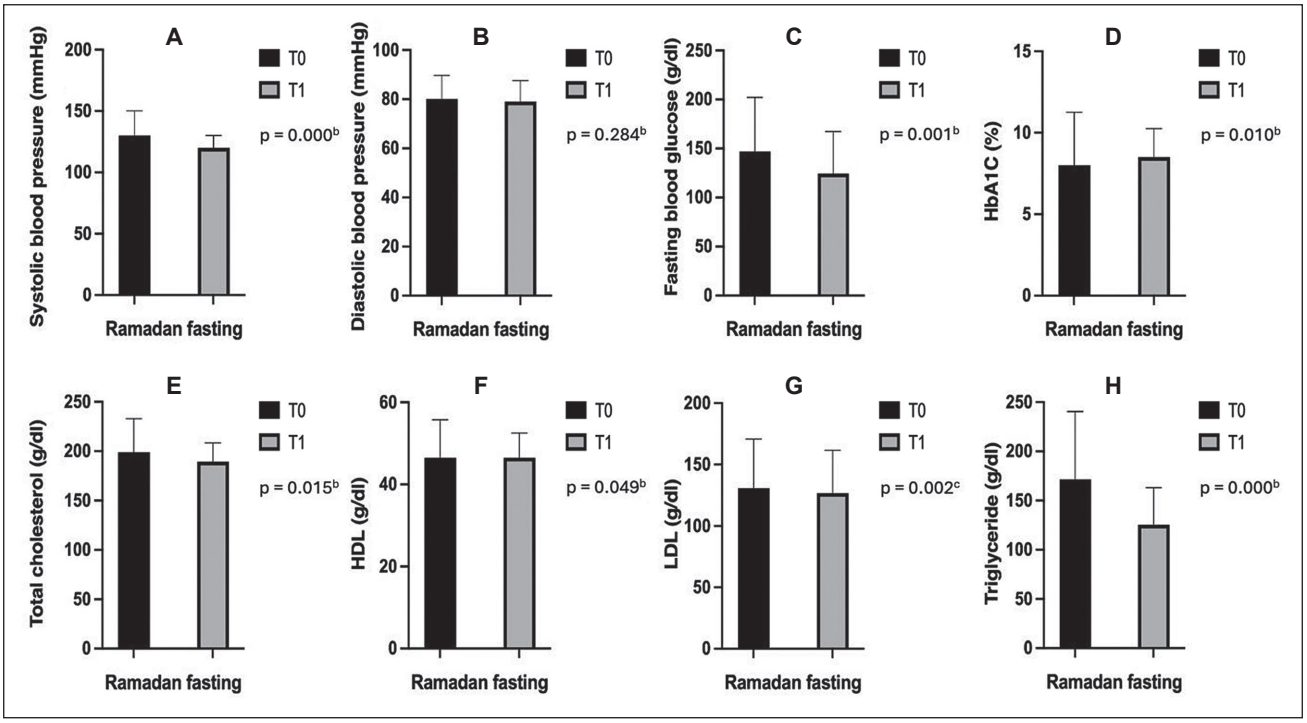


Figure 3. Changes in metabolic parameters after fasting; **(A)** systolic blood pressure, mmHg (median [IQR]), **(B)** diastolic blood pressure, mmHg (median [IQR]), **(C)** fasting blood glucose, g/dl (median [IQR]), **(D)** HbA1c, % (median [IQR]), **(E)** total cholesterol, g/dl (median [IQR]), **(F)** HDL, g/dl (median [IQR]), **(G)** LDL, g/dl (mean [SD]), **(H)** triglyceride, g/dl (median [IQR]).
Note: [b] Wilcoxon test, [c] Paired t-test, significant *p*-value <0.05

diseases mediated by chronic-low grade inflammation and oxidative stress.[20] A decrease in total calorie intake may affect the nutrient-sensing pathway by stimulating sirtuin 1 (SIRT1), AMP-activated protein kinase (AMPK), and inhibit mammalian target of rapamycin (mTOR), which plays a role in autophagy stimulation, suppressing chronic inflammation, and stimulating mitochondrial biogenesis. SIRT1 is also known to stimulate telomerase activity directly. After fasting, cells may exert an improved adaptive response to stress and DNA damage. Thus, we may infer that telomere shortening in patients with T2DM is inhibited by other factors that are suppressing chronic inflammatory processes in adipose tissue.[21,22]

In our study, hypoglycemic episodes did not occur in all subjects. This may be due to the recruitment process that did not include patients who are high-risk for fasting based on the IDF-DAR stratification. A study conducted by Harbuwono et al.,[23] also assessed blood glucose variability using the mean amplitude of glycemic excursion (MAGE) to evaluate glycemic profile before and after Ramadan fasting in patients with T2DM on oral anti-diabetic agents. The study showed no significant difference before and after fasting.[23] We may conclude that Ramadan fasting is relatively safe if patients are educated to carefully monitor their blood glucose, most importantly before iftar, as hypoglycemic management before iftar may undermine their fasting on that day. Also, to reduce the risk of hypoglycemia, preliminary efforts such as hypoglycemia risk assessment and adjustment of drug dosage and food intake may be beneficial before Ramadan fasting.

To our knowledge, this was the first study discussing telomere length differences on subjects with T2DM in Indonesia. This study also pioneered evidence regarding the effects of Ramadan fasting on leukocyte telomere length in patients with T2DM. However, there were several limitations to our study. We did not include subjects with T2DM who did not undergo Ramadan fasting, because the focus of this study was to determine the association of rLTL on patients with T2DM who did RF. We also used secondary data retrospectively and encountered data availability issues, resulting in a reduced number of subjects being analyzed due to incomplete data on metabolic profile and anthropometric measures. Furthermore, data obtained from the questionnaire were relatively subjective, bringing about the issue of recall bias. However, to minimize this risk, patient data was adjusted with objective data obtained. Additionally, the minimum duration of Ramadan fasting was set to only 14 days to minimize lost-to-follow-up occurences in the study due to subjects' unavailability during Eid-al-Fitr (end of Ramadan celebration); consequently, effects may not have reached the optimum. Lastly, this study did not consider the subjects' previous sunnah (optional) fasting habits, which may have a cumulative positive effect on telomere length.

CONCLUSION

This study showed that there was no significant difference in rLTL before and after at least 14 days of Ramadan fasting in subjects with T2DM; however, this study showed a tendency to have an increase in rLTL. Therefore, further

research is needed to evaluate the effects of time-restricted feeding, such as Ramadan fasting, on telomere length in patients with T2DM and correlate this with telomere and telomerase levels.

Acknowledgments
The authors would like to convey their appreciation to Fauzan Illavi, Yoga Dwi Oktavianda, Tika Pradnjaparamita, Maria Fajri, Cicia Firakania, and Brama Ihsan for their technical assistance during data collection, as well as Rona Kartika for her laboratory assistance.

Statement of Authorship
All authors certified fulfilment of ICMJE authorship criteria.

CRediT Author Statement
MDH: Formal Analysis, Writing – original draft preparation; **FK**: Methodology, Data Curation, Writing – review and editing; **PWL**: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft preparation, Writing – review and editing, Supervision; **SW**: Methodology, Data curation, Writing – review and editing; **RMM**: Writing – review and editing; **AJB**: Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing; **DSH**: Conceptualization, Methodology, Data curation, Writing – original draft preparation, Writing – review and editing, Supervision, Funding acquisition; **DLT**: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition.

Data Availability Statement
Datasets analyzed in the study are under license and not publicly available for sharing.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
This study was supported by Penelitian Dasar Unggulan Perguruan Tinggi Tahun 2020 grant from Universitas Indonesia (grant number NKB-146/UN2.RST/HKP.05.00/2020).

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

How Filipinos View Obesity: Findings From the ACTION APAC Study

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Abstract

Objectives. This sub-analysis of the ACTION APAC study aimed to identify perceptions, attitudes and behaviors related to obesity and its management among people with obesity (PwO) and healthcare providers (HCPs) in the Philippines, identifying barriers to effective care and contributing to management strategies.

Methodology. ACTION APAC was a cross-sectional, non-interventional, descriptive survey conducted from April 14 to May 23, 2022 across nine countries, involving 1,000 PwO and 201 HCPs.

Results. Most participants agreed that obesity is an illness but 91% of PwO felt losing weight was entirely their responsibility. Both groups identified similar motivators and barriers to weight loss. Weight stigma significantly impacted PwO but fewer than half discussed weight with their HCPs. Many PwO were happy with their weight and did not consider themselves as having obesity. Lifestyle modifications were preferred for weight management by both groups, while HCPs were reluctant to prescribe pharmacotherapy or recommend bariatric surgery due to lack of knowledge and cost, respectively.

Conclusion. The study revealed a discrepancy between recognizing obesity as an illness and attitudes towards its treatment, highlighting a need for better education and tailored management strategies that consider cultural factors in the Philippines.

Key words: obesity, chronic disease, socioeconomic factors, weight stigma, Philippines

INTRODUCTION

Obesity is a chronic disease characterized by excessive fat accumulation.[1] Since 1990, global adult obesity rates have more than doubled, while adolescent obesity has quadrupled.[1] This increase in the prevalence of obesity has been exacerbated by the coronavirus disease 2019 (COVID-19) pandemic due to the substantial reduction in physical activity, along with the tendency to overeat resulting from the sudden shift to a work-from-home setup.[2] Obesity is a leading risk factor for multiple comorbidities, including heart disease, stroke and diabetes, underscoring the urgent need to address this global obesity crisis.[1]

In the Philippines, the prevalence of overweight and obesity increased from 20.2% in 1998 to 37.2% in 2018.[3] One study reported a sevenfold increase in the prevalence of obesity in women from Metro Cebu between 1983 and 2005.[4] Childhood obesity rates are also increasing in the Philippines, with a survey showing a rise in obesity from 8.6% in 2015 to 11.7% in 2018.[3]

This trend is correlated with an increase in socioeconomic status, urbanization and other factors.[4] The Philippines has been described as an obesogenic environment,[5] partly due to its cultural background. For example, one study found a positive association between overweight/obesity and the frequency of observing *merienda* (a light meal taken between breakfast and lunch or lunch and dinner).[6] Another study found that Filipina women in the Philippines had a higher prevalence of obesity than Filipina women in Korea, indicating the effect of the environment. However, the same study found that Filipina women in Korea had a higher prevalence of obesity than Korean women in Korea[7] indicating that genetics are also involved. Lifestyle also has a role to play and Filipina women overburdened with work and childcare had the highest body mass index (BMI) values.[8]

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Nicodemus, et al.
Received: July 3, 2025. Accepted: September 15, 2025.
Published online first: April 25, 2026.
https://doi.org/10.15605/jafes.041.01.5121

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It is well reported that Asians are particularly susceptible to insulin resistance and cardiovascular risk at lower body weights[9–11] and according to 2021 data, heart disease, stroke and diabetes are among the top conditions responsible for death and disability in the Philippines.[12] In Filipino patients with COVID, obesity was significantly correlated with higher in-hospital mortality and increased need for intensive care unit admission.[13] These figures illustrate the severe impact of obesity-related illnesses on the nation's health and underscore the need for effective obesity care and intervention strategies.

The obesity crisis in the Philippines has not gone unnoticed and several initiatives aimed at curbing obesity are underway. These include:

- Executive Order No. 51 or the "Philippine Milk Code" (1986): this regulated the marketing of breast milk substitutes.[14,15]
- The Department of Education's Order No. 13, "Policy and Guidelines on Healthy Food and Beverage Choices in Schools" (2017): some local government units have enacted ordinances prohibiting the sale and promotion of unhealthy food and beverages to students inside and near public and private school premises.[5]
- The Overweight and Obesity Prevention and Management Program: part of the Philippine Plan of Action for Nutrition (2017–2022), this government-led initiative addresses obesity prevention and management.[15,16]
- The Republic Act 10963 "Tax Reform for Acceleration and Inclusion (TRAIN) Law" (2018): a tax on sweetened beverages depending on the sugar content.[5,15]
- Philippine Association for the Study of Overweight and Obesity (PASOO): a non-profit organization, PASOO promotes healthy weight management through continuing medical education, public health campaigns, recommendations, and the Exercise is Medicine campaign.[17]

However, these measures have had limited success, and obesity continues to rise,[2] proving that the problem of obesity in the Philippines is complex and the underlying psychosocial factors influencing individuals with obesity and their carers require further investigation. Understanding these factors is essential for developing tailored and effective obesity management strategies.

Effective obesity care relies heavily on the interactions between HCPs and PwO. A cooperative, respectful relationship between HCPs and PwO is crucial for providing optimal care and supporting individuals in achieving and maintaining a healthy weight.[18,19]

The ACTION APAC (Awareness, Care and Treatment in Obesity Asia-Pacific Region) study was conducted to gain further insight into the dynamics of effective obesity care. This study aimed to identify perceptions, attitudes and behaviors related to obesity and its management among both PwO and HCPs. It also sought to uncover potential barriers to effective obesity care in the Asia-Pacific (APAC) region.

Although the primary results from the regional ACTION APAC dataset have been previously reported,[20] this paper presents the findings from the ACTION APAC survey specifically focused on the Philippines. This local perspective aims to provide deeper insights into the challenges and opportunities for improving obesity management in the Philippines.

OBJECTIVES

The primary objective of ACTION APAC was to identify perceptions, attitudes, behaviors and potential barriers to effective obesity care across PwO and HCPs in the APAC region.

The secondary study objectives were to generate insights to guide collaborative action to improve care, education and support for PwO and to create a communication platform to help change how patients and HCPs manage, treat and support obesity.

METHODOLOGY

Study design

The ACTION APAC study was a cross-sectional, non-interventional, descriptive study that collected data from an anonymous, online survey conducted between April 14, 2022 and May 23, 2022. Nine countries in the APAC region were included: Bangladesh, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, Thailand and Vietnam. The survey was conducted by a healthcare consultancy firm (KJT Group, Inc., Rochester, New York, United States) through existing online databases/panels. The study received an exemption from the Western Institutional Review Board Copernicus Group (WCG International Review Board – Washington, USA), as it contained adequate protections for the privacy of subjects and maintained confidentiality of data. The full methodology for the ACTION APAC survey has been reported previously.[21]

Study cohorts

Separate surveys were completed by PwO and HCPs. All participants provided informed consent.

PwO were eligible for inclusion if they lived in the Philippines, were aged ≥18 years, and had a current BMI of ≥25 kg/m^2 based on self-reported height and weight. PwO were excluded if they were pregnant, had previously participated in the survey, were actively participating in intense fitness programs (defined as more than 150 minutes of mild-to-moderate intensity exercise per week), or had experienced significant, unintentional weight loss in the past 6 months. PwO who were currently receiving weight loss medications were also eligible for inclusion.

HCPs were eligible for inclusion if they were a medical practitioner in the Philippines, aged ≥18 years, has been in practice for ≥2 years, had seen ≥100 patients (including ≥10 PwO) in the past month, and spend at least half of their professional time in direct patient care. HCPs with previous study participation or language barriers precluding adequate understanding or cooperation with the study were excluded.

Sample sizes were selected to balance statistical power, recruitment feasibility and cost. PwO sample sizes for the Philippines were targeted to achieve a 2–3% margin of error around a proportion estimate of 50%, with the margin of error calculated from a standard normal (Z-) distribution with z=1.96, or approximately a 95% level of confidence.

Survey design

Survey questions were based on three previous ACTION studies (United States,[22] Canada,[23] and International Observation [IO][24]) and adjusted for the APAC region using feedback from a panel of local scientific experts.

Different questionnaires were developed for PwO (Supplement A) and HCPs (Supplement B) and were available in both English and Tagalog.

In both the PwO version and the HCP version of the survey, topics addressed included perceptions, behaviors and awareness related to obesity and obesity management. Questions were also included on the stigma associated with being overweight, as this is an important topic with implications for healthcare.

Responses were quantified using single- and multiple-item selections reported as frequencies and percentages. A five-point Likert scale was used to measure certain attitudes or opinions. A commonly used scale within the study was agreement, measured from 1 "strongly disagree" to 5 "strongly agree."

Ethical approval

The WCG Institutional Review Board prospectively reviewed and approved the study. The study and data accumulation conformed to Philippine laws and local guidelines, informed consent was obtained from participants and the study was in adherence to the tenets of the Declaration of Helsinki.

Data collection

Pre-test interviews lasting 60 minutes were conducted with six PwO and six HCPs (three each of primary care physicians and specialists) in Indonesia, India, Pakistan, Thailand and Singapore, to assess face validity prior to launch of the quantitative surveys. Participants took the survey online while speaking with an in-country moderator by telephone or in person.

The PwO and HCP surveys were reviewed by the WCG International Review Board and approved per local regulations.

Data were collected in the survey with Decipher Survey Software (Focus Vision Worldwide Inc., Stamford, Connecticut, United States), which was administered via online panels, telephone and in person.

The study was conducted under the Declaration of Helsinki and the European General Data Protection Regulation. All data were stored on secure servers and transferred anonymously (without participants' personal information) to Novo Nordisk in an encrypted Study Data Tabulation Mode format at the end of the study. Participants completing the survey received modest compensation for their participation.

Data analysis

Analysis of de-identified data was conducted by KJT Group using various statistical software packages, including IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, New York, United States), STATA/IC, version 14.2 (Stata Corp LLC, College Station, Texas, United States) and Excel, version 365 (Microsoft Corporation, 2024). Descriptive statistics (means, frequencies) were calculated using Q Research Software, version 5.14.2.0 (Displayr Pty, Ltd., New South Wales, Australia). Categorical data are presented as counts and percentages.

To minimize selection bias, PwO data were weighted to representative demographic targets within each country for age, gender, household income, education and region based on data from the 2011 International Standard Classification of Education, the International Data Base and other public data. Weights were calculated using a raking technique to achieve the nearest possible sample and target balance, with individual respondent's weights capped at 0.5 and 5.00 to avoid extreme design effects.

Outliers were identified as falling outside 1.5 × the interquartile range and extreme outliers were identified as those outside 3 × the interquartile range. Extreme outliers were removed subjectively from mean calculations throughout the report based on data distribution implications on reported findings.

RESULTS

Demographics

A total of 1,000 PwO and 201 HCPs completed the survey. Of the PwO, 53% were female and 47% were male. The mean age was 37.2 years and the majority (59%) had Class I obesity (BMI: 25–29.9 kg/m^2), 27% had Class II obesity (BMI: 30–34.9 kg/m^2), 8% had Class III obesity (BMI: 35–39.9 kg/m^2), and 6% had Class IV obesity (BMI: ≥40 kg/m^2).

Most of the HCPs were male (87%) and had an average of 9.8 years in practice. Nearly three-quarters of the HCPs (71%) were obesity specialists (i.e. ≥50% of patients seen primarily for obesity), 90% considered themselves as experts in obesity, and 91% had received advanced training in obesity. See Tables 1 and 2 for the characteristics of the study sample.

Perceptions of obesity, weight loss motivations, and barriers

It was agreed by 65% of PwO and 88% of HCPs that obesity is a chronic disease.

Table 1. Key demographics and characteristics of the study population (PwO)

	PwO (n=1,000)
Age, years, mean	37.2
Male (%)	47
Female (%)	53
Obesity class [a]***, (%)***	
Class 1 (BMI 25–29.9 kg/m^2)	59
Class 2 (BMI 30–34.9 kg/m^2)	27
Class 3 (BMI 35–39.9 kg/m^2)	8
Class 4 (BMI ≥40 kg/m^2)	6
Setting, (%)	
Urban area	56
Suburban area close to a city	30
Rural area	14
Comorbidities, (%) [b]	
High blood pressure	27
High cholesterol	15
Eating disorder	11
Depression/anxiety	13
Type 2 diabetes	10
Cardiovascular disease	9
None listed	41
Education, (%) [c]	
No education	1
Primary	5
Secondary	22
Undergraduate	22
Graduate	51

[a] Obesity class definitions differ between countries.
[b] Percentages do not add to 100 because respondents could select multiple responses.
[c] Due to rounding, the percentages stated do not add up to 100% exactly.
BMI, body mass index; PwO, people with obesity

Table 2. Key demographics and characteristics of the study population (HCPs)

HCP practice category, (%)	HCPs (n=201)
Received advanced training in obesity	91
Provides care for obesity as primary treatment objective	93
Time providing obesity care to patients, (mean years)	7.1
Part of interdisciplinary obesity treatment team	93
Considered self an obesity expert, (%)	90
Obesity specialist, (%) [a]	71

[a] An obesity specialist is defined as a physician who reported seeing ≥50% of patients specifically for obesity/weight management.
HCP, healthcare provider

The majority of PwO (91%) believed that they were responsible for their weight loss, but 80% considered that their HCP had a responsibility to support their efforts (Figure 1a).

For PwO, top goals for weight loss were to prevent a health condition and/or to reduce the risks associated with excess weight (40%), to live a longer life (31%) and to feel more confident/less judged by others (27%). In terms of motivation, PwO wanted to feel better physically and to have more energy (44%), to be more confident (36%) and more fit (36%). HCPs were broadly aligned; they believed that wanting to feel better physically (37%), general health concerns (23%) and wanting to be more confident (26%) were the top motivators for PwO to lose weight. The top 10 weight-loss motivators according to PwO and HCPs are shown in Figure 2. Both PwO and HCPs agreed that a lack of exercise (91% and 90%, respectively), preference for unhealthy food (88% and 93%, respectively) and metabolism (91% and 94%, respectively) were among the top barriers for PwO to lose weight. The top 10 barriers to weight loss according to PwO and HCPs are shown in Figure 3.

Perceptions of current weight, weight-loss attempts, and outcomes

Most participants were aware that they carried excess weight, yet 3 out of 5 (61%) believed that they were of normal weight or overweight rather than obese.

Some PwO (39%) believed that their life was controlled by their weight and more than half (58%) believed that, despite their best efforts to diet, they would revert to previous eating habits. Almost half (47%) felt that fate and/or other factors beyond their control had an impact on their weight.

At the time of the survey, the cohort of PwO had made an average of three serious attempts at weight loss, while 27% of PwO reported making no weight loss attempt. On average, PwO set a goal to lose 22% of their current weight. Of those who lost weight, 68% reported weight regain after successfully maintaining weight loss for 6 months or more. HCPs believed that just over half (56%) of the PwO under their care had made a serious weight loss effort and that only 52% of those were successful. PwO cited not following their eating plan (48%), discontinuing exercise (42%) and difficulty maintaining the changes they had made (35%) as the most common reasons for weight regain (Figure S1).

Perceptions of weight stigma

PwO and HCPs believed that having obesity made it harder for PwO to form a romantic relationship (63% and 37%, respectively), get a job (57% and 32%) and be successful in the workplace (50% and 33%). Obesity was viewed as having a somewhat or very negative impact on others' perception in terms of being athletic (61% and 24%, respectively), healthy (62% and 25%) and/or how much willpower a person has (52% and 18%).

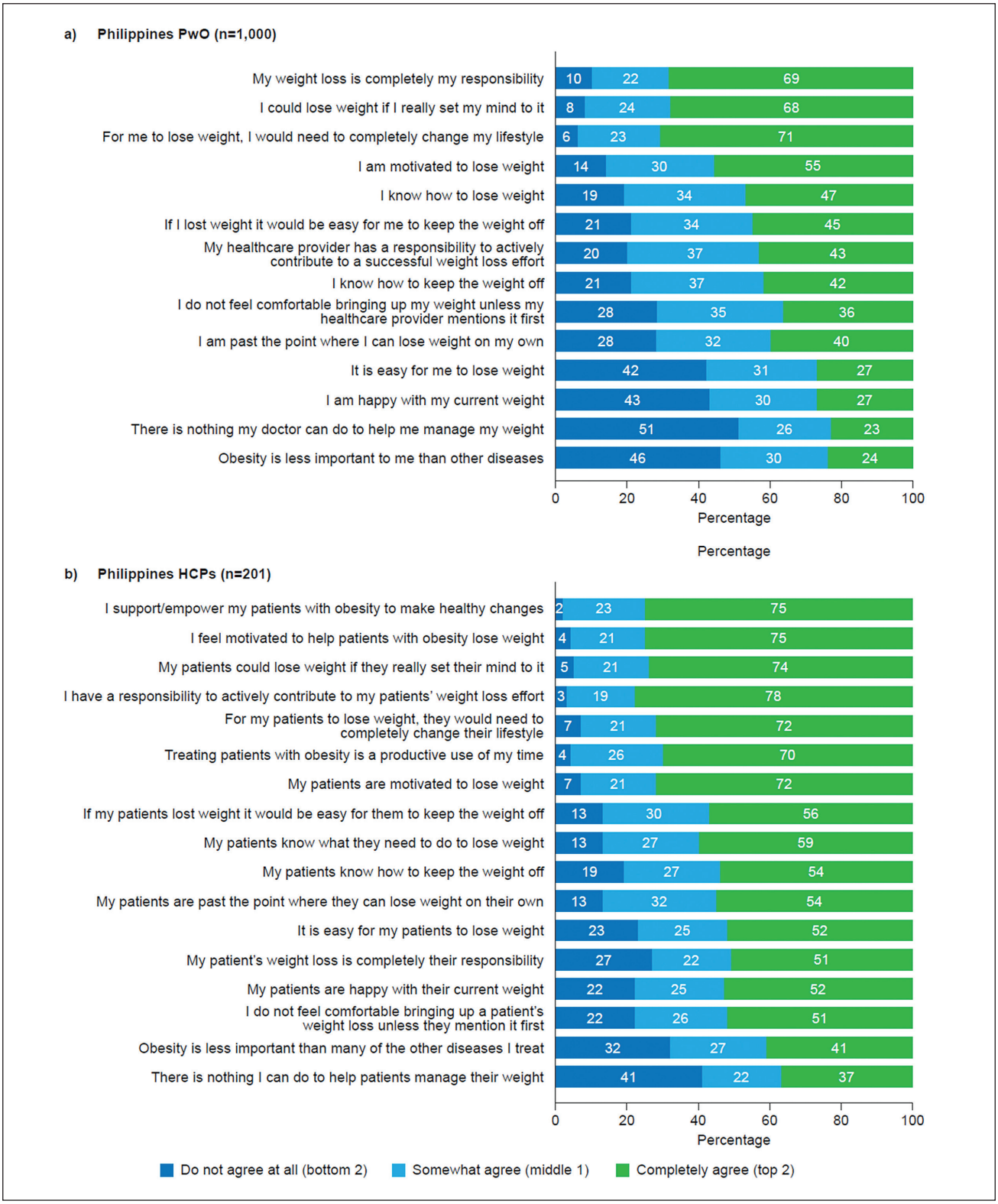


Figure 1. PwO and HCPs' attitudes toward obesity and weight management.

[a] Based on the question to PwO, "Please indicate how much you agree with each of the following…"

[b] Based on the question to HCPs, "Thinking of your patients with obesity as a whole, please indicate how much you agree with each of the following…"

Due to rounding, the total of the three categories within each entry may not add up to exactly 100% when calculated based on the whole numbers shown.

Interactions between PwO and HCPs

Fewer than half of PwO (44%) reported discussing weight with their HCPs in the past 5 years, with only one-third having spoken with an HCP regarding weight loss in the past 6 months. On average PwO spent 2 years struggling with their weight before discussing it with an HCP. HCPs acknowledged discussing weight with slightly more than half (58%) of their patients with obesity. Barriers to dialogue are shown in Figure 4.

The dialogue was initiated by PwO just under half the time (46%, self-reported), complementing the HCPs' belief that they initiated the conversation just over half the time (59%). PwO generally liked it when HCPs initiated the dialogue (63%) or, where this did not happen, they would have liked their HCP to do so (69%). Most PwO (74%) felt positive after a discussion.

The main reason cited by PwO for not discussing weight with HCPs was a lack of financial means to support their weight-loss efforts (41%) (Figure 4a). HCPs were likely to initiate a conversation about weight if their patients had a high BMI (36%), if they had obesity-related comorbidities (46%), or if they were at risk of developing new/additional obesity-related disease (48%). Most (86%) were very comfortable or extremely comfortable discussing weight with their patients. However, about a third of HCPs perceived their patients having a lack of interest (32%) and not feeling motivated (29%) as two of the top reasons for which they would not initiate a weight-loss discussion with patients (Figure 4b).

Most HCPs (84%) reported that they recorded the obesity diagnosis in their patients' charts most or all the time, but only informed 56% of PwO of their diagnosis and scheduled a follow-up appointment in 56% of cases. The majority of PwO who discussed weight in the previous 5 years

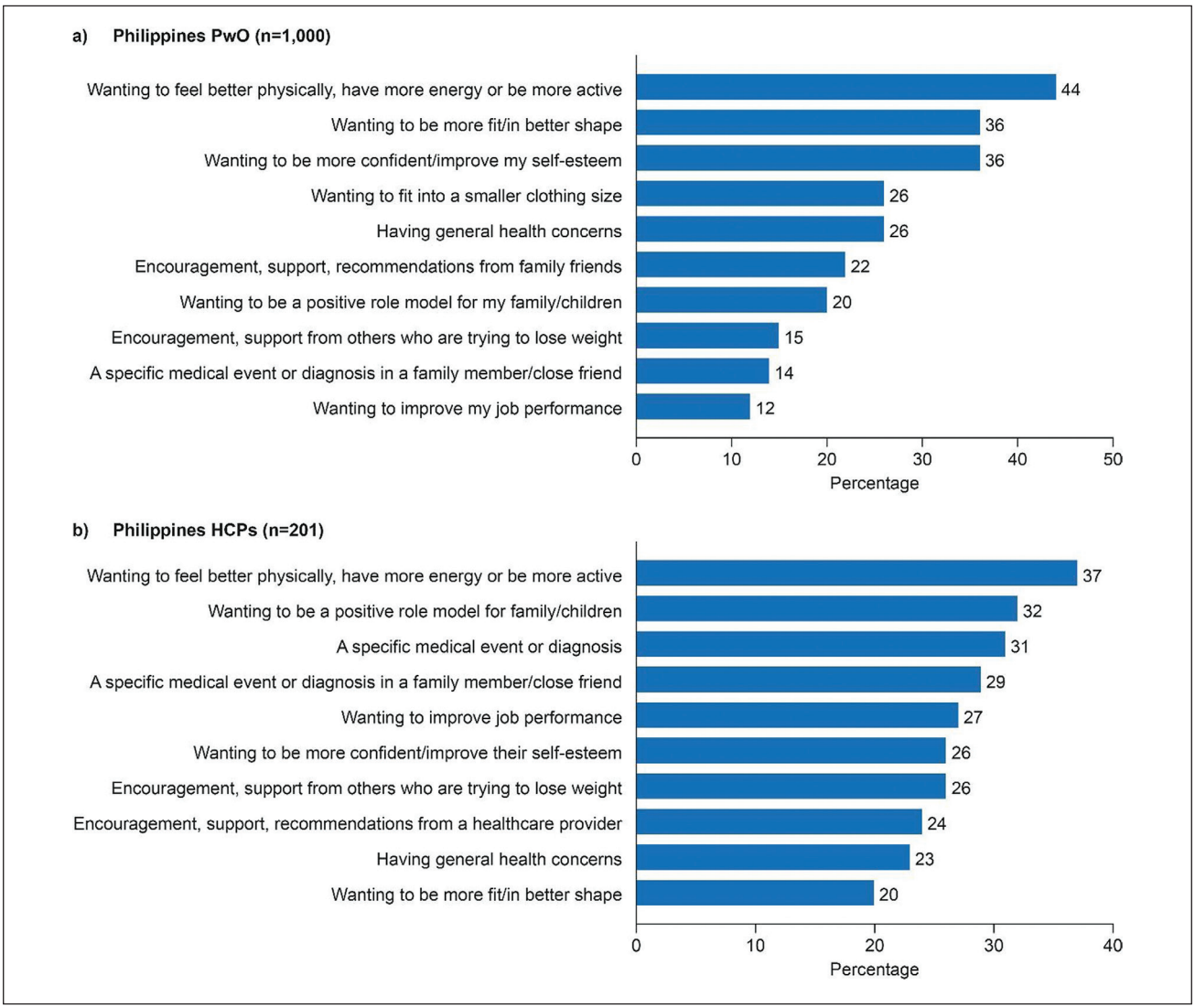


Figure 2. Top 10 motivators for weight loss in PwO.

[a] Based on the question to PwO, "Which of the following, if any, have motivated you the most to lose weight?"

[b] Based on the question to HCPs, "In your experience, which of the following motivates people to lose weight?"

talked to an obesity specialist (63%), with slightly fewer engaging in discussion with a dietitian (42%) or primary care physician (46%).

Attitudes and perceptions of obesity management behaviors PwO reported using the internet, including social media (55%) and smartphone applications (40%) and HCPs (33%) for resources for obesity management.

The most common method recommended for obesity management by HCPs was an electronic app featuring weight loss tracking, healthy eating guidance and physical activity suggestions (30%). Most PwO (70%) preferred to lose weight without medications, despite 53% believing that good weight loss medications are available.

Over half of HCPs (53%) reported not being comfortable with prescribing weight loss medications due to a lack of knowledge. Notably, nearly 40% of HCPs did not believe weight loss medications were useful and expressed concerns about adverse effects (73%) and long-term safety (71%).

Both PwO (80%) and HCPs (71%) would rather use lifestyle changes than undergo or recommend bariatric surgery for weight loss, with most HCPs reporting bariatric surgery to be the last resort for weight loss (68%). Most HCPs believed that there were good surgical options available for weight loss (75%) but felt that cost is a major barrier (61%). HCPs' recommended methods for weight loss and strategies for management are shown in Figure 5.

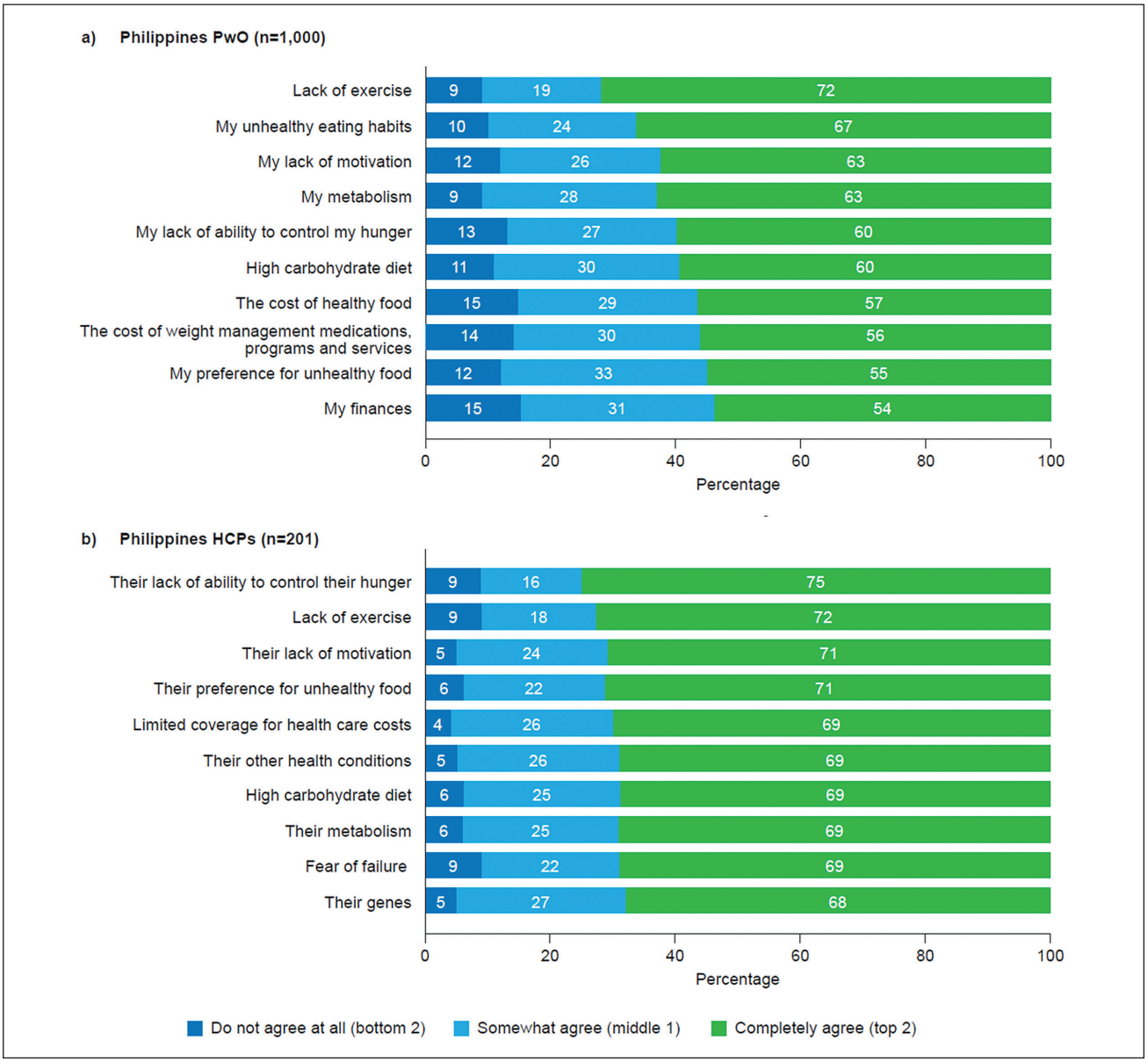


Figure 3. Top 10 barriers for weight loss in PwO.

[a] Based on the question to PwO, "How much do you agree that each of the following is a barrier to you losing weight?"

[b] Based on the question to HCPs, "How much do you agree that each of the following is a barrier to your patients losing weight?"

Due to rounding, the total of the three categories within each entry may not add up to exactly 100% when calculated based on the whole numbers shown.

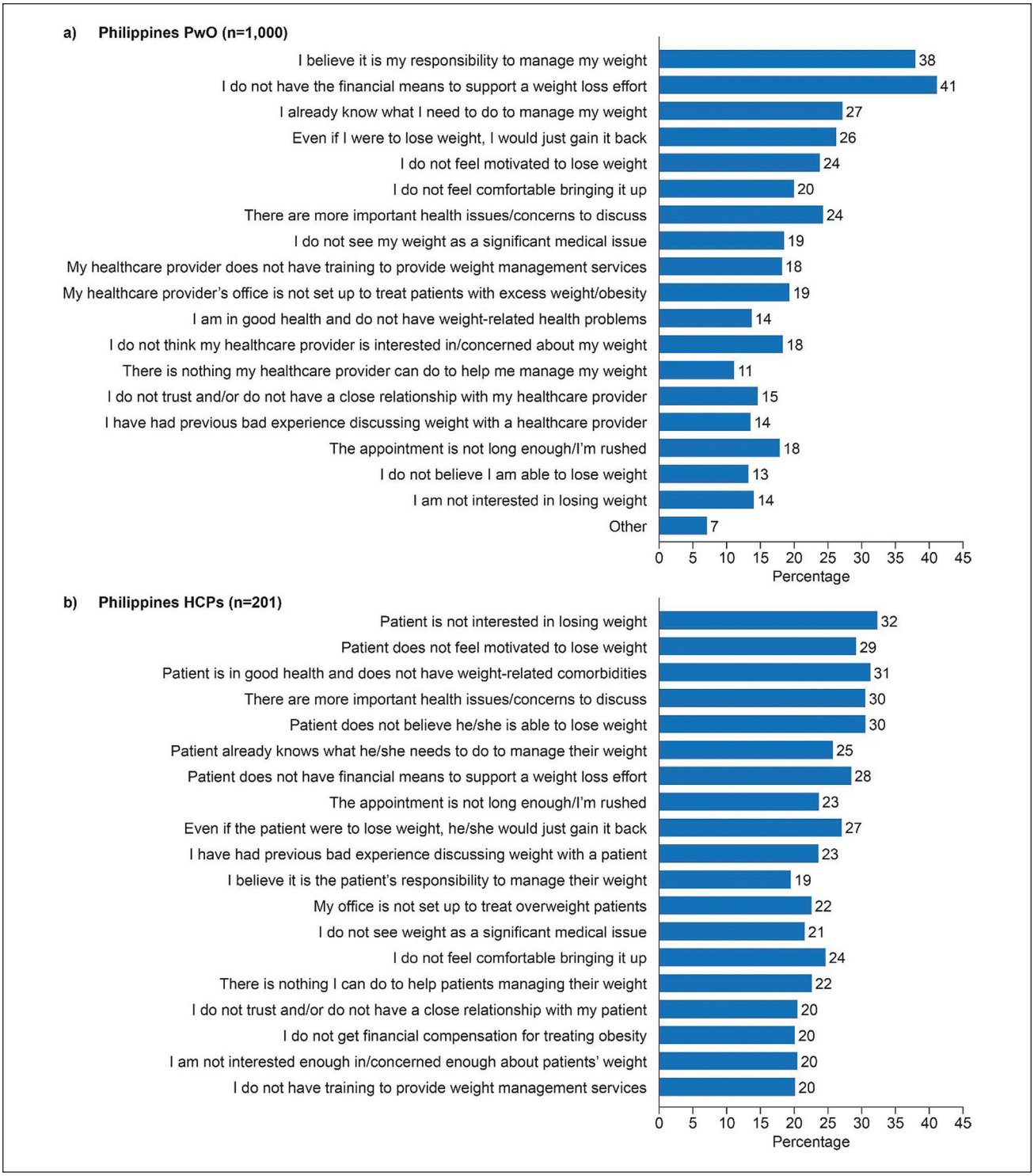


Figure 4. Top reasons for not having a weight discussion.

[a] Based on the question to PwO, "Which of the following are/would be the top five reasons for which you might not discuss managing your weight with your healthcare provider?"

[b] Based on the question to HCPs, "What are the top 5 reasons for which you might not discuss obesity with a patient?" Respondents could select up to five answers in response to this question.

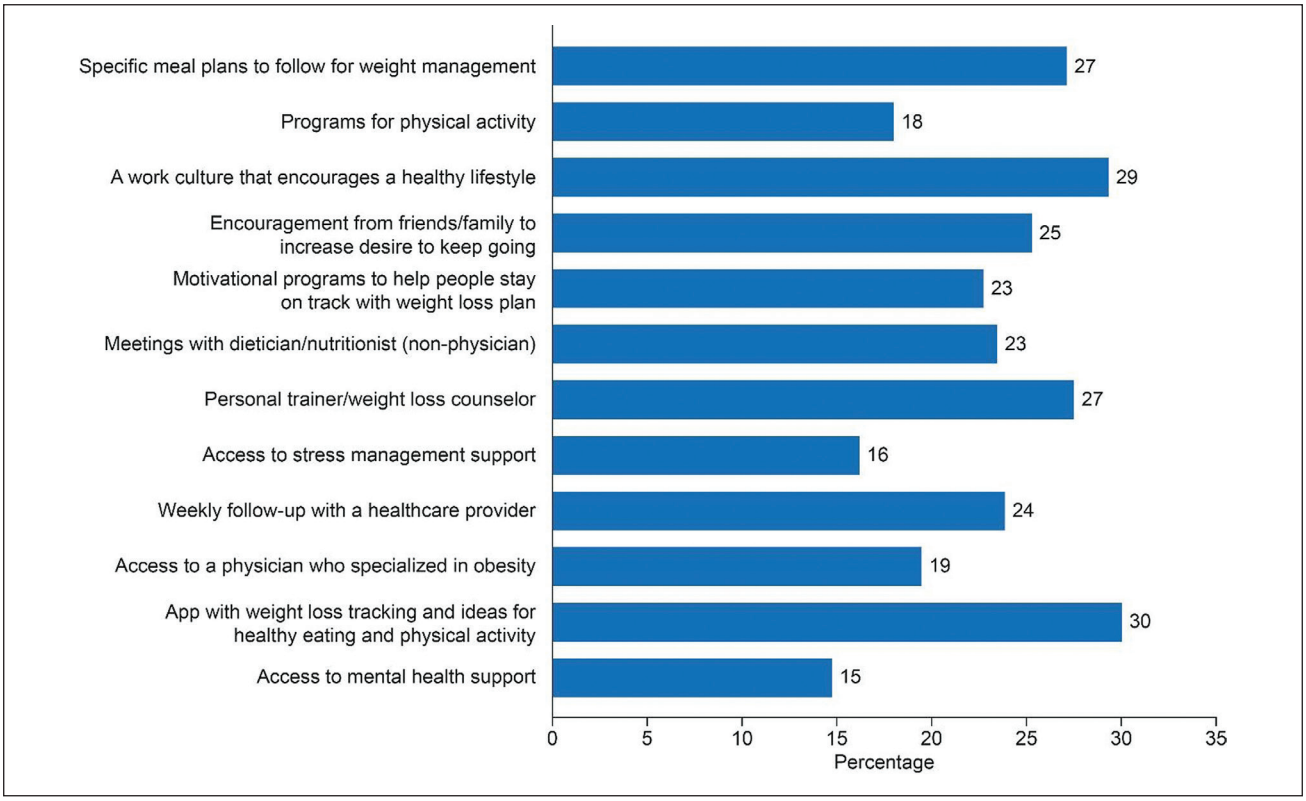


Figure 5. Methods recommended by HCPs for weight management.
Based on the question to HCPs, "What are the top 5 types of support that would be most helpful for your patients to be successful with managing their weight?"

DISCUSSION

The results of the ACTION APAC study provided a comprehensive exploration of the perceptions and attitudes on obesity and its treatment in the Philippines, incorporating the perspectives of both PwO and HCPs. The results of this study largely corroborated those from the rest of the APAC region,[20] and from other ACTION studies,[22–24] with a few notable exceptions, which will be discussed.

HCPs and PwO: Where do they agree and where are they misaligned?

HCPs and PwO were generally aligned in motivations for weight loss and broadly agreed that some of the top barriers for PwO to lose weight were lack of exercise, preference for unhealthy food and metabolism.

However, HCPs identified the impact of other health conditions, including limited mobility due to physical health problems and a lack of understanding of what obesity is as greater barriers to weight loss than PwO. These discrepancies are most likely due to HCPs having more medical knowledge than PwO and recognizing how obesity fits in the bigger picture of overall health.

There was also a discrepancy between HCPs and PwO over perceptions of the stigma surrounding obesity. Fewer HCPs than PwO believed that having obesity made it harder for PwO to form a romantic relationship, get a job and be successful in the workplace. Similarly, HCPs considered the negative impact that obesity had on other people's perception of the athleticism, health and willpower of the PwO to be less than what the PwO themselves considered. Although the stigma itself will be discussed later, the misalignment in the perception of stigma is an important finding.

Interactions between PwO and HCPs

The misalignment in the perception of stigma between PwO and HCPs may explain the communication gap that the study reveals. The study found that fewer than half of PwO chose to discuss their weight with their HCPs in the past 5 years. This is a critical finding, as early and regular dialogue about weight could facilitate more effective management strategies.

The initiation of dialogue about weight loss was roughly evenly split between PwO and HCPs, with 46% of PwO versus 59% of HCPs believing they started the conversation. Around a third of HCPs cited their patients' lack of interest (32%) and motivation (29%) as reasons for not initiating a conversation about weight loss, though it is worth noting that these figures are higher in the rest of the APAC region (41% and 37%, respectively).[20] PwO, on the other hand, were generally in favor of HCPs initiating such dialogue, citing the top reasons for not discussing weight as lack of financial means to support their weight-loss effort (41%) and believing it was their responsibility

(38%). Additionally, most PwO felt positive after such a discussion. These discrepancies indicate that there is a feeling among both HCPs and PwO that the burden and responsibility of obesity management lies with the patient and highlights a problem with the understanding of the condition. In a separate question, a very substantial 91% of PwO agreed that their weight loss was completely their responsibility. This figure was higher than the rest of the APAC region (87%),[20] the IO (81%),[24] Canada (74%)[23] and the US (82%).[22] Why it is so high in the Philippines is unclear and warrants further investigation.

Patients' concerns about financial implications can be addressed when considering the allocation of resources and the inclusion of obesity treatment in healthcare insurance, but feelings of responsibility for their health condition, along with assumptions by HCPs about the patient's interest and motivation place an unhelpful burden on patients. Such a burden may lead to feelings of shame that are not fully understood by the HCP, as reported by their lack of understanding around weight stigma.

Weight stigma and its impact

Internalized and external stigma is a common experience for PwO, with negative consequences for both their physical and mental health and is a reason that PwO may be reluctant to seek medical care.[25] The psychosocial aspects that create barriers to obesity management must therefore not be underestimated and can be addressed by involving psychologists and counsellors in obesity management and employing techniques such as motivational interviewing.[26,27] HCPs must be vigilant about their attitudes towards PwO since their assumptions, even if not stated explicitly, can undermine trust in the therapeutic relationship.[21]

The need for education: PwO and HCPs

Much of this stigma can be overcome by increasing the understanding that obesity is a chronic illness. As seen in the APAC study,[20] and in other ACTION studies,[22–24] the majority of HCPs (88%), and to a lesser extent PwO (65%), agree with this statement but this is not reflected in the management of the condition. Here, education of both PwO and HCPs and a deeper understanding of the biological mechanisms that make achieving and maintaining weight loss so difficult,[28–30] will help to set realistic weight-loss goals. This will also highlight the need for support and a collaborative approach to obesity management, encouraging PwO to seek medical help. It is important that when speaking to patients about their weight, HCPs acknowledge the roles of genetics, environmental influences and individual physiology in obesity risk,[21] reinforcing the understanding that obesity is an illness and reducing the focus on personal responsibility, willpower and motivation.

On a similar note, both PwO and HCPs show a preference for lifestyle modifications over pharmacological or surgical interventions. This preference, while understandable, may limit the utilization of potentially beneficial treatments, especially when lifestyle changes alone prove insufficient. The reluctance of HCPs to prescribe weight-loss medications or refer for bariatric surgery, primarily due to a lack of knowledge and concerns about side effects, indicates a need for better education and training. This should include up-to-date information about the safety and efficacy of potential treatments, which would give HCPs the confidence to make full use of medical interventions. Bariatric surgery results in more extensive and often longer-lasting weight loss compared with lifestyle changes and pharmacotherapy with little risk of serious complications[21] but HCPs consider it a last resort, with 61% considering the cost a major barrier. Again, education about the benefits of surgery and its potential to reduce future costs of accumulating comorbidities should be considered when investing in healthcare.

Cultural factors

Although stigma and lack of education play a key role in preventing PwO from seeking medical help, it is worth noting that there may be cultural aspects at play that have similar results, but for opposite reasons. Of PwO in the Philippines, 57% said they were happy with their current weight. This figure is higher than in the rest of the APAC region (39%)[20] and considerably higher than Canada (20%),[23] IO (6%),[24] or the US (20%).[24] Similarly, 62% of PwO in the Philippines regarded themselves as normal or overweight rather than obese, compared with 45% in the APAC region overall[20] and 50% in both the IO[24] and the US.[22] This may be partly due to confusion regarding different BMI thresholds for obesity. The general public in the Philippines may know obesity as meeting the World Health Organization BMI threshold of ≥30 kg/m^2 rather than the APAC cutoff of ≥25 kg/m^2. The difference in thresholds is based on the evidence that Asian populations are at a higher risk of obesity-related comorbidities at lower BMI levels compared with other populations.[17] However, the acceptance of a higher BMI agrees with one study that found no correlation between health-related quality of life and higher BMI in Filipino adults, and some evidence that those with higher BMIs had better social functioning.[31] It is important to note that acceptance of higher BMIs as healthy and normal may be partly responsible for problems with obesity in the Philippines. In more traditional cultures, large bodies have positive associations[32] and higher body weight is associated with higher social status, particularly in lower- and middle-income countries like the Philippines.[33] This can in part be remedied by public education about obesity awareness and healthy weight, considering cultural differences (discussed below) and biological differences such as the increased adiposity of Asian populations[34] and their increased risk for non-communicable diseases.[9–11,34] However, as countries develop, the positive association observed between obesity and socioeconomic status can be reversed[33] and the message of public education should be carefully considered, as preliminary evidence suggests that anti-obesity messaging leads to an increase in anti-obesity stigma.[32]

Nevertheless, education is particularly important owing to the discordance between known future risks of health complications and the current quality of life related to an increased BMI.[31] A study of adults in Metro Cebu found a significant correlation between obesity awareness and both higher educational attainment and socioeconomic status,[2] indicating that public education should focus on those who have lower educational attainment and socioeconomic status. However, there is also a link between higher educational attainment and the odds of having excess weight,[3] indicating that awareness of obesity alone is not sufficient to prevent it. An effective educational strategy aimed at PwO and those at risk of obesity should take the form of practical workshops with an emphasis on applying knowledge on obesity, rather than lectures alone.[2]

The Better Health Project showed success using a collaborative approach and Local Learning Networks in the Philippines to provide continuing professional development courses on non-communicable disease topics to HCPs using e-Learning platforms and could prove informative about how such education could be delivered to both HCPs and PwO.[35,36]

Informed by the success of the Better Health Project and results from this survey, including the information that 95% of PwO reported using the internet, social media and smartphone applications for obesity management resources, a communication platform could be created to help change how PwO and HCPs manage, treat and support obesity.

Strengths and limitations

A key strength of this study was the large number of participants and high response rate. The inclusion of both PwO and HCPs gave an excellent insight into both sides of what should be a collaborative relationship. The breadth of questions addressed in the survey allowed for consideration of a wide number of topics, including aspects of weight bias and stigma.

As similar surveys were used in the other ACTION studies, we were able to compare data across these countries and draw conclusions about cultural and socioeconomic factors affecting obesity care.

A key limitation of this study was that it was a self-reported cross-sectional survey and therefore may not be a true representation of all PwO and HCPs. Geographic distribution showed a bias toward urban areas, and whilst selection bias was mitigated by weighting the PwO data to represent demographic targets for age, gender, household income, education and region, this remains a potential limitation.

The BMIs of HCPs may also be considered as a limitation as their own body weight may have affected their perceptions of obesity; the BMI of HCPs was not recorded in the survey so this cannot be examined but may be interesting for future study.

Another key limitation of this study is the potential mismatch between self-identified expertise and actual knowledge or competence, particularly in pharmacologic management of obesity. Additionally, our definition of 'obesity specialist' – based on patient volume – may not fully capture the breadth or depth of clinical expertise.

Finally, the weights were self-reported and it has been previously shown that when self-reporting, participants may underestimate their BMI.[37] Moreover, BMI may not be a true representation of adiposity, since a higher BMI in Filipina women is associated with a higher grip strength and muscle mass.[38] Central obesity may be a more useful measure, as it directly causes physical/mobility limitations and indirectly affects activities of daily living through chronic disease morbidity.[38]

CONCLUSION

The ACTION study in the Philippines gives critical insights into perceptions, attitudes and behaviors surrounding obesity management. The recognition of obesity as a chronic disease by both PwO and HCPs is a positive foundation for the management of obesity, but this requires greater focus on the impact of stigma, improving communication between PwO and HCPs and better understanding of treatment options.

To enhance obesity care in the Philippines, several strategies could be considered:

- Enhanced training for HCPs: providing HCPs with more comprehensive education on the psychosocial aspects of obesity and the full range of treatment options, including pharmacological and surgical interventions.
- Facilitating open dialogue: encouraging more proactive discussions about weight between PwO and HCPs through routine check-ups and creating a supportive environment that mitigates stigma.
- Addressing weight stigma: implementing public health campaigns and policies aimed at reducing the stigma associated with obesity to encourage PwO to seek help early and frequently.
- Addressing attitudes to obesity: public health campaigns and policies should consider the specific cultural aspects of the Philippines and ensure that they include culturally relevant discussions on healthy weight and how it is affected by biological differences in the Filipino body type.

By addressing these areas, the gap between understanding obesity as a chronic condition and effectively managing it can be bridged, leading to better health outcomes for individuals with obesity in the Philippines.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
NNJ: Conceptualization, Methodology, Investigation, Writing – review and editing; **EJT:** Conceptualization, Methodology, Software; **CJ:** Conceptualization, Writing – original draft preparation, Writing – review and editing, Visualization; **JF:** Writing – review and editing; **CP:** Resources, Writing – original draft preparation, Supervision, Project administration, Funding acquisition; **DL:** Conceptualization, Validation, Investigation, Writing – original draft preparation, Writing – review and editing, Funding acquisition.

Data Availability Statement
The data used and/or analyzed in this manuscript are proprietary but will be made available from the corresponding author upon reasonable request.

Author Disclosure
Dr. Nemencio Nicodemus Jr. is the immediate past President of the Philippine Association for the Study of Overweight and Obesity and has received speakership honoraria for obesity-related discussions from pharmaceutical companies.

Dr. Edgardo Juan Tolentino is a past President of the Philippine Association for the Study of Overweight and Obesity.

Dr. Cecilia Jimeno is the Vice Editor-in-Chief of the Journal of the ASEAN Federation of Endocrine Societies. She receives honoraria as a member of the speakers' bureau of Sanofi Aventis, Merck, Abbott, Menarini, and GSK, and serves as a member and Treasurer of the Board of Directors of the Philippine Lipid and Atherosclerosis Society.

Dr. Joy Arabelle Fontanilla receives consulting fees from Novo Nordisk and Zuellig Pharma as an Advisory Board member and receives speakership honoraria from the same companies. She is a Board Member of the Philippine Society for Parenteral and Enteral Nutrition, past President of the American Association of Clinical Endocrinologists – Philippine Chapter, and Head of the Center for Weight Intervention and Nutrition Services at St. Luke's Medical Center Global City, Philippines.

Drs. Cyrus Pasamba and Danieson Lampano are employees of Novo Nordisk Pharmaceuticals Philippines.

Funding Source
This study was sponsored by Novo Nordisk, which also provided financial support for medical editorial assistance from Dr. Charlotte Mulcare and Dr. Liam Sebag-Montefiore of The Salve Health Ltd.

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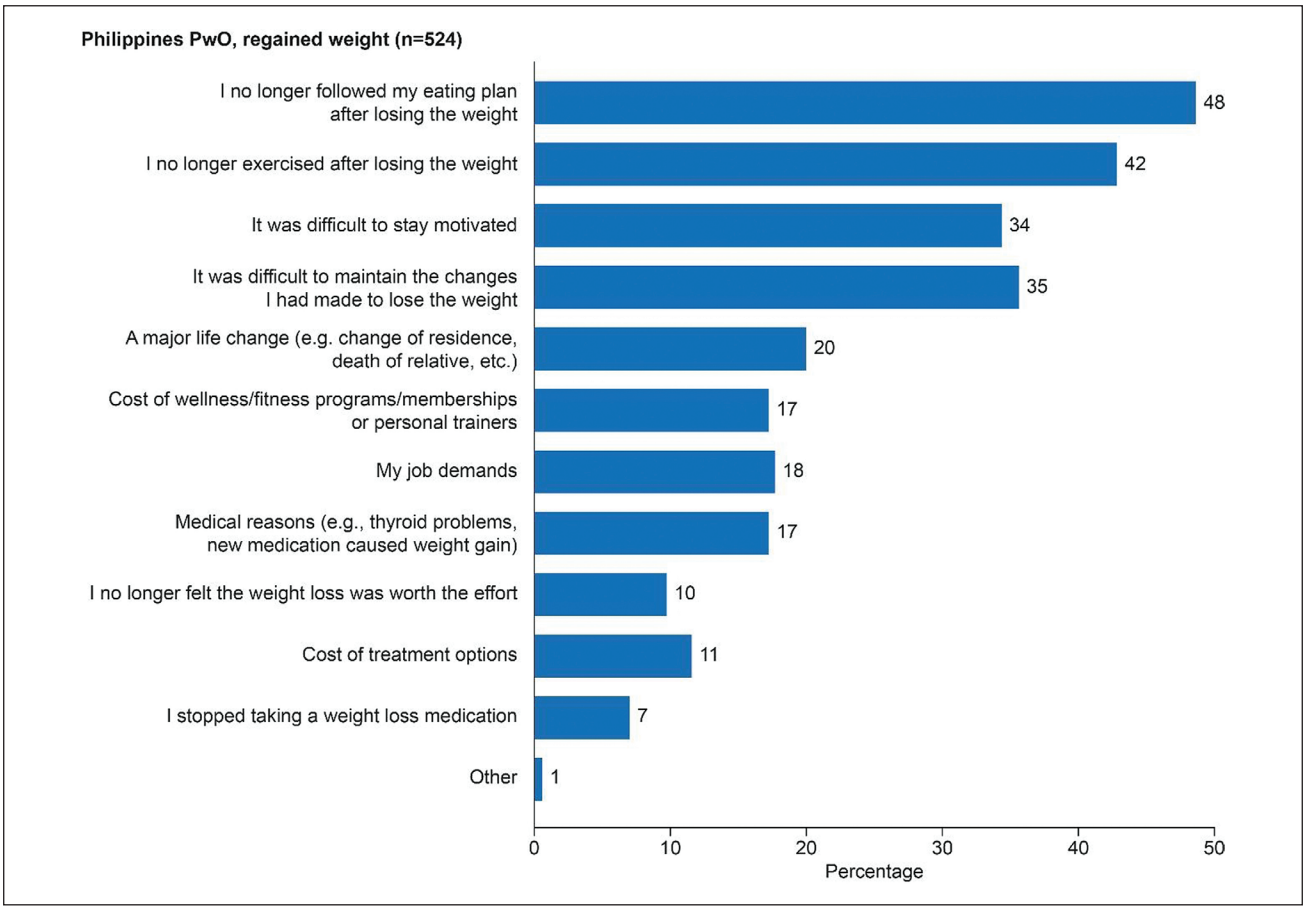


Figure S1. Reasons for regaining weight according to PwO.

Percentage of people with obesity (PwO) who indicated their level of agreement was a 4 or a 5 on a 5-point scale where 1 meant “Do not agree at all” and 5 meant “Completely agree.”

ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

The Prevalence and Risk Factors for Persistent Hyperparathyroidism in Post-Kidney Transplant Patients: A Single-Center Retrospective Study

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Abstract

Background. Persistent hyperparathyroidism (PHPT) remains a notable challenge among kidney transplant recipients due to its impact on calcium-phosphorus metabolism, potentially hindering recovery and long-term renal function. Understanding its prevalence and risk factors is vital for enhancing patient outcomes.

Objective. To determine the prevalence and identify risk factors for persistent hyperparathyroidism in adult Filipino kidney transplant recipients at a tertiary care hospital.

Methodology. A retrospective chart review was conducted for 80 kidney transplant recipients at Cardinal Santos Medical Center from January 1, 2014, to July 31, 2024. Data included demographics, comorbidities, medications, and laboratory profiles pre- and post-transplant.

Results. Persistent hyperparathyroidism was found in 58.8% of patients. Their mean age was 55.3 years, and 53.8% were male. Hypertension was present in 76.3%, and 60% had diabetes mellitus. Diabetic kidney disease was the leading cause of renal failure (57.5%). Post-transplant use of vitamin D supplements and calcimimetics increased by 31.3% and 26.3%, respectively. Pre-transplant hyperparathyroidism was a key risk factor, with a prevalence of 26.3%.

Conclusion. Regular monitoring and management of hyperparathyroidism are essential to improving long-term outcomes in kidney transplant recipients.

Key words: hyperparathyroidism, kidney transplantation, prevalence, risk factors

INTRODUCTION

Chronic kidney disease (CKD) is frequently complicated by renal hyperparathyroidism (rHPT), driven by imbalances in calcium, phosphate, and vitamin D. This condition causes elevated parathyroid hormone (PTH) levels and is associated with increased cardiovascular complications and bone disease. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend routine screening and management of rHPT in CKD stage 3 patients (eGFR <60 mL/min/1.73 m²). Despite advances in medical treatment such as vitamin D analogues, phosphate binders, and calcimimetics, some patients still require parathyroidectomy to manage long-term effects.[1]

Kidney transplantation is the preferred treatment for end-stage renal disease, offering improved long-term survival and quality of life compared to dialysis.[2,3]

However, post-transplantation persistent hyperparathyroidism (PHPT) remains a significant complication even after successful kidney transplantation (KT). Persistent HPT is linked to adverse outcomes such as renal allograft dysfunction, increased cardiovascular morbidity, bone resorption with a higher fracture risk, and diminished quality of life.[5-10] Tertiary hyperparathyroidism (THPT), a specific type of PHPT, is associated with nephrolithiasis, pancreatitis, soft tissue calcification, and peptic ulcer disease. The management of PHPT is challenging due to the lack of a universally accepted definition for THPT, ongoing debates over optimal treatment approaches, and unclear treatment goals for this patient population.[11]

The reported prevalence of persistent hyperparathyroidism (PHPT) and tertiary hyperparathyroidism (THPT) post-KT varies widely (10-70%) due to differences in diagnostic criteria, such as PTH and calcium thresholds,

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Gaerlan et al.
Received: January 3, 2026. Accepted: February 17, 2026.
Published online first: April 27, 2026.
https://doi.org/10.15605/jafes.041.01.5475

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and the timing of post-transplant assessments.[5,6,12,13] While PTH levels typically decrease significantly within the first 3 months post-KT, diagnosing PHPT can take up to two years, resulting in increased morbidity due to delayed treatment.[5,14,15] As a result, the true prevalence of PHPT and THPT, as well as the patient and transplant-related factors contributing to their development, remain largely undetermined.

Several studies suggest a link between the severity of pre-operative secondary hyperparathyroidism (SHPT) and higher rates of post-transplant graft dysfunction and persistent PHPT.[15-17] However, limited data exists on how advancements in SHPT treatment over the past two decades have impacted the development of THPT. Moreover, specific pre-operative PTH and calcium thresholds for reducing THPT risk remain undefined.

Despite successful kidney transplantation leading to normalization of serum calcium, phosphorus, and calcitriol levels within one year, some patients with well-functioning grafts may still exhibit persistent PTH elevation and hypercalcemia,[18-21] with hyperparathyroidism remaining unresolved in over half of kidney transplant recipients.[22]

This persistent issue may result from incomplete normalization of renal function or residual pre-transplant parathyroid gland hyperplasia.[19] Despite some improvements, the risk factors for persistent hyperparathyroidism are not yet fully understood.[23]

Effective management of persistent hyperparathyroidism (PHPT) requires a clear understanding of how pre-operative secondary hyperparathyroidism (SHPT) management influences post-transplant outcomes. Furthermore, establishing standardized diagnostic and treatment guidelines is essential.

This research aims to clarify the mechanisms underlying PHPT and its impact on patient health. Specifically, the study investigates the relationship between pre-operative SHPT management and PHPT development in kidney transplant recipients. It also analyzes factors contributing to the persistence of hyperparathyroidism in patients with well-functioning grafts (creatinine <2 mg/dL) receiving immunosuppressive therapy.

Understanding these factors is key to enhancing patient care and refining PHPT management strategies, ultimately leading to better outcomes for kidney transplant recipients.

METHODOLOGY

Study design and ethics

This retrospective, single-center observational cohort study focuses on post-kidney transplant patients at a tertiary hospital. Ethics committee approval was granted for this study prior to data collection (Research Ethics Review Committee of Cardinal Santos Medical Center, CSMC RERC CODE 2024-054). Participants include Filipino adults who underwent renal transplantation between January 1, 2014, and July 31, 2024. They must have complete records on demographic data, baseline characteristics, pre-transplant tertiary hyperparathyroidism (THPT), pre-transplant treatment for secondary hyperparathyroidism (SHPT), pre-transplant parathyroid hormone (PTH) levels, post-transplant vitamin D deficiency, BMI, cause of kidney failure, dialysis history, and hypertension history. The study specifically considers post-operative laboratory results within 6 to 12 months after transplantation. Patients excluded from the study include pregnant or breastfeeding women, those who underwent parathyroidectomy as treatment for pre-transplant hyperparathyroidism, and those with incomplete medical records on specified data points.

Definitions and criteria

Persistent hyperparathyroidism (PHPT) was defined as PTH ≥70 pg/mL measured 6 to 12 months post-transplantation, regardless of calcium status. Pre-transplant PTH levels were identified from records obtained within 6 months prior to kidney transplantation. Patients who underwent parathyroidectomy for pre-transplant hyperparathyroidism were excluded to avoid confounding biochemical trajectories resulting from surgical intervention.

Sampling and sample size

Based on institutional census records indicating approximately 10 KT patients per year, the study target was the entire available transplant population from the last decade. Using OpenEpi version 3, the minimum sample size was computed as 73 patients, assuming a population of 100 KT patients, a 95% confidence level, and an estimated PHPT prevalence of 21.5% based on existing literature.[11] The minimum sample size of 73 was met with a final cohort of 80 patients. While the overall sample is powered for primary prevalence, it is acknowledged that subgroup analyses may have limited statistical power due to the cohort size.

Statistical analysis

Summary statistics were collated and tabulated as mean ± SD for continuous data and frequency (%) for categorical data. Normality of continuous data was first checked via formal statistical tests (Shapiro-Wilk and Kolmogorov-Smirnov) and analysis of z-scores. No data imputation was performed; analyses were conducted only on available cases. Sensitivity analysis was performed by excluding outliers to check the robustness of the correlation between PTH and creatinine. Non-normal data were presented as median and interquartile range. Correlations were assessed via Pearson correlation coefficients. This study is exploratory in nature; therefore, *p*-values should be interpreted cautiously as no formal correction for multiple testing was applied.

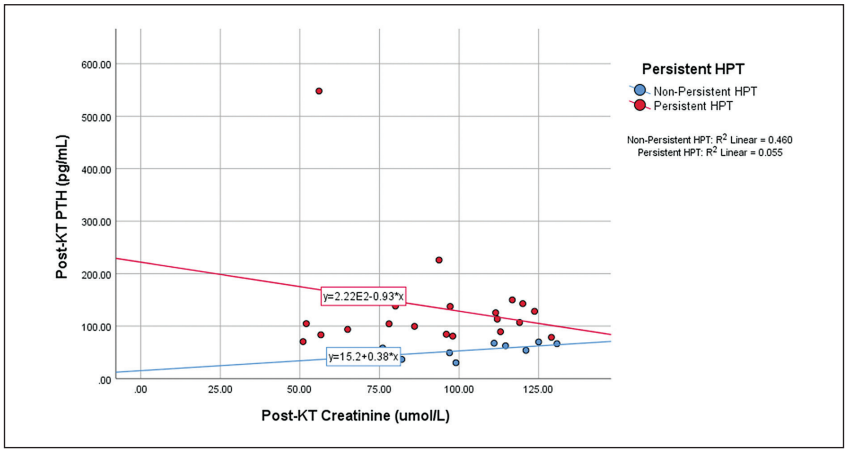


Figure 1. Scatterplot of Post-KT creatinine and PTH levels stratified according to presence of persistent hyperparathyroidism.

Post-transplant PTH measurements, when available, were also used to classify individuals with and without persistent hyperparathyroidism. Tabulations of demographics, independent variables and dependent variables were made as well using these groups.

Statistics were computed using SPSS version 26.

RESULTS

The average age of kidney transplant recipients was 55.3 years (SD = 13.5), with a range of 23 to 79 years (Table 1). Pre-transplant, 26.3% (n = 21) of the sample had secondary hyperparathyroidism (SHPT) (Table 1). Medications taken prior to transplant included calcium supplements (n = 15; 18.8%), various Vitamin D supplements (n = 12; 15.0%), and cinacalcet (a calcimimetic) (n = 2; 2.5%). However, the majority of patients were recorded as not taking any medications or supplements. Available pre-transplant laboratory values for at least five patients each included total serum calcium (n = 11) and serum ionized calcium (n = 6).

Following kidney transplant, medication use increased, particularly for Vitamin D supplements (n = 25; 31.3%) and calcimimetics (n = 21; 26.3%) (Table 2). Other post-transplant medications included alendronic acid (n = 1) and denosumab (n = 1), while calcium supplement use decreased (n = 12; 15.0%). Post-transplant laboratory data were available for serum creatinine (n = 76), serum ionized calcium (n = 70), parathyroid hormone (PTH) (n = 34), and Vitamin D (n = 13). Vitamin D levels and serum creatinine followed a normal distribution. However, serum ionized calcium and PTH levels were both right-skewed, with several outliers exhibiting extremely high values. Of the 34 PTH measurements, 20 (58.8%) exceeded the cutoff of 70 pg/mL, indicating persistent hyperparathyroidism (PHPT) (Table 2).

An initial correlation analysis between PTH levels and serum creatinine revealed a weak, inverse, but statistically non-significant relationship (r = -0.15, R^2 = 2.3%, p = 0.404) (Figure 1). A sensitivity analysis, excluding two outliers (one with a significantly high PTH level and another with a significantly high creatinine level), showed a weak, positive correlation with a slightly improved fit to the data, but it remained non-significant (r = 0.24, R^2 = 5.6%, p = 0.192).

Table 1. Pre-kidney transplant factors abstracted from charts of post-kidney transplant patients

Pre-Kidney Transplant Factors	Post-KT Patients (n = 80)
Age at Kidney Transplant (M, SD)	55.3 (13.5)
History of Hemodialysis (n, %)	
Yes	30 (37.5)
No	50 (62.5)
Secondary Hyperparathyroidism (n, %)	
Yes	21 (26.3)
No	59 (73.8)
Medications Taken (n, %)	
Calcium Supplements	15 (18.8)
Vitamin D Supplements	12 (15.0)
Calcimimetics	2 (2.5)
Others	0 (0)
Laboratory Values (M, SD)	
Serum calcium (mg/dL)	9.2 (0.5)
Serum ionized calcium (mmol/L)	1.2 (0.1)

n = 78 for age, n = 11 for pre-KT serum Ca, n = 6 for pre-KT serum iCa

Table 2. Post-kidney transplant factors abstracted from charts of post-kidney transplant patients

Post-Kidney Transplant Factors	Post-KT Patients (n = 80)
Medications Taken (n, %)	
Calcium Supplements	12 (15.0)
Vitamin D Supplements	25 (31.3)
Calcimimetics	21 (26.3)
Others	2 (2.5)
Laboratory Values (M, SD)	
Serum ionized calcium (mmol/L)*	1.3 (1.2 – 1.4)
Serum creatinine (umol/L)	92.3 (26.9)
Parathyroid hormone (pg/mL)*	82.2 (52.8 – 116.5)
Vitamin D (ng/mL)	27.7 (11.7)

n = 76 for serum creatinine, n = 70 for serum iCa, n = 34 for serum PTH, n = 13 for Vitamin D

*values presented as median and interquartile range

Stratified results

Patients with persistent hyperparathyroidism (PHPT) post-transplant had a higher baseline prevalence of pre-transplant secondary hyperparathyroidism compared to the non-PHPT group (30.0%, n = 6 vs. 14.3%, n = 2; Table 3), though this difference was not statistically significant (p = 0.42). Regarding pre-transplant medications, a higher percentage of PHPT patients used calcium supplements (30.0%, n = 6), while Vitamin D supplementation was more frequent in the non-PHPT group (21.4%, n = 3). Post-transplant, PHPT patients showed higher rates of Vitamin D supplement (45.0%, n = 9) and calcimimetic use (85.0%, n=17) (Table 4). While pre-transplant calcium and post-transplant calcium and creatinine levels were comparable between groups, PTH levels were significantly higher in the PHPT subset (Mdn = 105.95, IQR = 52.34). Mean Vitamin D levels were similar across groups, but the PHPT group exhibited much lower variability (SD = 4.15). Stratified correlation analysis revealed that in the non-PHPT group, PTH levels correlated moderately and positively with serum creatinine (r = 0.68, R^2 = 46.0%, p = 0.011). Conversely, the correlation in the PHPT group remained non-significant, even after excluding the high-PTH outlier.

Table 3. Pre-kidney transplant factors abstracted from charts of post-kidney transplant patients with persistent hyperparathyroidism

Pre-Kidney Transplant Factors	PHPT Patients (n = 20)	Non-PHPT Patients (n = 14)
Age at Kidney Transplant (M, SD)	54.5 (12.9)	56.3 (13.1)
History of Hemodialysis (n, %)		
Yes	6 (30.0)	5 (35.7)
No	14 (70.0)	9 (64.3)
Secondary Hyperparathyroidism (n, %)		
Yes	6 (30.0)	2 (14.3)
No	14 (70.0)	12 (85.7)
Medications Taken (n, %)		
Calcium Supplements	6 (30.0)	0 (0)
Vitamin D Supplements	1 (5.0)	3 (21.4)
Calcimimetics	1 (5.0)	1 (7.1)
Laboratory Values (M, SD)		
Serum calcium (mg/dL)	9.18 (0.57)	9.66 (0.23)
Serum ionized calcium (mmol/L)	–	1.25 (0.13)

Table 4. Post-kidney transplant factors abstracted from charts of post-kidney transplant patients with persistent hyperparathyroidism

Post-Kidney Transplant Factors	PHPT Patients (n = 20)	Non-PHPT Patients (n = 14)
Medications Taken (n, %)		
Calcium Supplements	2 (10.0)	1 (7.1)
Vitamin D Supplements	9 (45.0)	4 (28.6)
Calcimimetics	17 (85.0)	4 (28.6)
Others	1 (5.0)	0 (0)
Laboratory Values (M, SD)		
Serum ionized calcium (mmol/L)*	1.3 (1.3–1.4)	1.3 (1.3–1.4)
Serum creatinine (umol/L)	92.7 (25.9)	94.9 (23.8)
Parathyroid hormone (pg/mL)*	105.9 (85.7–138.0)	47.2 (37.2–63.6)
Vitamin D (ng/mL)	29.8 (4.2)	31.9 (10.0)

DISCUSSION

This retrospective, single-center observational study assessed the prevalence and clinical correlates of PHPT one year after KT. Analysis revealed a 58.8% prevalence of PHPT among the study cohort. The majority of participants (76.3%) had hypertension and diabetes (60%). Predominant etiologies of end-stage renal disease necessitating KT were diabetic kidney disease (57.5%) and hypertensive nephrosclerosis (26.3%). While these findings suggest a link or association between pre-transplant SHPT and post-transplant PHPT, the retrospective nature of the study precludes the determination of causation.

Previous studies report prevalence of PHPT one-year post-KT ranged from 10% to 70%.[11] This variability is likely attributable to inconsistencies in definitions, diagnostic thresholds, and monitoring protocols for PHPT. For instance, a study defined post-transplant PHPT as the concurrent presence of elevated parathyroid hormone (PTH) levels (≥70 pg/mL) regardless of calcium levels at 1 year post-KT.[11] Variations in PTH and calcium monitoring practices across different chronic kidney disease (CKD) stages may also contribute to these disparate rates.[24] The prevalence of 58.8% observed in this Philippine cohort, suggests a higher burden of PHPT compared to global averages, likely driven by several contributing factors.

A high baseline prevalence of pre-transplant secondary hyperparathyroidism (SHPT) often predisposes individuals to post-KT PHPT, while Vitamin D deficiency may further exacerbate both secondary and tertiary hyperparathyroidism. Additionally, genetic predispositions within certain populations may influence the development of severe hyperparathyroidism.[11] Moreover, post-transplant management – including the use of immunosuppressive medications affecting calcium metabolism, calcium and vitamin D supplementation protocols, and monitoring practices – play a significant role in of post-KT PHPT prevalence.[11]

In this study, patient-specific factors likely contributed to the higher observed PHPT prevalence. Most PHPT cases occurred in individuals with pre-transplant hyperparathyroidism, with advanced age, diabetes, and vitamin D deficiency identified as additional risk factors. Consistent with previous data, an increased pre-KT PTH level was associated with a higher likelihood of PHPT post-KT,[11,25] highlighting the importance of pre-transplant PTH levels as a key predictor of post-transplant PHPT.[25]

Notably, only 37.5% of the study population underwent pre-transplant renal replacement therapy, with the majority receiving preemptive kidney transplantation. Although there is no clear association regarding PHPT post-KT and early transplantation, studies have proven that pre-emptive KT provides a lower risk of allograft failure and acute rejection. Potential risks from hemodialysis such as catheter-related infection, cardiovascular adverse

effects, intradialytic complications are also avoided in such patients.[26] Stratification by PHPT status revealed no significant differences between groups in terms of sex, hypertension prevalence, or age at kidney transplant. Pre-transplant, calcium supplement use was higher among PHPT patients, whereas vitamin D supplementation was more common in non-PHPT patients. Post-transplant, PHPT patients exhibited higher rates of both vitamin D supplement and calcimimetic use. Previous data suggest that pre-transplant calcium supplement intake may lead to a falsely high rate of hypercalcemia at the time of KT. Additionally, intake of calcimimetics pre-KT may also cause lowering of serum calcium levels, thereby masking patients with true hypercalcemia.[27] Data has also shown that there may also be a "rebound" effect of cessation of calcimimetics at the time of KT, which may lead to subsequent hyperparathyroidism and hypercalcemia, but the exact mechanism is not fully understood.[11]

While parathyroidectomy is the established gold standard treatment for tertiary hyperparathyroidism (THPT), its role in managing normocalcemic hyperparathyroidism (HPT) in kidney transplant recipients remains less clear. In the study conducted, 45% of patients with PHPT were treated with vitamin D supplementation, 85% were treated with calcimimetics, and none underwent surgical intervention. Studies have demonstrated that early surgical intervention for persistent hyperparathyroidism (PHPT) prior to one-year post-kidney transplantation has been shown to improve long-term allograft function compared to medical management. A study has shown that at 1-year-post-KT, THPT had a 1.37-fold higher risk of all-cause graft loss and 1.6-fold higher risk of death-censored graft loss due to promotion of vascular calcification and renal interstitial fibrosis. Other studies have shown significant worsening of allograft function as early as 3 months post-KT.[11,28] However, the optimal timing for intervention remains a subject of debate, with considerable variation observed across different clinical practices.[28]

Limitations

This study acknowledges several limitations. Primarily, the retrospective, single-center observational nature of this research restricts the generalizability of the findings. The relatively restricted sample size, particularly for subgroup analyses, may limit the statistical power and accuracy of the analysis. The relatively limited sample size, particularly when conducting subgroup analyses, may introduce bias and reduce the statistical power of the study. Furthermore, the reliance on retrospective chart review for data collection may have led to incomplete patient information, potentially influencing the accuracy and comprehensiveness of the analysis. Moreover, the sample size precluded the use of multivariable models to adjust for all potential confounders. Future research should prioritize prospective, multi-center study designs with larger, more diverse cohorts to enhance generalizability and statistical power for subgroup analyses. Implementing standardized data collection protocols would also improve the completeness and accuracy of patient information, thereby increasing the reliability and validity of the research.

Beyond methodological considerations, this study highlights the need for standardized clinical practices in managing post-transplant THPT. The development and implementation of evidence-based guidelines for the screening, diagnosis, and treatment of this condition could significantly improve patient outcomes. Such guidelines would serve to standardize care across different centers, ensuring timely and appropriate intervention to minimize the risk of allograft complications and optimize long-term graft function. This proactive approach to patient management would ultimately contribute to improved quality of life for kidney transplant recipients. Despite the limitations of this study, valuable insights into the prevalence and clinical correlates of persistent hyperparathyroidism (PHPT) following kidney transplantation have been gained. The findings underscore the need for vigilant monitoring of parathyroid hormone (PTH) levels both pre- and post-transplantation and emphasize the critical importance of optimizing therapeutic strategies to effectively manage PHPT. This is particularly crucial in the Philippines, where the high burden of chronic kidney disease, potential limitations in access to specialized nephrology care, nutritional factors, and potential genetic predispositions within the Filipino population may contribute to an elevated prevalence of PHPT.

Further investigation is warranted to fully determine the specific factors driving this elevated prevalence. This may involve analyzing patient records, comparing findings with other Filipino studies, and conducting further research to explore risk factors for PHPT within this specific demographic. Ensuring consistency between diagnostic criteria used in data collection and international standards is also crucial for accurate comparisons. A comprehensive understanding of these factors will facilitate the development of targeted strategies for improved prevention and management of PHPT in the Philippines, ultimately mitigating its potential adverse effects on graft function and overall patient outcomes.

CONCLUSION

This single-center observational study revealed a significant prevalence (58.8%) of persistent hyperparathyroidism (PHPT) among post-kidney transplant patients. Pre-transplant hyperparathyroidism was identified as a key risk factor for the development of PHPT. These findings underscore the need for close monitoring and optimized management of hyperparathyroidism in this population to improve long-term outcomes.

Acknowledgments
The authors wish to express their sincere gratitude to the Department of Internal Medicine at Cardinal Santos Medical Center for their exceptional support and collaboration throughout this study.

The authors used ChatGPT for assistance in summarizing and refining discussion points, which contributed to the comprehensive review, meticulous editing, and finalization of the manuscript. The authors have duly overseen, reviewed, edited, and finalized the content.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement (based on Author Form)
PAG: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Funding Acquisition; **HHC:** Conceptualization, Validation, Resources, Writing – review and editing, Visualization, Supervision, Project Administration; **MJF:** Investigation, Resources, Writing – review and editing, Supervision, Project Administration; **JC:** Resources, Writing – review and editing, Supervision, Project Administration

Data Availability Statement
Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Authors Disclosure
The authors declared no conflict of interest.

Funding Source
Self-funded.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Diagnostic Value of Key Clinical Characteristics and Baseline Cortisol in Assessing Adrenal Function in Patients Receiving Glucocorticoid Therapy

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Abstract

Background. Prolonged glucocorticoid therapy may result in multi-organ complications and adrenal insufficiency (AI). To mitigate these risks, clinicians typically taper and discontinue treatment once the underlying disease is controlled. Prior to withdrawal, adrenal function is assessed through dynamic testing. However, dynamic testing often requires multiple blood samples for cortisol measurement, continuous patient monitoring for several hours, and close supervision by medical staff throughout the procedure to assess potential adverse effects. In addition, dynamic tests are typically costly and not all healthcare facilities are equipped to perform such procedures.

Objective. Evaluate the diagnostic performance of baseline cortisol and clinical parameters in the assessment of adrenal insufficiency.

Methodology. Cross-sectional study of 96 patients on prolonged glucocorticoid treatment at Nguyen Tri Phuong hospital. Insulin tolerance test (IST) was the gold standard for diagnosis of adrenal insufficiency.

Results. Among 96 patients, 56 (58.3%) had AI. A positive correlation was observed between baseline cortisol levels and peak cortisol levels during the insulin tolerance test, demonstrating a moderately strong association (r = 0.62, p <0.001). Baseline cortisol had good diagnostic performance, with areas under the receiver operating characteristic curve (AUROC) of 0.83 [95% confidence interval (CI): 0.78-0.89]. If the optimal cutoff value for morning serum cortisol is set at 9.0 µg/dL, the test demonstrates a sensitivity of 69% and a specificity of 67%. We observed that the morning serum cortisol cutoff of 3 µg/dL had a positive predictive value (PPV) of 100% and the morning serum cortisol cutoff of 15 µg/dL had a negative predictive value (NPV) of 100%. Among the predictive models for AI, the model incorporating baseline characteristics such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension, and baseline cortisol demonstrated the highest predictive accuracy, with an AUC of 0.87 (95% CI: 0.80-0.94).

Conclusion. The assessment of baseline cortisol in conjunction with baseline characteristics offers a reliable method for predicting the risk of adrenal insufficiency, thereby minimizing the necessity for expensive and intricate dynamic testing. In circumstances where dynamic testing is not feasible due to limitations in resources, cost, or expertise, we advocate for the implementation of a model that incorporates baseline characteristics and cortisol levels. This approach provides a practical, cost-effective solution for evaluating adrenal function, requiring only a single blood sample and ensuring broader accessibility.

Key words: Adrenal insufficiency, glucocorticoid therapy, baseline cortisol level, insulin tolerance test, predictive model

INTRODUCTION

Adrenal insufficiency is a life-threatening condition that may be caused by primary adrenal insufficiency or secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis. The prevalence of secondary adrenal insufficiency is estimated to be approximately 150-280 cases per million people, with a higher prevalence in females compared to males.[1,2] Among the etiologies of secondary adrenal insufficiency, the use of exogenous glucocorticoids is the most prevalent cause.[1,3] A systematic review and meta-analysis reported a 48.7% risk of secondary adrenal insufficiency in patients using oral glucocorticoids, 7.8% with inhaled glucocorticoids, 4.7% with topical glucocorticoid application, and 4.2% with intranasal glucocorticoids. The highest risk, 52.2%, was

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Nguyen et al.
Received: July 10, 2025. Accepted: September 13, 2025.
Published online first: April 30, 2026.
https://doi.org/10.15605/jafes.041.01.5195

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observed in patients receiving intra-articular glucocorticoid injections.[4] The widespread overuse of glucocorticoids in Vietnam stemming from their easy accessibility and broad availability poses a significant clinical concern. In addition to over-the-counter use, these agents are commonly prescribed by specialists for various conditions. Prolonged glucocorticoid therapy may result in multi-organ complications and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, leading to adrenal insufficiency. To mitigate these risks, clinicians typically taper and discontinue treatment once the underlying disease is controlled. Before ceasing glucocorticoids, adrenal function should be assessed through dynamic testing to ensure that the risk of adrenal insufficiency is low, thereby allowing for the safe discontinuation of glucocorticoid therapy.[5] In Vietnam, dynamic tests commonly employed to evaluate adrenal function include the Synacthen stimulation test and the insulin tolerance test. Both procedures necessitate multiple blood draws for cortisol measurement and require continuous patient monitoring over a period of one to two hours. These tests must be conducted under strict medical supervision by the endocrinologist and nursing staff to ensure patient safety and to promptly identify any adverse effects. Moreover, the implementation of dynamic testing is challenged by high costs and the limited availability of essential reagents, such as Synacthen, within the local healthcare system. Furthermore, not all medical institutions are adequately equipped to perform these specialized procedures, and non-endocrinologist physicians often lack experience in conducting dynamic tests. Therefore, we questioned whether a simpler and more practical test could replace complex dynamic testing procedures, allowing physicians regardless of specialty to assess adrenal function before safely discontinuing glucocorticoid therapy.

According to the 2024 clinical guidelines of the European Society of Endocrinology and the Endocrine Society, dynamic testing is no longer routinely recommended for diagnosing adrenal insufficiency (AI) in patients who are tapering or discontinuing glucocorticoid therapy.[6] The current clinical practice trend favors the selection of common, inexpensive static tests with simple procedures, offering sensitivity and specificity approaching those of dynamic tests. In this regard, baseline cortisol levels measured 24 hours after the final dose of glucocorticoid are of significant value in assessing the risk of adrenal insufficiency in patients.[6]

Currently, there is no established model or scoring system for assessing the risk of adrenal insufficiency resulting from long-term glucocorticoid therapy. Therefore, our study was conducted with the objective to evaluate the diagnostic value of baseline cortisol level in detecting adrenal insufficiency and to develop a model that integrates clinical features with baseline cortisol level, aiming to assess the risk of adrenal insufficiency associated with long-term glucocorticoid use and to facilitate its application in routine clinical practice.

METHODOLOGY

Study design

This cross-sectional study was conducted at Nguyen Tri Phuong Hospital, a state hospital located in Ho Chi Minh City, Vietnam, from May 2023 to February 2024. The hospital provides both secondary and tertiary care services, receiving patients from within the city as well as referrals from lower-level healthcare facilities in surrounding regions. The hospital primarily serves an urban population with diverse clinical presentations. Patients were recruited based on specific inclusion and exclusion criteria, and all participants underwent the insulin tolerance test (ITT) to assess adrenal function before discontinuing glucocorticoids. Data collection included baseline characteristics, clinical features, underlying conditions, glucocorticoid treatment regimens, the baseline cortisol and serum cortisol levels during the ITT.

Eligibility criteria

Inclusion criteria included patients aged 18 and above with a history of intake of prednisolone greater than or equal to 5 mg per day or methylprednisolone greater than or equal to 4 mg per day, on a daily or alternate-day basis for at least 2 weeks and baseline cortisol levels between 3 and 17 μg/dL.

Exclusion criteria included patients using glucocorticoids for less than 2 weeks, those with baseline cortisol levels greater than or equal to 18 μg/dL or less than 3 μg/dL, night shift workers, pregnant women, patients with a history of epilepsy, coronary artery disease, cerebrovascular disease, cirrhosis with albumin less than 25 g/L, those on glucocorticoid therapy for acute conditions, or those taking estrogen-containing medications, neuropsychiatric medications or neuroleptics.

Baseline characteristics included age, gender, height, weight. Clinical features collected included Cushingoid appearance and glucocorticoid withdrawal syndrome. Underlying conditions indicated for glucocorticoid treatment, comorbidities and characteristics of glucocorticoid treatment are also collected. At the first visit, if the patient met the inclusion criteria and did not violate any exclusion criteria, we asked them to stop taking glucocorticoids for at least two days and scheduled another day for an 8:00 AM serum cortisol test. If the 8:00 AM serum cortisol fell between 3 and 17 μg/dL, we scheduled another day for an insulin tolerance test in the morning at 8:00 AM, and the patient had to ensure they had discontinued glucocorticoids for at least two days before undergoing the insulin tolerance test. Patients who met the inclusion criteria were required to discontinue glucocorticoid treatment for at least 2 days prior to undergoing the ITT. The test was started by intravenous injection of 0.1 to 0.15 UI/kg body weight insulin (Insulin Actrapid Human) to induce hypoglycemia. The patients remained supine and were constantly supervised by an experienced nurse and

doctor. Test quality was defined as adequate only if the plasma blood glucose was less than or equal to 2.2 mmol/L, regardless of the presence or absence of hypoglycemic symptoms. The patient must be alert and able to answer questions, with monitoring of hypoglycemic symptoms and capillary blood glucose every 5-15 minutes. When the blood glucose was less than or equal to 2.2 mmol/L, management depended on the severity of hypoglycemia and the serum cortisol levels were measured at 0 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes after insulin injection. Adrenal function was classified according to the highest cortisol level (peak cortisol). A peak serum cortisol level greater than or equal to 18 μg/dL following the insulin tolerance test (ITT) was considered indicative of normal adrenal function, whereas a peak cortisol level less than 18 μg/dL was diagnosed as adrenal insufficiency. If the blood glucose was greater than 2.2 mmol/L after 30 minutes, we repeated the same insulin dose and continued monitoring hypoglycemic symptoms and capillary blood glucose every 5 to 15 minutes until the target hypoglycemia was reached. If the target blood glucose was not achieved after two insulin injections, the test was discontinued. During the data cleaning process, patients who did not meet the inclusion criteria or met any of the exclusion criteria were removed from the study. In addition, those who declined to participate in our study, refused to undergo the insulin tolerance test, or had contraindications to the procedure were also excluded. Furthermore, patients with missing data on key variables – such as baseline cortisol levels, clinical parameters relevant to the predictive model, or insulin tolerance test results - were excluded from the final analysis.

Sample size

Based on a systematic review and meta-analysis of 30 studies (4), the prevalence of adrenal insufficiency in patients using oral glucocorticoids is estimated at 48.7%. The sample size was calculated using the formula:

$$N = \frac{Z_{(1-\alpha/2)}^2 \times [P(1-P)]}{d^2} = \frac{1.96^2 \times 0.487 \times (1-0.487)}{0.1^2} = \frac{0.9597}{0.01} = 96$$

Where:
N : sample size
z_α : Confidence level 0.95 and $z_{1-\alpha/2} = 1.96$
P : population proportion = 0.487
d : margin error with d = 0.1

Laboratory methods

The baseline cortisol levels in this study were measured using the Chemiluminescent Microparticle Immunoassay (CMIA) method, performed on the Architect system developed by Abbott, USA. The Laboratory Department of Nguyen Tri Phuong Hospital has been certified by the Ho Chi Minh City Center for External Quality Assessment in Medical Laboratory.

Statistical methods

Data were entered into Excel and analyzed using Stata software. Continuous variables with a normal distribution were presented as mean ± standard deviation (SD). Continuous variables without a normal distribution were expressed as median and interquartile range (IQR). Categorical variables were reported as percentages.. The diagnostic values of baseline cortisol levels included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of baseline cortisol levels, using the insulin tolerance test as the reference standard for assessing adrenal function. A peak serum cortisol level ≥18 μg/dL following the insulin tolerance test (ITT) was considered indicative of normal adrenal function, whereas a peak cortisol level <18 μg/dL was diagnostic of adrenal insufficiency.

Predictive models for adrenal insufficiency were constructed utilizing readily obtainable and clinically pertinent baseline characteristics along with baseline cortisol levels, using logistic regression models. Due to the limited sample size, we selected nine clinical characteristics based on their potential in terms of clinical usage and statistical significance (p <0.2 from univariable analyses). We then built a model including all nine clinical variables (model #1), then used stepwise backward to reduce the number of variables (model #2). For model #3 we added baseline cortisol to model #2. Finally we built a model with baseline cortisol as the only covariable (model #4) to see how it performed. The discriminative ability and predictive performance of each model were evaluated using the area under the receiver operating characteristic curve (AUC). Significance was determined according to p <0.05.

Ethics

Ethics approval was obtained from the Ethics Committee of Nguyen Tri Phuong Hospital. Patients were informed about the study and had the right to consent or decline participation. All related testing costs were covered, and data confidentiality was maintained.

RESULTS

During the study period, a total of 96 patients met the inclusion criteria and were enrolled in the study. Among them, 74 were female (77.1%) with a mean age of 47.5 ± 14.3 years. There were no statistically significant differences in age, sex, weight, height, BMI, waist circumference, or blood pressure between the adrenal insufficiency and non-adrenal insufficiency groups. As our sample collection was primarily conducted in three clinics: Rheumatology, Otorhinolaryngology, and Endocrinology, the analysis results showed that the majority of underlying conditions indicated for glucocorticoid treatment were rheumatoid arthritis at 31.3%, followed by lupus at 23.9%, pharyngitis

Table 1. Baseline characteristics of participants

Characteristics	Total, N = 96
Gender, n (%)	
Female	74 (77.1%)
Male	22 (22.9%)
Age, years Mean ± SD = 47.5 ± 14.3	
Underlying conditions indicated for glucocorticoid, n (%)	
Rheumatoid arthritis	30 (31.3%)
Lupus	23 (23.9%)
Pharyngitis	18 (18.8%)
Exogenous Cushing syndrome	9 (9.4%)
Sinusitis	4 (4.2%)
Otitis media	3 (3.1%)
Dermatomyositis	2 (2.2%)
Sjogren syndrome	1 (1.0%)
Nephrotic syndrome	3 (3.1%)
Knee osteoarthritis	1 (1.0%)
Lumbar disc herniation	1 (1.0%)
Sciatic nerve pain	1 (1.0%)
Clinical characteristics of patients on glucocorticoid, n (%)	
Abdominal obesity	23 (24.0%)
Thin skin with easy bruising	15 (15.6%)
Fatigue	13 (13.5%)
Exhaustion	11 (11.5%)
Loss of appetite	11 (11.5%)
Moon face	9 (9.4%)
Cataracts	8 (8.3%)
Dizziness	4 (4.2%)
Abdominal or thigh striae	4 (4.2%)
Nausea and vomiting	5 (5.2%)
Buffalo hump	3 (3.1%)
Neuropsychiatric symptoms	3 (3.1%)
Comorbidities of patients on glucocorticoid, n (%)	
Dyslipidemia	38 (39.6%)
Hypertension	29 (30.2%)
Gastritis	28 (29.2%)
Osteoporosis	19 (19.8%)
Diabetes mellitus	12 (12.5%)
Neuropsychiatric disorders	9 (9.4%)

Mean ± SD: Mean ± Standard Deviation

at 18.8%, exogenous Cushing's syndrome at 9.4%, sinusitis at 4.2% and the remaining conditions accounted for 12.4%. Most clinical symptoms commonly observed in patients on glucocorticoid therapy were abdominal obesity at 24%, thin skin with easy bruising at 15.6%, fatigue at 13.5%, exhaustion and loss of appetite at 23%, and moon facies at 9.4%. The rest were attributed to other symptoms. Comorbidities among patients receiving glucocorticoid therapy were diverse. Dyslipidemia was the most frequently reported comorbidity, affecting 39.6% of patients. This was followed by hypertension (30.2%), gastritis (29.2%), osteoporosis (19.8%), diabetes mellitus (12.5%), and neuropsychiatric disorders (9.4%) (Table 1). Comparing the two groups, the adrenal insufficiency group had greater number of patients with comorbidities compared to the non-adrenal insufficiency group, but this difference was not statistically significant (Table 3).

All patients were receiving glucocorticoid therapy as prescribed by physicians in the outpatient clinic. The treatment protocol is presented in Table 2. The entire study population was treated with either methylprednisolone or prednisolone and were receiving maintenance doses, as their underlying conditions had been stabilized.

Given that the underlying diseases were stable, glucocorticoid tapering and discontinuation were considered in order to minimize the risk of AI. All patients underwent ITT to assess adrenal function. Baseline cortisol levels and cortisol levels response at various time points following the test are presented in Table 3. After performing the ITT, we determined that the prevalence of adrenal insufficiency was 58.3%, while the non-adrenal insufficiency group accounted for 41.7%.

Figure 1 illustrates a statistically significant positive correlation between baseline cortisol levels and the peak cortisol response during the insulin tolerance test (ITT), with a correlation coefficient of r = 0.62 (p <0.001), indicating a moderately strong association. Receiver operating characteristic (ROC) analysis identified multiple cut-off values of baseline cortisol, each associated with corresponding sensitivity and specificity, in the prediction of AI. The ROC curve was generated using a peak cortisol response greater than 18 μg/dL as the reference standard for normal adrenal function. The area under the curve (AUC) was 0.83 (95% CI: 0.78–0.89), indicating good diagnostic accuracy (Figure 2).

Based on the morning cortisol cutoff points derived from the ROC curve, we determined the diagnostic performance of the optimal cortisol cutoff value according to Youden's Index, as shown in Table 4.

Predictive models for adrenal insufficiency were constructed utilizing readily obtainable and clinically pertinent clinical characteristics along with baseline cortisol

Table 2. Baseline characteristics between the adrenal insufficiency and no adrenal insufficiency groups

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Age (years), Mean ± SD	47.5 ± 14.3	46.0 ± 14.1	48.6 ± 14.5	0.384
Gender: n (%)				0.219
Female	74 (77.1%)	28 (70.0%)	46 (82.1%)	
Male	22 (22.9%)	12 (30.0%)	10 (17.9%)	
Weight (kg), Mean ± SD	57.5 ± 10.4	57.0 ± 11.2	57.9 ± 9.9	0.695
Height (cm), Mean ± SD	158 ± 7	159 ± 7	158 ± 7	0.645
BMI (kg/m²), Mean ± SD	22.9 ± 3.6	22.5 ± 3.7	23.1 ± 3.5	0.438
Systolic blood pressure (mmHg), Mean ± SD	116.5 ± 14.3	117.7 ± 15.5	115.6 ± 13.4	0.501
Diastolic blood pressure (mmHg), Mean ± SD	71.3 ± 10.5	73.0 ± 12.0	70.0 ± 9.3	0.180

Mean ± SD: Mean ± Standard Deviation

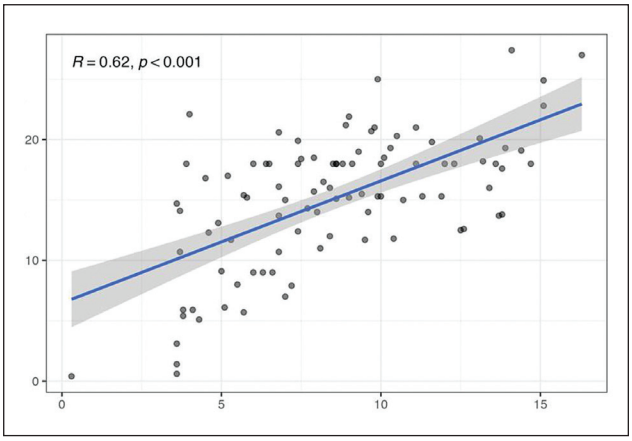


Figure 1. Correlation between baseline cortisol and peak cortisol levels during the insulin tolerance test.

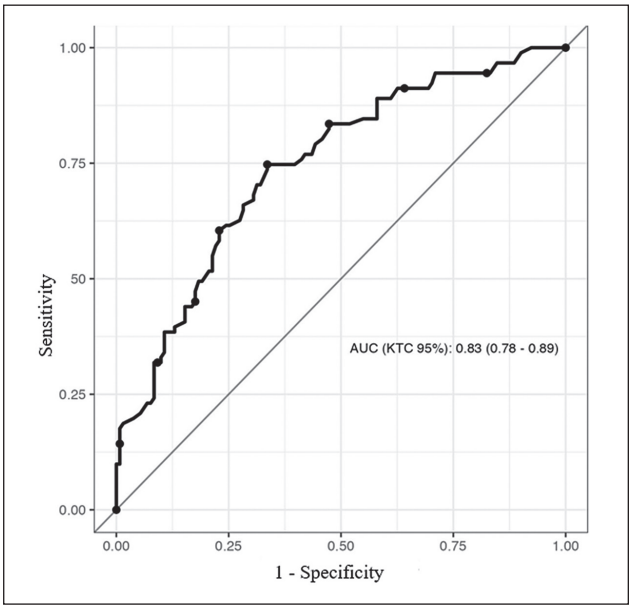


Figure 2. Receiver operating characteristic (ROC) curve illustrating the predictive performance of baseline cortisol levels for adrenal insufficiency.

levels. These models were designed to facilitate early identification of adrenal dysfunction. In Model 1, clinical factors were selected based on two criteria: (1) potential association identified through univariate analysis (p <0.2), and (2) established clinical significance. Accordingly, nine variables were included: age, sex, dyslipidemia, hypertension, osteoporosis, total duration of glucocorticoid treatment, abdominal obesity, moon facies, and cataracts. The diagnostic performance of this model for adrenal insufficiency was good, with an area under the receiver operating characteristic curve (AUC) of 0.81. In Model 2, to streamline the predictive model, we performed a stepwise backward elimination based on statistical significance thresholds. Starting from the full set of variables included in Model 1, variables were sequentially removed if they did not contribute significantly to the model's predictive power. This process resulted in the identification of three key clinical predictors: hypertension, total duration of glucocorticoid treatment, and moon facies. Consistent with Model 1, Model 2 also demonstrated an AUC of 0.81. Model 3 was developed by integrating the key clinical predictors identified in Model 2 with baseline cortisol levels to enhance the prediction of adrenal insufficiency risk. This combined model demonstrated superior diagnostic accuracy, achieving an area under the curve (AUC) of 0.87, thereby outperforming both preceding models. Model 4, based solely on baseline cortisol levels, demonstrated the lowest diagnostic accuracy compared to the other models, with an AUC of 0.75 (Table 5).

DISCUSSION

Among the 96 patients included, the mean age was 47.5 ± 14.3 years. A predominance of female participants was noted, comprising 77.1% of the cohort. In our study, the higher proportion of female patients may be due to autoimmune and musculoskeletal diseases being more common in women than in men. Additionally, women tend to use healthcare services more frequently than men, including for the diagnosis and treatment of chronic diseases. This

Table 3. Comorbidities of patients between the adrenal insufficiency and no adrenal insufficiency groups

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Comorbidities, n (%)				
Dyslipidemia	38 (39.6%)	11 (27.5%)	27 (48.2%)	0.057
Hypertension	29 (30.2%)	8 (20.0%)	21 (37.5%)	0.075
Gastritis	28 (29.2%)	12 (30.0%)	16 (28.6%)	0.999
Osteoporosis	19 (19.8%)	5 (12.5%)	14 (25.0%)	0.194
Diabetes mellitus	12 (12.5%)	3 (7.5%)	9 (16.1%)	0.348
Psychiatric disorders	9 (9.4%)	4 (10.0%)	5 (8.9%)	0.999

Table 4. Characteristics of glucocorticoid treatment

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Type of glucocorticoid, n (%)				0.541
methylprednisolone	49 (51.0%)	22 (55.0%)	27 (48.2%)	
prednisolone	47 (49.0%)	18 (45.0%)	29 (51.8%)	
Glucocorticoid dose, (mg) MED (IQR)	5 (4; 5)	5 (4; 8)	5 (4; 5)	0.022
Total duration of treatment, (months) MED (IQR)	8 (2; 17)	3 (1; 9)	12 (6; 24)	<0.001

MED (IQR): Median (Interquartile Range)

Table 5. Cortisol levels during the insulin tolerance test

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Cortisol level (mcg/dL), MED (IQR)				
Baseline cortisol level	8.4 (6.0; 10.6)	9.9 (8.3; 12.5)	6.9 (5.0; 9.4)	<0.001
Cortisol T0 (mcg/dL)	8.3 (5.8; 10.6)	9.8 (7.8; 12.1)	6.8 (5.1; 9.1)	<0.001
Cortisol T30 (mcg/dL)	8.1 (5.6; 11.4)	10.9 (8.0; 12.8)	6.7 (4.9; 8.6)	<0.001
Cortisol T60 (mcg/dL)	15.3 (11.0; 18.0)	18.4 (18.0; 20.8)	11.8 (7.8; 15.1)	<0.001
Cortisol T90 (mcg/dL)	12.8 (8.5; 15.5)	16.8 (13.7; 19.0)	9.8 (5.7; 12.6)	<0.001
Cortisol T120 (mcg/dL)	10.0 (6.6; 13.0)	12.9 (11.0; 15.4)	8.3 (5.1; 10.1)	<0.001

MED (IQR): Median (Interquartile Range)

may result in a higher detection rate of chronic adrenal insufficiency due to long-term glucocorticoid therapy in women compared to men. However, there was no statistically significant difference in gender between the groups with and without adrenal insufficiency in our study (Table 2). Most patients had underlying conditions typically managed within internal medicine subspecialties, including musculoskeletal, otolaryngologic, and endocrine conditions (Table 1). Clinical manifestations related to glucocorticoid-associated adverse effects were infrequent among patients in our study (Table 1). This can be attributed to the fact that participants were sampled during the maintenance phase, when low-dose glucocorticoid therapy was being administered and the underlying disease was already well controlled. At this stage, the impact of exogenous glucocorticoids on the body is likely minimal. Consequently, this is also the point at which clinicians typically consider discontinuing glucocorticoid therapy, prompting the need for adrenal function assessment to ensure safe withdrawal. When comparing the comorbidities between two groups, in the adrenal insufficiency group, the proportion of patients with comorbidities was higher compared to the non-adrenal insufficiency group, but this difference was not statistically significant (Table 3). However, a study by Tran Quang Nam et al., reported that most of comorbidities are statistically significantly higher in the adrenal insufficiency group compared to the non-adrenal insufficiency group.[7] The lack of statistically significant differences in comorbidities between the two groups may be due to a smaller sample size, which reduces the power of the study to detect significant differences between groups. Although the total sample size was 96 patients, dividing them into two groups reduced the sample size of each group, diminishing the ability to detect statistically significant differences. To address this, increasing the sample size could enhance accuracy and the ability to detect statistically significant differences between the group.

All patients were prescribed glucocorticoid therapy, predominantly prednisolone and methylprednisolone. The cumulative duration of glucocorticoid treatment in the adrenal insufficiency group was 12 months, which was significantly longer compared to 3 months in the non-adrenal insufficiency group (Table 2). Our findings are consistent with the 2024 Clinical Practice Guidelines jointly issued by the European Society of Endocrinology and the Endocrine Society, which state that among the risk factors contributing to the development of adrenal insufficiency, a duration of glucocorticoid therapy ranging from 1 to 3 months is associated with a moderate risk, whereas treatment exceeding 3 months is associated with a high risk of adrenal insufficiency.[6] The observed association is biologically plausible, as prolonged exposure to exogenous glucocorticoids leads to sustained suppression of the hypothalamic-pituitary-adrenal (HPA) axis, impairing the body's endogenous cortisol production. This prolonged suppression contributes to the pathophysiology underlying secondary adrenal insufficiency.

All patients underwent the insulin tolerance test (ITT), during which we observed that serum cortisol levels at all time points were significantly lower in the adrenal insufficiency group compared to the non-adrenal insufficiency group (Table 3). Currently, there is a global trend toward recommending the replacement of dynamic stimulation tests with simpler, more affordable, and widely accessible static measurements that maintain comparable diagnostic efficacy. In this light, we further investigated the correlation between baseline cortisol levels and peak cortisol levels following the ITT. We found a moderately strong positive correlation between these two parameters ($r = 0.62$, $p < 0.001$) (Figure 1). Our findings are consistent with previous studies. Eturk et al. reported a significant correlation between morning cortisol and peak cortisol after hypoglycemia ($r = 0.63$), as did Hagg et al., ($r = 0.73$) and Tran Quang Nam et al. ($r = 0.8$).[7-9] A moderate-to-strong positive correlation indicating that as baseline cortisol level increased, peak cortisol level from ITT tended to increase correspondingly. This finding suggests a statistically and clinically meaningful association between the two parameters. Given the strength of the observed correlation, it is reasonable to hypothesize that baseline cortisol level may serve as an important clinical indicator for predicting changes in peak cortisol level from ITT. This potential association could have practical implications for screening, risk stratification, and disease monitoring in clinical practice.

In addition, ROC curve analysis of morning baseline serum cortisol for diagnosing adrenal insufficiency yielded an area under the curve (AUC) of 0.83 (95% CI: 0.78–0.89; $p < 0.05$). Our findings are consistent with those of Tran Quang Nam, who reported an AUC of 0.71 (95% CI: 0.6–0.8; $p < 0.0005$).[7] Similarly, Ashley et al., demonstrated good diagnostic performance of baseline cortisol, with an AUC of 0.81 (95% CI: 0.77–0.84).[10] Given the range of AUC values reported across the aforementioned studies, morning serum cortisol demonstrates good discriminative ability

in differentiating between individuals with and without adrenal insufficiency. Therefore, it may serve as a reliable alternative to dynamic testing in the evaluation of adrenal function.

Based on the sensitivity and specificity at different cut-off points in Table 6, we constructed a ROC curve to illustrate the diagnostic value of morning serum cortisol for adrenal insufficiency in Figure 2. At the same time, the optimal cut-off value of morning serum cortisol was determined using the Youden Index, as shown in the Table 7. When different baseline cortisol cut-off values were applied, notable variations in diagnostic performance were observed. At a cut-off of 8 μg/dL, sensitivity was relatively low (59%), which increases the false negatives (41%), although specificity remained acceptable (76%). By contrast, cut-offs of 10 μg/dL and 11 μg/dL yielded substantially higher sensitivities (78% and 82%, respectively), thereby reducing the false negatives. However, this improvement in sensitivity was offset by a marked decline in specificity (57% and 49%, respectively), resulting in a greater number of false positives. From a clinical perspective, lower cut-offs such as 8 μg/dL may provide greater diagnostic confidence for confirming adrenal insufficiency, whereas higher cut-offs (10–11 μg/dL) are more suitable for excluding the disease, where sensitivity is prioritized over specificity. These findings highlight the importance of selecting cut-off thresholds based on the clinical context and the relative balance between minimizing false negatives versus false positives. If the optimal cut-off value for morning serum cortisol is set at 9.0 μg/dL, the test demonstrates a sensitivity of 69% and a specificity of 67%. This means that the test can correctly identify 69% of patients with true adrenal insufficiency, but 31% of true cases may go undetected, which could lead to premature discontinuation of glucocorticoid therapy by the treating physician without proper monitoring. These patients are at risk of acute adrenal insufficiency during periods of acute stress. On the other hand, the test identifies 67% of patients without adrenal insufficiency, meaning 33% of patients who actually have normal adrenal function may be misdiagnosed and continue unnecessary glucocorticoid therapy (Table 7). When compared to other studies, we found that Hagg et al., reported a morning serum cortisol cutoff of 10.9 μg/dL, which yielded a sensitivity of 67% and a specificity of 94%.[8] Eturk et al., found that at a morning serum cortisol cutoff of 10 μg/dL, the sensitivity was 62% and the specificity was 77%.[7] Tran Quang Nam et al., observed that at a cutoff of 9.9 μg/dL, the sensitivity was 64% and the specificity was 72%.[9] Furthermore, we observed that the morning serum cortisol cutoff of 3 μg/dL had a positive predictive value (PPV) of 100%, meaning that when morning serum

Table 6. The diagnostic value of cortisol

Cortisol cutoff	Sen	Spe	PPV	NPV
3	0.01 (0.00 - 0.04)	1.00 (0.96 - 1.00)	1.00 (0.03 - 1.00)	0.41 (0.35 - 0.48)
4	0.11 (0.06 - 0.17)	0.98 (0.92 - 1.00)	0.88 (0.62 - 0.98)	0.43 (0.36 - 0.50)
5	0.21 (0.15 - 0.29)	0.95 (0.88 - 0.98)	0.85 (0.68 - 0.95)	0.46 (0.38 - 0.53)
6	0.37 (0.29 - 0.46)	0.91 (0.83 - 0.96)	0.86 (0.74 - 0.94)	0.50 (0.42 - 0.58)
7	0.48 (0.39 - 0.57)	0.84 (0.74 - 0.90)	0.81 (0.70 - 0.89)	0.53 (0.44 - 0.61)
8	0.59 (0.50 - 0.67)	0.76 (0.66 - 0.84)	0.78 (0.68 - 0.86)	0.56 (0.47 - 0.65)
9	0.69 (0.61 - 0.77)	0.67 (0.56 - 0.77)	0.75 (0.67 - 0.83)	0.60 (0.50 - 0.70)
10	0.78 (0.70 - 0.85)	0.57 (0.46 - 0.67)	0.72 (0.64 - 0.80)	0.64 (0.53 - 0.75)
11	0.82 (0.74 - 0.88)	0.49 (0.39 - 0.60)	0.70 (0.62 - 0.77)	0.65 (0.53 - 0.76)
12	0.89 (0.83 - 0.94)	0.38 (0.28 - 0.49)	0.68 (0.60 - 0.75)	0.71 (0.57 - 0.83)
13	0.92 (0.85 - 0.96)	0.29 (0.20 - 0.39)	0.65 (0.58 - 0.72)	0.70 (0.53 - 0.84)
14	0.99 (0.96 - 1.00)	0.18 (0.10 - 0.27)	0.63 (0.56 - 0.70)	0.94 (0.71 - 1.00)
15	1.00 (0.97 - 1.00)	0.08 (0.03 - 0.15)	0.61 (0.54 - 0.67)	1.00 (0.59 - 1.00)

Sens: Sensitivity; Spec: Specificity; PPV: Positive Predicted Value; NPV: Negative Predicted Value

Table 7. The diagnostic performance of the optimal cortisol cutoff value determined by Youden's index

	Value
Optimal cortisol cutoff value (μg/dL)	9.0
Sensitivity (%)	69 (61-77)
Specificity (%)	67 (56-77)
Positive predicted value	75 (67-83)
Negative predicted value	60 (50-70)

Table 8. Multivariate logistic regression analysis for predictors of adrenal insufficiency

Model	N	Variable	Model 1	Model 2	Model 3	Model 4
Intercept			-0.61 (-2.57; 1.29)	-1.02 (-1.81; -0.30)	1.60 (0.09; 3.23)	2.80 (1.51; 4.29)
Age (per 10-year increase)	96	0.13 (-0.16; 0.42)	-0.11 (-0.52; 0.29)			
Male sex	96	-0.68 (-1.66; 0.28)	-0.09 (-1.27; 1.07)			
Dyslipidemia	96	0.90 (0.05; 1.80)	0.57 (-0.70; 1.88)			
Hypertension	96	0.88 (-0.04; 1.87)	0.85 (-0.60; 2.32)	1.12 (0.08; 2.24)	1.77 (0.52; 3.19)	
Osteoporosis	96	0.85 (-0.22; 2.05)	0.07 (-1.42; 1.57)			
Total duration of glucocorticoid treatment (months)	96	0.08 (0.04; 0.14)	0.08 (0.03; 0.14)	0.08 (0.04; 0.14)	0.10 (0.04; 0.17)	
Abdominal obesity	96	0.90 (-0.09; 2.01)	0.10 (-1.30; 1.48)			
Moon face	96	17.40 (-88.63; NA)	16.82 (-58.33;NA)	16.96 (-72.83; NA)	17.83 (-87.49; NA)	
Cataracts	96	1.72 (-0.07; 4.67)	0.50 (-1.94; 3.72)			
Baseline cortisol levels (μg/dL)	96	-0.28 (-0.44; -0.14)			-0.33 (-0.52;-0.16)	-0.28 (-0.44; -0.14)
AUC (KTC 95%)			0.81 (0.73; 0.90)	0.81 (0.72; 0.90)	0.87 (0.80; 0.94)	0.75 (0.65; 0.85)

cortisol levels are below 3 μg/dL, it can accurately detect 100% of patients with glucocorticoid-induced adrenal insufficiency. In contrast, the morning serum cortisol cutoff of 15 μg/dL had a negative predictive value (NPV) of 100%, indicating that cortisol levels above 15 μg/dL can reliably identify 100% of patients with normal adrenal function (Table 6).Therefore, using morning serum cortisol alone may not be sufficiently reliable for determining adrenal function, as it could result in misdiagnosis in certain cases.

Based on the analyses presented, we found that morning serum cortisol demonstrates a reasonable capacity for distinguishing between adrenal insufficiency and normal adrenal function. However, it cannot be considered an ideal test to fully replace dynamic testing. Therefore, we propose that, to enhance the diagnostic value of morning serum cortisol, it should not be employed in isolation for the assessment of adrenal function. Instead, it should be used in conjunction with clinical characteristics of the study population to improve the diagnostic accuracy for adrenal insufficiency. When comparing diagnostic models, we found that Model 4, which relied solely on the morning serum cortisol test, demonstrated a reasonable diagnostic performance with an AUC of 0.75. In contrast, Model 2, which included only the clinical characteristics of the study population, achieved an AUC of 0.81. This further emphasizes the critical role of taking a thorough medical history, considering patient comorbidities, and conducting clinical examinations, highlighting that the morning serum cortisol test alone should not be solely relied upon for diagnosing adrenal insufficiency. Model 3, which incorporated both the clinical characteristics of the study population such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension and morning serum cortisol levels, demonstrated the highest diagnostic performance for adrenal insufficiency, with an AUC of 0.87. This finding underscores the enhanced diagnostic value derived from integrating clinical characteristics with biochemical markers, thus providing the most accurate assessment of adrenal insufficiency. Based on the models outlined above, we conclude that in clinical practice, when approaching a patient with stable underlying disease who has been tapered to a daily dose of ≥5 mg of prednisone (or an equivalent dose of another glucocorticoid), and is under consideration for adrenal function assessment, it is crucial to gather baseline characteristics such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension and perform a morning serum cortisol test. The combination of these factors offers superior diagnostic value for adrenal insufficiency, with an AUC of 0.87, enabling the clinician to make informed decisions regarding the continuation or safe discontinuation of glucocorticoid therapy. Another notable point, according to the guidelines by Hosmer and Lemeshow, models with an AUC ranging from 0.9 to 1.0 demonstrate excellent discriminative ability between disease and non-disease cases.[11] Our combined model, with an AUC of 0.87, approaches the threshold for excellent diagnostic performance, suggesting that it may serve as a potential alternative to insulin tolerance test for assessing adrenal function - particularly in healthcare settings where such testing is not feasible, such as in Vietnam.

CONCLUSION

After the ITT, we determined that the prevalence of adrenal insufficiency was 58.3%, while the non-adrenal insufficiency group accounted for 41.7%. The morning serum cortisol test demonstrated a diagnostic performance with an AUC of 0.83 (95% CI: 0.78–0.89), indicating its strong ability to distinguish between adrenal insufficiency and normal adrenal function. If the optimal cutoff value for morning serum cortisol is set at 9.0 μg/dL, the test demonstrates a sensitivity of 69% and a specificity of 67%. Besides, we observed that the morning serum cortisol cutoff of 3 μg/dL had a positive predictive value (PPV) of 100% and the morning serum cortisol cutoff of 15 μg/dL had a negative predictive value (NPV) of 100%. Model 3, which integrates clinical characteristics such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension with morning cortisol levels, exhibited the highest diagnostic accuracy with an AUC of 0.87 and may serve as a reliable alternative to the insulin tolerance test for adrenal insufficiency assessment. In settings where dynamic testing is not feasible due to cost, complexity, or lack of experience, we recommend implementing Model 3 as a practical and cost-effective approach for adrenal function evaluation, as it requires only a single blood sample and is widely accessible.

This study has several strengths, including the integration of key clinical characteristics with baseline cortisol level, which significantly improved diagnostic accuracy and provided a cost-effective, accessible alternative to insulin tolerance test. The insulin tolerance test, as our reference standard, strengthened the validity of our findings, while the identification of clinically relevant cortisol thresholds (<3 μg/dL and >15 μg/dL) offers immediate applicability in practice. However, certain limitations should be acknowledged. The single-center, cross sectional design with a modest sample size may limit generalizability. In addition, the predictive model was not externally validated, and further studies are required to confirm its utility across diverse healthcare settings. Nevertheless, our findings support the use of baseline cortisol combined with key clinical characteristics as a practical approach for assessing adrenal function, particularly in settings where dynamic testing is not feasible, such as in Vietnam.

Acknowledgments

We would like to express our sincere gratitude to all those who contributed to the completion of this study. Special thanks to the medical staff and the laboratory team at Nguyen Tri Phuong Hospital for their technical assistance in data collection and testing. We also appreciate the support from the Department of Endocrinology, University of Medicine and Pharmacy, Ho Chi Minh City, for providing the resources necessary for this study. Lastly, we are deeply grateful to the patients who participated in this study for their cooperation and commitment.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
DTN: Conceptualization, Methodology, Validation, Writing – original draft preparation, Writing – review and editing, Data curation; **TTN:** Formal Analysis, Methodology, Writing – review and editing; **KQT:** Conceptualization, Writing – review and editing, Supervision.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Retrospective Study of Clinical Characteristics, Natural History and Predictive Factors for Mild Autonomous Cortisol Secretion (MACS) in Patients with Adrenal Incidentalomas in Malaysia

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Abstract

Introduction. Adrenal incidentalomas (AIs) are frequently discovered during imaging performed for unrelated conditions. While most are benign and non-functional, a subset demonstrates hormonal activity or malignant potential. This study aimed to describe the clinical and radiological characteristics, natural history and predictors of mild autonomous cortisol secretion (MACS) in a Malaysian cohort.

Methodology. This retrospective multicentre study reviewed medical records of 251 patients with AIs from three tertiary hospitals in Malaysia. Data on demographics, imaging findings, hormonal evaluations, histopathological diagnoses and longitudinal follow-up, including serial imaging and hormonal assessments, were collected and analysed.

Results. The median age of the cohort was 58 years (IQR 19), with a slight female predominance (53%). The population was predominantly Malay (n = 126, 50.2%), followed by Chinese (36.3%) and Indian (12.7%). The median follow-up duration was 39 months.

Most AIs were non-malignant (92%) and non-functioning (72%). Bilateral lesions were present in 9.6% of patients. Among non-malignant AIs, 27% were functioning, with higher rates of hypertension and osteoporosis, larger tumour size and greater tumour density. Adrenalectomy was more commonly performed in the functioning group, mainly for MACS and pheochromocytoma. In contrast, 94% of benign non-functioning AIs were managed conservatively, with no cases of malignant transformation and only one case developing hormonal activity over a median follow-up of 30 months. Among the 20 malignant AIs, 12 were primary adrenal carcinomas. Malignant AIs were associated with larger size, overt Cushing's syndrome, higher Hounsfield units, lower contrast washout and increased mortality.

MACS was identified in 12.7% of the cohort. It was associated with bilateral lesions, larger tumour size, and higher prevalence of diabetes, dyslipidaemia, obesity and osteoporosis. On multivariate analysis, only bilaterality and osteoporosis remained significant predictors of MACS.

Conclusion. This study reinforces that most benign non-functioning AIs carry minimal risk of progression, supporting less intensive follow-up in stable cases. Bilaterality and osteoporosis were identified as independent predictors of MACS, emphasizing the importance of targeted hormonal and bone health monitoring in these patients.

Key words: adrenal incidentalomas, mild autonomous cortisol secretion (MACS), metabolic disorders, osteoporosis, bilateral adrenal incidentalomas

INTRODUCTION

Adrenal incidentaloma (AI) refers to a clinically silent adrenal lesion that is incidentally discovered during imaging for non-adrenal-related conditions. The prevalence of AI in the general population is estimated to be 2-4%, based on radiological series.[1,2] The incidence of adrenal nodules at autopsy is as high as 32% among patients who had no evidence of adrenal disease prior to their deaths.[3] While most of these lesions are benign and non-functional, the natural history of these tumors remains incompletely understood. One of the critical challenges in managing AI is differentiating between benign and malignant lesions. Additionally, it is crucial to determine whether these

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Devaraja et al.
Received: August 15, 2025. Accepted: October 1, 2025.
Published online first: April 30, 2026.
https://doi.org/10.15605/jafes.041.01.5143

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typically asymptomatic tumors may be hormonally active, potentially leading to autonomous cortisol secretion, catecholamine excess, hyperaldosteronism, or hyperandrogenism.

Currently, most guidelines for the management of AIs recommend that all patients with AI must be screened for cortisol excess, whereas the evaluation for pheochromocytoma or primary aldosteronism (PA) is recommended for those with Hounsfield Unit (HU) more than 10 on pre-contrast computed tomography (CT) imaging or arterial hypertension, respectively.[4-6] While there is general agreement on the initial evaluation of AIs, significant differences exist among these guidelines regarding re-imaging, repeat hormonal testing, and the management of AIs that cannot be easily characterized as benign or malignant based on CT scans. The recommendations range from advising against repeated imaging and hormonal screening to follow-up imaging within 3 to 6 months and annual hormone testing for several years. The discordance between these guidelines complicates coordinated management, which often requires input from a multidisciplinary team.

Mild autonomous cortisol secretion (MACS), the most common functional form of AI characterized by biochemical abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis without overt clinical signs of Cushing's Syndrome, has been reported in 5-20% of AI patients.[7,8] A well-established concept is that cortisol secretion in the adrenal gland follows a continuum from physiological to pathologically increased levels.[9] Detecting MACS is vital as it has been associated with several cardiometabolic risk factors, including obesity, arterial hypertension, dyslipidaemia and osteoporosis.[9,10] Some studies have shown that these complications may improve after adrenalectomy, while others suggest worsening in untreated patients.[11,12] Consequently, the optimal management and long-term follow-up of AI patients remain subjects of debate. While numerous studies on AIs have been conducted in Western countries, there is a lack of data from this region. The primary objective of this study was to describe the natural history, clinical and radiological characteristics of patients with AI. The secondary objective was to identify clinical predictors associated with MACS.

METHODOLOGY

Study design

This was a retrospective observational study conducted in three urban tertiary hospitals under the Ministry of Health, Malaysia. Medical records of patients with adrenal incidentaloma referred to the endocrine units of participating centers between January 2010 and June 2020 were reviewed and analyzed. This study was approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health of Malaysia.

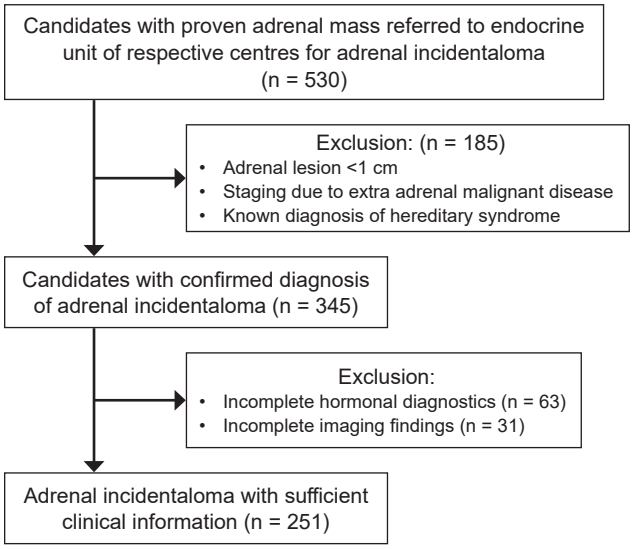


Figure 1. Flow diagram of patient selection for inclusion in the study and Consort diagram.

Patient selection

Adult patients aged 18 years and above diagnosed with AI between January 2010 and December 2020, who were referred to the endocrine units at the respective centers mentioned above were recruited. We excluded patients with AIs measuring less than one centimeter, pregnant individuals, those who did not undergo biochemical and radiological evaluation to assess for functioning adrenal lesions, individuals with a history of extra-adrenal malignancies or hereditary syndromes of endocrine neoplasia and patients taking medications such as glucocorticoids, estrogens, or antipsychotics that interfere with hormonal assessments.

Study Procedure

Medical records of patients with AI referred to the endocrine units of participating centers between January 2010 and June 2020 were reviewed. A data collection form was used to obtain relevant information. Baseline demographics, including age, gender, ethnicity, relevant comorbidities such as hypertension, diabetes mellitus, dyslipidaemia, obesity (body mass index >27.5 kg/m^2), osteoporosis or a history of fragility fracture, were obtained. Indications for the initial CT imaging resulting in the detection of adrenal incidentalomas were obtained from medical records when available and most frequently included evaluation for abdominal pain, sepsis of unknown origin, renal calculi and gynaecological conditions. Patients were classified as having diabetes if they were receiving antidiabetic treatment, hypertension if they were on antihypertensive medication and dyslipidaemia if they were taking lipid-lowering drugs. Osteoporosis was diagnosed if the individual had a T-score of less than -2.5 on dual-energy X-ray absorptiometry (DEXA), if performed, or was on osteoporosis medications. Not all patients underwent routine bone mineral density (BMD) testing.

The clinical symptoms or signs suggestive of a functional tumour: uncontrolled hypertension, hypokalaemia, easy bruising, thinning of skin, weight gain, proximal muscle weakness, uncontrolled blood glucose level, paroxysms of palpitations, headache, diaphoresis or indicators of malignancy like significant weight loss, were documented.

Results of biochemical evaluation, including morning serum cortisol after 1 mg dexamethasone suppression test (1 mg-DST), 24-hour urine catecholamine or metanephrine, plasma aldosterone renin ratio (ARR), serum dehydroepiandrostenedione-sulfate (DHEA-S), serum testosterone and 17-hydroxy progesterone levels were recorded, if performed. MACS was diagnosed if there was a lack of suppression in the 1 mg-DST and low dose DST (cut-off cortisol value less than 50 nmol/L), with suppressed DHEA-S (if performed), without any symptoms or signs of overt Cushing's syndrome. Potential causes of false positive DST (e.g., poor dexamethasone absorption, concurrent illness, or interfering medications) were considered at the time of interpretation. In most cases, a single DST was performed; repeat testing was not routinely undertaken across participating centers. Pheochromocytoma was diagnosed by an elevated 24-hour urine catecholamine or metanephrine level and confirmed based on histological findings post-adrenalectomy. PA was diagnosed based on an elevated ARR and confirmed by the lack of suppression in plasma aldosterone levels after saline infusion or fludrocortisone suppression test.

All AIs were further characterized by a three-phase CT adrenal protocol. The laterality, size (largest transverse diameter in centimeters), HU and absolute contrast washout (in percentage) of the adrenal lesion were captured. The histopathological findings of the resected adrenal tumours of individuals who underwent adrenalectomy or adrenal biopsy were recorded.

The treatment modality (observation or surgical intervention), repeated biochemical evaluations and imaging findings (if conducted), including changes in tumor size, HU, functioning status or malignant transformation, follow-up duration and outcome at the last follow-up, were captured for all patients.

Sample size calculation

Sample size was estimated a priori using Epi Info™ StatCalc (version 5.5.9, Cohort module) with a two-sided confidence level of 95%, power of 80%, and a 1:1 unexposed-to-exposed ratio. Assuming an outcome rate of 6.4% in the unexposed group[4,8] and a relative risk of 3.0 (19.2% in the exposed group), the minimum required sample size was 212 patients (106 per group). Of 530 patients screened, 251 were eligible and included, exceeding the required number.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) for normally distributed variables, or as median (interquartile range, IQR) for non-normally distributed variables. All data were analyzed using the IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Data completeness exceeded 95% for all key variables. The highest missingness was observed for body mass index (32%), which was excluded from relevant analyses.

The normality of data was determined by the Kolmogorov–Smirnov test (if sample size>50) or the Shapiro-Wilk test (if sample size is ≤50). Student's T-test or Mann-Whitney U test (if the data were not normally distributed) was used to assess the difference in variables between two groups. The Chi-square test or Fisher's exact test (when expected cell counts were <5) was used to assess associations between categorical variables in independent groups, while McNemar's test was applied for paired before-and-after data within the same group. The Wilcoxon ranked test was used to compare variables for paired subjects for data that was not normally distributed. Univariate and multivariate logistic regression analyses were performed to assess the association between patient characteristics and MACS, with the binary dependent variable defined as the presence of MACS. The p-value <0.05 was considered statistically significant.

RESULTS

Of the 530 patients screened during their follow-up at the endocrine clinics of the three Ministry of Health hospitals, 251 were included. Data completeness exceeded 95% for all key variables. The highest missingness was observed for body mass index (32%), which was excluded from relevant analyses.

The baseline clinical and radiological characteristics of the study population are summarized in Table 1.

The median age of the cohort was 58 years (IQR 19), and was mostly women (53%), with the majority being Malay (n = 126, 50.2%), followed by Chinese (36.3%) and Indian (12.7%). The median follow-up duration was 39 months.

Most (83.6%) of the AIs were unilateral. The median tumour diameter was 2.0cm (IQR 1.6). Examination of tumour density on CT scans indicated that 34% of the lesions had a HU of 10 or less, while 36.8% had a HU of 20 or less. Majority (83.6%) of the lesions had an absolute contrast washout of more than 60%. Bilateral AIs were identified in 24 (9.6%) patients. All were non-malignant. Ten were functioning, with MACS being the most common subtype (80%) (Figure 2). All bilateral MACS lesions were macronodular, whereas 2 of the 14 non-functioning bilateral AIs were disseminated tuberculosis.

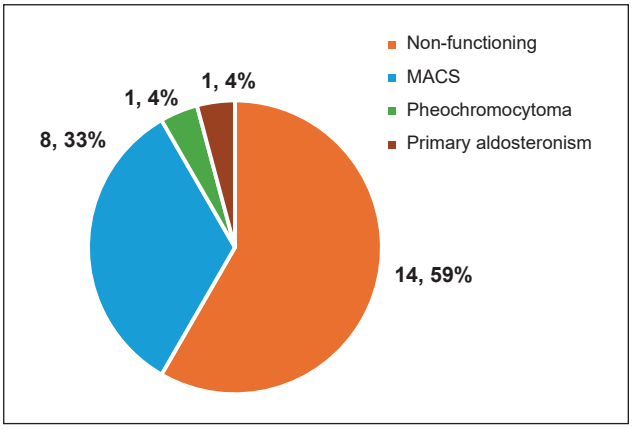


Figure 2. Pie chart describing diagnostic distribution among patients with bilateral adrenal incidentalomas (n = 24).

Table 1. Baseline clinical and radiological characteristics of all individuals with adrenal incidentaloma (N = 251)

Characteristics	Value
Age (years)	58 (19)
Male	118 (47.0%)
Ethnicity	
Malay	126 (50.2%)
Chinese	91 (36.3%)
Indian	32 (12.7%)
Others	2 (0.8%)
Comorbidities	
Diabetes	112 (44.6%)
Hypertension	175 (69.7%)
Dyslipidaemia	141 (56.2%)
Obesity	89 (35.4%)
Osteoporosis / Fragility Fracture	29 (11.5%)
Radiological features	
Size (cm)	2 (1.6)
Density, HU	15 (28.3)
Number of patients with:	
HU <10	85 (34.0)
HU 11-20	73 (29.2)
HU >20	92 (36.8)
Characteristic (N, %)	
Homogenous	177 (70.8)
Heterogenous	56 (22.4)
Uncharacterized	17 (6.8)

Values are presented as number (%) or median (interquartile range). Percentages were calculated using available data. One case had missing characterization data

Non-malignant functioning and non-functioning adrenal incidentalomas

A total of 231 (92.0%) patients were diagnosed with non-malignant AI, of whom 27% were characterized as functioning. The comparison of clinical and radiological characteristics of patients with non-malignant functioning AI with non-functioning AIs was summarized in Table 2. Functioning AI was associated with a higher prevalence of hypertension (88.8% vs. 63.1%, p <0.001) and osteoporosis (20.6% vs. 8.3%, p = 0.012). They were larger in size (2.5 cm vs. 1.7 cm, p <0.001), had higher density (16 HU vs. 12 HU, p <0.001) and a lower rate of absolute contrast washout greater than 60% (84.1% vs. 97.0%, p <0.001) compared to patients with non-functioning AIs. The surgical intervention rate was much higher among patients with functioning Ais, with 63.5% undergoing adrenalectomy mainly due to MACS (41.5%) and pheochromocytoma (41.5%). There were 10 patients with non-malignant, non-functioning AI subjected to adrenalectomy due to tumour size more than 4 cm. Five of them had HU less than 10, while almost all (90%) had absolute contrast washout of 60% or more. Histopathologically, all the tumours were benign, with myelolipoma accounting for 5 cases, followed by 4 cases of lipid-poor adenomas and a single case of extramedullary haematopoiesis.

Of the 63 (25%) individuals with benign functional tumors, 32 (50.8%) were diagnosed with MACS, 17 (27.0%) with pheochromocytoma, 13 (20.6%) with primary aldosteronism and one person (1.6%) with overt Cushing's syndrome.

Malignant adrenal incidentalomas

Twenty patients (8.0%) were diagnosed with malignant adrenal lesions. Primary adrenal cancer was discovered in twelve patients, out of which eleven were adrenocortical carcinomas and one was leiomyosarcoma. The remaining eight patients had adrenal metastasis. Primary sites of malignancy were the lungs (n = 4), kidneys (n = 2), ovaries (n = 1) and pancreas (n = 1).

In comparison with benign AIs, malignant AIs were associated with significantly higher incidence of weight loss and overt Cushing, larger tumour size (5.8 cm vs.1.9 cm, p <0.001), higher HU (51 vs. 14, p <0.001) and higher proportion of absolute contrast washout less than 60% (80.0% vs. 8.7%, p <0.001) on imaging. A significantly higher proportion of malignant AIs exhibited androgen secretion (15% vs. 0%, p <0.001), with no significant difference in the secretion of other hormones. Only 50% of the malignant AIs underwent surgical intervention, with a 70% mortality rate. A total of six patients (2.4%) had functioning malignant adrenal incidentalomas, with the majority (n = 4) being females. All were cortisol-secreting adrenocortical carcinoma (ACC) except one, which was a cortisol-secreting metastatic ovarian teratoma. Three out of the five cases of cortisol-secreting ACC also secrete androgen. Overt Cushing's syndrome was the most common presentation in this specific cohort (n=4, 66.6%).

Natural history of non-functioning benign adrenal incidentalomas

A total of 168 patients (66.9%) had benign non-functioning AIs, of whom 158 (94%) were treated conservatively. We included 108 patients with at least 2 follow-up CT imaging with a median follow-up of 30 months to examine the natural history of non-functioning benign AIs. There was no clinically significant change in the median tumor size over follow-up (1.7 cm to 1.8 cm, p = 0.699), and the proportion with contrast washout >60% remained stable (97.5% vs. 96.3%, p = 1.000. Despite the median HU remaining constant

at 12, the change in HU from baseline to final follow-up was significant (p = 0.001), likely due to variations in the distribution and spread of the data. Only one patient (0.6%) progressed to become functional after a year, associated with an increase in nodule size by 0.3 cm and worsening glycemia with underlying diabetes. None of the patients in this sub-cohort developed malignant transformation over time.

MACS: Clinical predictors and natural history

MACS was present in 12.7% (n=32) of our study population. Compared with the rest of AIs, patients with MACS exhibited larger tumor size, were more likely to be bilateral with higher rates of diabetes, dyslipidemia, obesity, osteoporosis and spinal fractures (Table 3). A representative CT image of the right adrenal adenoma in one of the patients with MACS from our cohort is shown in Figure 3.

Table 2. Comparison of clinical and radiological characteristics of patients with non-malignant functioning vs. non-functioning adrenal incidentalomas (n = 231)

Characteristic	Functioning AIs (n = 63)	Non-functioning AIs (n = 168)	*P* value[c]
Age	59 (24.5)	58 (0.9)	0.519
Male	31 (49.2%)	79 (47.0%)	0.814
Comorbidities			
Diabetes Mellitus	36 (57.1%)	70 (41.6%)	**0.050**
Hypertension	56 (88.8%)	106 (63.1 %)	**<0.001**
Dyslipidemia	42 (66.7%)	91 (54.1%)	0.125
Obesity	25 (39.7%)	51 (30.4%)	0.455
Osteoporosis /Fragility Fractures	13 (20.6)	14 (8.3%)	**0.012**
Symptoms			
Overt Cushing	1 (1.6%)	NA	NA
Uncontrolled hypertension[a]	12 (19.0%)	NA	NA
Hypokalemia[b]	3 (4.7%)	NA	NA
Paroxysms of headache, palpitations, diaphoresis	9 (14.3%)	NA	NA
Radiological characteristics			
Size (cm)	2.5 (2.0)	1.7 (0.9)	**<0.001**
Density/ HU	16 (20.0)	12 (31.0)	**<0.001**
Absolute contrast washout >60%	53 (84.1%)	163 (97.0 %)	**<0.001**
Bilateral	10 (15.8%)	14 (8.3%)	0.106
Outcome			
Adrenalectomy	40 (63.5%)	10 (6.0%)	**<0.001**
Duration of follow up (months)	24 (4.0)	36 (1.0)	**0.004**
Mortality	0	3 (1.8%)	0.903

Values are presented as number (%) or median (interquartile range)

[a] defined as high blood pressure on either 3 or more antihypertensives or controlled on 4 antihypertensives

[b] defined as serum potassium less than 3.5 mmol/L

[c] chi squared test for categorical data and Mann-Whitney U Test for continuous data set

P value ≤0.05 is considered statistically significant

NA, not applicable.

Table 3. Baseline characteristics of MAC vs. Non-MACS

	MACS (n = 32)	Non-MACS (n = 219)	*P* value*
Demographic			
Age, years	59 (24)	58 (19)	0.649
Male	13 (40.6%)	105 (47.9%)	0.438
Metabolic comorbidities			
Diabetes Mellitus	21 (65.6%)	91 (41.6%)	**0.011**
Hypertension	27 (84.4%)	148 (67.6%)	0.053
Dyslipidemia	25 (78.1%)	116 (53.0%)	**0.007**
Obesity	18 (56.3%)	71 (32.4%)	**0.008**
Osteoporosis	12 (37.5%)	17 (7.8%)	**<0.001**
Spinal Fracture	6 (18.8%)	5 (2.3%)	**<0.001**
Outcome (Alive)	32 (100%)	202 (91.8%)	0.103
Radiological characteristics			
Size, cm	2.4 (1.1)	1.9 (1.5)	**0.019**
HU	13 (0.6)	15 (25.7)	0.931
Contrast Washout >60%	31 (97%)	192 (87.7%)	0.122
Bilateral	8 (25%)	16 (7.3%)	**0.001**

*Chi-squared test for categorical variables and Mann Whitney U test for continuous variables.

P value<0.05 was considered statistically significant.

Values are expressed as number (%) or median (interquartile range).

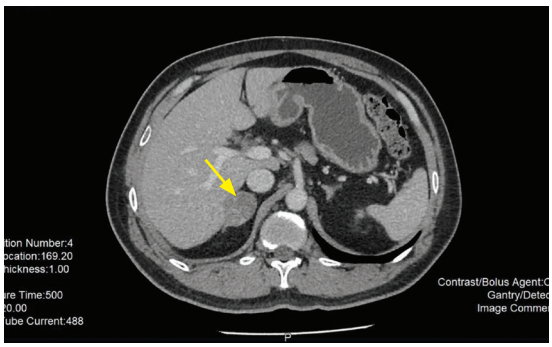


Figure 3. Representative CT image from our cohort: right adrenal adenoma in a patient with mild autonomous cortisol secretion (MACS). Axial CT showing a well-circumscribed right adrenal mass (3.3 × 3.4 × 3.2 cm) in a patient with MACS, predominantly hypodense with scattered hyperdense areas, no calcification, and >60% washout. Clear fat planes are seen with adjacent structures, with mild abutment of the liver margin.

MACS was associated with diabetes mellitus, dyslipidaemia, obesity and osteoporosis in the univariate analysis. After adjustment for potential confounders in the multivariate analysis, bilateral lesions and osteoporosis remained independently associated with MACS, conferring 4.5-fold and 10.9-fold increased odds, respectively (Table 4, Figure 4).

A total of 17 patients (53%) with MACS underwent adrenalectomy. Surgical intervention was associated with significant improvement in glycemic control and a reduction in the number of antihypertensives, with no tumor recurrence. For the 15 patients (47%) with MACS who were managed conservatively, there was a significant increase in median tumor size from 2.1 cm to 2.5 cm

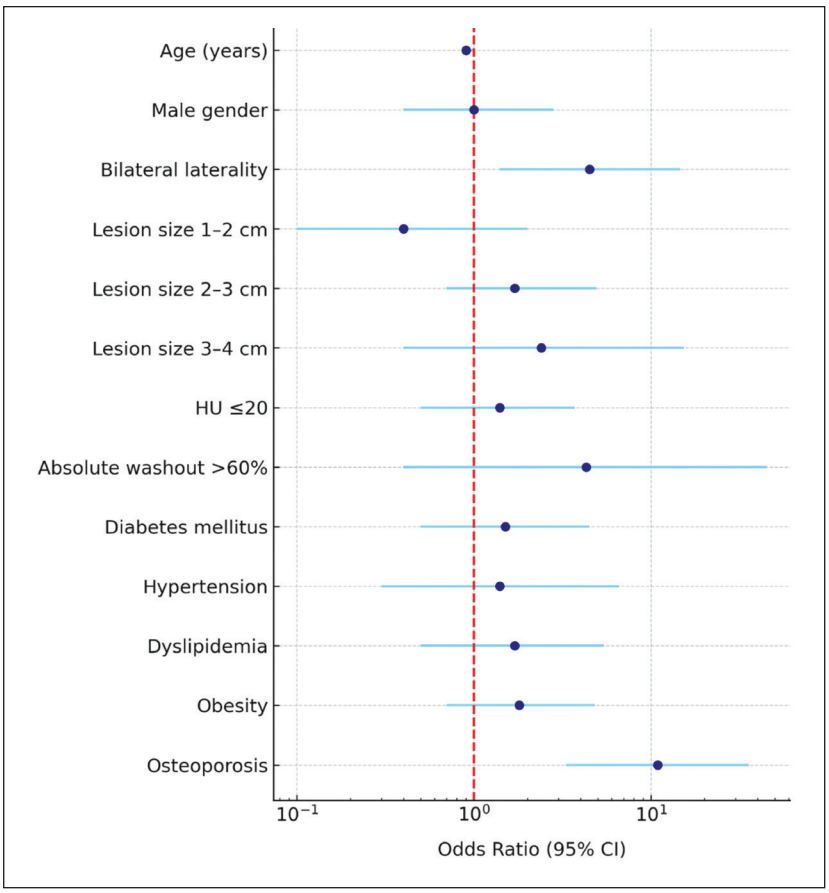


Figure 4. Multivariate predictors of mild autonomous cortisol secretion (MACS). Forest plot illustrates the odds ratios (OR) and 95% confidence intervals (CI) for predictors of MACS from multivariate logistic regression analysis. The vertical dashed line represents the null value (OR = 1.0).

Table 4. Clinical parameters associated with the development of MACS (N = 32)

	Univariate analysis*		Multivariate analysis*,#	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years	4.8 (0.7 – 29.9)	0.656	0.9 (0.9 – 1.0)	**0.123**
Gender				
Male	1.3 (0.6 – 2.9)	0.439	1.0 (0.4- 2.8)	0.928
Laterality				
Bilateral	0.2 (0.9- 0.6)	**0.003**	4.5 (1.4–14.6)	**0.012**
Size of lesion at diagnosis, cm				
1–2 cm (vs >4 cm)	0.6 (0.2–2.3)	0.500	0.4 (0.1–2.0)	0.271
2–3 cm (vs >4 cm)	2.8 (0.9–9.2)	0.085	1.7 (0.4–7.9)	0.500
3–4 cm (vs >4 cm)	2.4 (0.6–10.1)	0.222	2.4 (0.4–15.3)	0.341
HU				
≤20	1.3 (0.6–2.9)	0.498	1.4 (0.5- 3.7)	0.560
Absolute Contrast Washout				
>60	4.4 (0.6–33.3)	0.156	4.3 (0.4–45.0)	0.222
Comorbidities				
Diabetes mellitus	2.7 (1.2–5.8)	**0.013**	1.5 (0.5–4.5)	0.466
Hypertension	2.6 (0.9 – 7.0)	0.061	1.4 (0.3–6.6)	0.667
Dyslipidemia	3.2 (1.3 – 7.6)	**0.010**	1.7 (0.5–6.4)	0.428
Obesity	2.7 (1.2 – 5.7)	**0.010**	1.8 (0.4–7.5)	0.431
Osteoporosis	5.4 (2.3 – 12.5)	**<0.001**	10.9 (3.3–35.5)	**<0.001**

* Based on logistic regression analysis, the statistical significance level was 0.05.

Variables with an association of p <0.20 were selected for a multivariable analysis; OR: Odd ratio; CI: Confidence interval.

[a] Race was analyzed using Chi-square test (overall association with MACS).

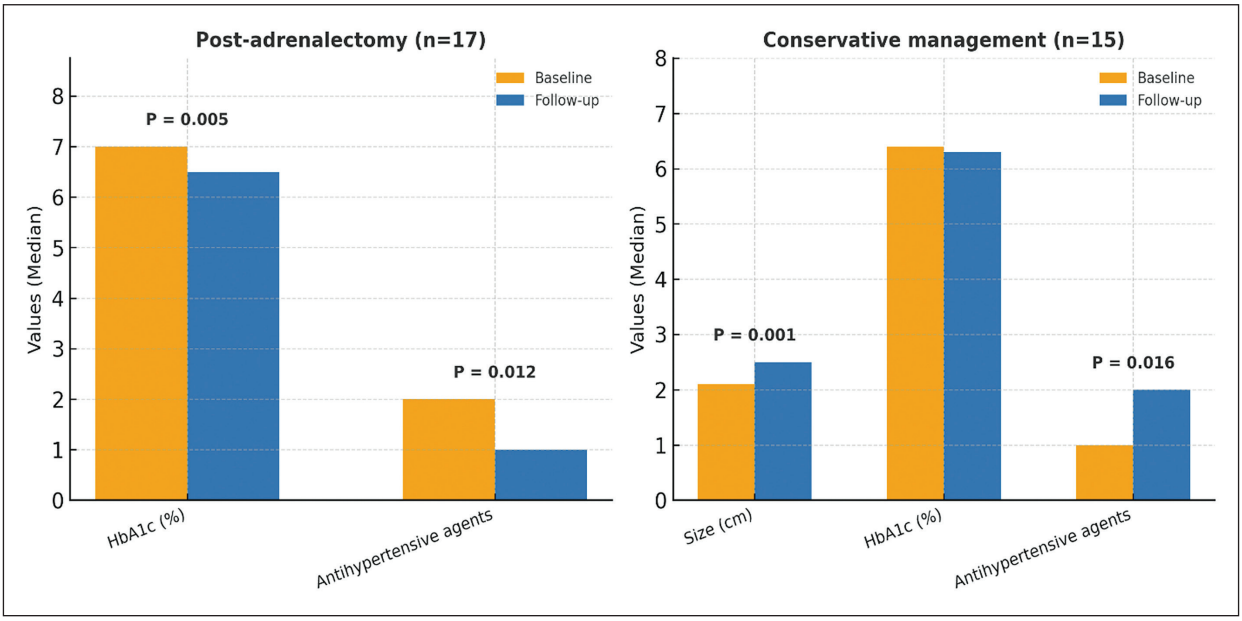


Figure 5. Outcomes of patients with MACS undergoing surgical versus conservative management.

Values are expressed as median (IQR). *P*-values were obtained using the Wilcoxon signed-rank test for continuous paired outcomes (HbA1c, size, HU) and McNemar's test for categorical paired outcomes (antihypertensive use). *P* value <0.05 was considered statistically significant.

(p=0.001) and the number of antihypertensive medications after a median follow-up of 50 months (Figure 5).

DISCUSSION

Population-based epidemiological data on the prevalence of malignant and hormonally active adrenal tumors and their natural history are vital for devising a cost-effective diagnostic and follow-up strategy for incidentally discovered adrenal tumors. Here, we describe the first Malaysian cohort of patients with AI. The high prevalence of hypertension (63%), diabetes (42%) and obesity (30%) in patients with benign non-functioning AIs aligns with existing literature that indicates their association with metabolic syndrome.[9,13] This is attributed to a mild hypercortisolemic state, where even small amounts of cortisol secretion can lead to insulin resistance and resultant hyperinsulinemia, exacerbating conditions like hypertension and diabetes.[14] Notably, studies by Terzolo et al., and Androulakis highlight the critical link between mild hypercortisolism and metabolic disturbances, underscoring the need for metabolic monitoring in patients diagnosed with BNAI.[15,16]

In this study cohort, both HU cut-offs below 10 and 20 were highly specific for non-malignant lesions, as all malignant AIs had HU above 20, consistent with the established evidence that low HU on non-contrast CT strongly indicates benign adenoma.[17,18] Among the ten patients who underwent adrenalectomy for benign non-functioning AIs due to their size (greater than 4 cm), half presented with HU values less than ten. These findings highlight the utility of HU thresholds, rather than tumor size, in guiding the surgical management of adrenal incidentalomas.[5] The absolute contrast washout of less than 60% was also useful in our cohort, demonstrated in 80% of the malignant AIs compared to only 8.7% of benign AIs.

Functioning adrenal lesions were present in 27.3% of all benign AIs, with MACS being the most prevalent diagnosis at 13.9%. This corresponds with the literature reporting that 15-30% of AIs display hormonal activity, with MACS being the commonest functional lesion (5-20%), followed by primary aldosteronism (1-10%) and pheochromocytomas (2-7%).[4,5,13,19-21] Only 1 out of the 158 benign non-functioning AIs treated conservatively progressed to become functional, which again corresponds with the current literature reporting a very low risk of functional progression, typically less than 1% thus supporting conservative management strategies for most patients as per current guideline recommendations.[5,22,23] None of the benign AIs in our cohort experienced a significant change in the radiological characteristics, including HU and contrast washout, supporting the recommendation that small, radiologically and biochemically stable lesions do not require extensive serial imaging and hormonal re-evaluation.[5]

A total of 10 out of 63 (15.8%) patients with functioning AI presented with bilateral adrenal lesions, 80% of which were MACS-associated, with macronodular lesions suggestive of primary bilateral macronodular adrenocortical hyperplasia (PBMAH).[4,24] Unfortunately, none of them had an adrenal biopsy done. This underscores the importance of tailored clinical management in these patients, as systemic causes or genetic predispositions are often at play in bilateral functioning AIs. All patients with malignant AIs, including those with metastases, had unilateral lesions suggesting a low probability of malignancy in bilateral AIs. Bilateral adrenal lesions are more commonly associated with benign conditions such

Table 5. Prevalence and outcomes of adrenal incidentalomas and macs in asian cohorts: A literature review

Author (Year)	Country	Study Design	N	MACS Prevalence (%)	Key Outcomes
Cho et al., 2013[35]	South Korea	Retrospective	282	7.1%	First Korean AI cohort: MACS patients had higher prevalence of diabetes and hypertension; emphasized long-term follow-up.
Liu et al., 2024[36]	China	Prospective	36	Not specified	MACS patients showed cognitive impairment compared to non-functioning adenomas; adrenalectomy improved memory function.
Luk et al., 2025[37]	Hong Kong	Retrospective	340	23.5% among functioning AIs	Female sex, larger size, hypertension, and prediabetes predicted MACS; surgery, when done, prevented metabolic progression
Current study, 2025	Malaysia	Retrospective	251	12.7%	Bilateral lesions and osteoporosis are significant predictors of MACS. Improvement in HbA1c and reduction in antihypertensive requirements after adrenalectomy.

as adrenal hyperplasia or systemic diseases, whereas unilateral adrenal lesions require careful consideration of the probability of malignancy. Bilateral adrenal lesions were independently associated with MACS in our cohort. Studies by Vassiliadi et al., and Di Dalmazi et al., suggested that the larger adrenal mass in bilateral lesions increases the risk of subclinical cortisol overproduction, potentially due to dysregulation of the hypothalamic-pituitary-adrenal axis.[25,26] The increased tissue volume may result in low-grade autonomous cortisol secretion that escapes normal feedback mechanisms. Clinically, this may substantiate the need for closer hormonal monitoring for autonomous cortisol secretion in patients with bilateral non-functioning adenomas.

Our patients with MACS had significantly higher rates of diabetes, hypertension, dyslipidemia, obesity, and osteoporosis compared to the non-MACS cohort, a finding consistent with the current literature. Chiodini et al. reported that MACS patients are 60-80% more likely to develop type 2 diabetes due to cortisol-induced insulin resistance, while Araujo-Castro et al. found that hypertension is 2-3 times more common in MACS due to cortisol's impact on the renin-angiotensin system.[10,27] Additionally, Barzon et al., documented a 50-70% higher prevalence of dyslipidemia and central obesity in MACS patients, likely due to cortisol's role in fat redistribution and lipid metabolism.[28] However, osteoporosis was the only comorbidity that was independently associated with MACS in our cohort. Even mild hypercortisolism significantly increases bone resorption and decreases bone formation by suppressing osteoblast activity and promoting osteoclast activity, leading to an increased risk of osteoporosis and vertebral fractures.[29-33] The strong and independent association between MACS and osteoporosis in our cohort underscores the importance of routine bone health assessment and early intervention to diagnose osteoporosis and prevent fragility fractures, in addition to periodic monitoring of diabetes, hypertension, dyslipidemia and obesity in patients with MACS, as recommended by the European Society of Endocrinology.[5]

Patients with MACS who underwent surgical intervention experienced significant improvement in blood pressure and glycemic control, while those managed conservatively showed worsening of blood pressure control and increased tumour size. These findings are consistent with the recent CHIRACIC trial, which demonstrated improved blood pressure control after adrenalectomy compared with conservative management.[34] The improvement is largely attributed to the removal of the adrenal tumour, which reduces hormone secretion that drives hypertension, while persistent tumour activity in conservatively managed patients may contribute to progressive growth and worsening metabolic comorbidities over time.[35] The decision to manage such tumours non-surgically should therefore be weighed carefully against the potential for progressive growth and related metabolic complications.

Table 5 summarizes published Asian studies on adrenal incidentalomas and MACS,[36-38] While earlier cohorts from Korea, China, and Hong Kong reported variable prevalence and outcomes, our Malaysian data add to the limited regional evidence, particularly by highlighting improvements in glycemic control and antihypertensive requirements following surgery.

This study provides a comprehensive analysis of a Malaysian cohort, an underrepresented population in the global literature on adrenal incidentalomas and mild autonomous cortisol secretion (MACS). Its multicentre design, incorporating data from three urban tertiary centres, and relatively large sample size compared with most Asian studies, enhance representativeness and statistical power. The evaluation of readily available clinical and radiological parameters as potential predictors of MACS supports applicability in routine clinical practice and may facilitate personalised follow-up strategies. In addition, the findings provide a foundation for future research, including the potential development of a regional risk-stratification or scoring system for adrenal incidentalomas. The study was conducted in accordance with ethical standards and employed a well-structured retrospective methodology, further strengthening its credibility.

Nevertheless, several limitations should be acknowledged. The retrospective design is inherently subject to selection bias, incomplete medical records, and inconsistent documentation, which may limit generalisability. The inclusion of patients with different subtypes of functioning adrenal incidentalomas introduces population heterogeneity and may reduce predictive accuracy. Not all patients underwent bone mineral density assessment, potentially leading to an underestimation of osteoporosis

prevalence. Furthermore, most patients underwent only a single 1 mg dexamethasone suppression test without routine confirmatory testing, raising the possibility of misclassification due to false-positive results. Follow-up duration was variable and may have been insufficient to detect delayed hormonal progression or malignant transformation in some patients.

These strengths and limitations highlight the need for prospective, multi-center, longitudinal studies to validate predictive factors for MACS and malignant adrenal pathologies, with longer follow-up to clarify the natural history of both functioning and non-functioning AIs. Randomized controlled trials are also required to determine the long-term impact of adrenalectomy in MACS, refine treatment guidelines, and define the comparative benefits of surgical versus conservative management.

CONCLUSION

This study demonstrated that most benign non-functioning AIs exhibit minimal risk of progression in terms of functionality or malignancy, suggesting that after an initial period of stability, the frequency of imaging and hormonal assessments can be safely reduced or omitted for the majority of patients. Bilateral adrenal lesions and osteoporosis emerged as the most robust independent predictors of MACS. This reinforces the importance of monitoring for autonomous cortisol secretion in patients with bilateral AIs and evaluating bone health in patients with MACS to prevent metabolic complications or spinal fractures associated with cortisol overproduction.

Statement of Authorship
All authors fulfilled ICMJE authorship criteria.

CRediT Author Statement
VD: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation; **SR:** Validation, Resources, Supervision, Project administration; **VMM:** Validation, Resources, Supervision, Project administration; **FSH:** Conceptualization, Methodology, Validation, Resources, Writing – review and editing, Supervision, Project administration.

Data Availability Statement
Datasets generated and analysed are included in the published article

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Evaluating the Two-Step TSH Screening Protocol for Congenital Hypothyroidism: Prevalence and Diagnostic Accuracy in Ninh Binh, Vietnam

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Abstract

Objectives. This study aimed to determine the prevalence of congenital hypothyroidism (CH) among newborns in Ninh Binh Province, Vietnam, and to evaluate whether adding a second thyroid-stimulating hormone (TSH) screening reduces false positives and improves diagnostic accuracy compared with the traditional single-step screening commonly practiced in Vietnam.

Methodology. A retrospective cohort study was conducted on 11,306 newborns screened between January 2019 and December 2020. TSH levels were measured from dried blood spot samples, with a threshold of >9 mU/L indicating high risk. High-risk cases underwent a second screening, followed by confirmation with serum TSH and free thyroxine. Screening performance (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) and risk factors for CH were analyzed.

Results. The prevalence of high-risk CH was 2.40% (271/11,306 newborns), with four confirmed cases (incidence: 1:2,826). The two-step screening program achieved a sensitivity of 75.00%, with one false-negative case later detected clinically. Specificity improved from 97.64% in the first screening to 99.81% in the second, while PPV increased more than tenfold (1.11% → 11.54%). Low birth weight infants (≤2,500 g) had a significantly higher CH risk (OR: 10.04, 95% CI: 1.053–95.820, $p = 0.004$).

Conclusions. This first provincial evaluation of two-step CH screening in Vietnam demonstrated that repeat testing significantly reduced false positives and improved diagnostic accuracy without compromising sensitivity. The findings highlight the value of implementing a two-step strategy to optimize newborn screening, reduce unnecessary referrals and save resources in developing countries.

Key words: congenital hypothyroidism, thyroid-stimulating hormone screening, newborn screening, prevalence, two-step TSH screening

INTRODUCTION

Congenital hypothyroidism (CH) is a significant endocrine disorder in newborns, marked by insufficient thyroid hormone production, potentially causing severe developmental delays and intellectual disability if not detected early.[1-3] Globally, CH incidence ranges from 1:2,000 to 1:4,000 live births, influenced by geographic regions and screening protocols.[1,2,4] In Vietnam, with approximately 1.4–1.5 million annual births, an estimated 400 CH cases are diagnosed yearly. Newborn screening began in 1999, and at the National Hospital of Pediatrics, the number of diagnosed cases has risen to 70–80 per year since 2017. However, many infants remain unscreened, particularly in rural areas like Ninh Binh Province, where iodine deficiency is a concern.[5,6]

Prior to 2019, the standard approach in Vietnam was a single-step TSH screening, in which newborns with elevated TSH levels in dried blood spots were directly referred to central hospitals for confirmatory testing. This practice often resulted in a high proportion of false positives due to transient neonatal TSH elevations, prematurity or maternal factors, leading to parental anxiety and unnecessary referrals that placed heavy burdens on families and healthcare resources.[2,3]

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Viet et al.
Received: August 15, 2025. Accepted: September 25, 2025.
Published online first: April 23, 2026.
https://doi.org/10.15605/jafes.041.01.5795

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To address these limitations, a two-step TSH screening protocol was introduced in Ninh Binh Province in 2019. In this approach, high-risk infants identified in the first screen undergo repeat testing locally before confirmatory diagnostics. This method has the potential to reduce false positives and improve positive predictive value (PPV) without increasing false negatives, while also optimizing resource use at the provincial level.

We therefore conducted a retrospective cohort study of 11,306 newborns in Ninh Binh Province between January 2019 and December 2020. The objectives were to determine the prevalence of CH, to evaluate the performance of two-step TSH screening compared with the traditional single-step approach and to examine risk factors such as low birth weight. This study represents the first provincial evaluation of the two-step screening strategy in Vietnam and highlights its potential to strengthen newborn screening programs in resource-limited settings.

METHODOLOGY

Research objects

This retrospective cohort study was conducted at the Ninh Binh Provincial Obstetric and Pediatric Hospital in Vietnam from January 1, 2019 to December 31, 2020. All consecutive live births within this period who underwent congenital hypothyroidism (CH) screening were included.

Study population and sampling

A total of 11,306 newborns were screened. Convenience sampling of all eligible consecutive live births during the study period was applied, ensuring the sample reflected the provincial birth cohort.

Sample collection and handling

Heel-prick blood samples were obtained from newborns aged 24–72 hours by trained healthcare personnel. Five dried blood spots (DBS) were prepared on Whatman Protein Saver Cards (USA), air-dried, stored appropriately and transported within 24 hours to the Chemedic Vietnam Joint Stock Company testing center. Missing or incomplete records (e.g., incomplete demographic or laboratory data, poor-quality DBS, or biologically implausible results) were excluded; these accounted for <0.5% of the dataset and no imputation was performed.

Instruments and reagents

The Victor-2D system (PerkinElmer, USA), Cobas 6000 Chemiluminescence Apparatus (Roche, Switzerland), and Panthera-Puncher™9 Puncher (3 mm column diameter, PerkinElmer) were used. Kits included the Thyroid-stimulating hormone assay kit (time-resolved fluorescence, PerkinElmer), TSH detection kit, and free thyroxine detection kit (electrochemiluminescence, Roche).

Screening procedure

TSH concentrations in dried blood spots were measured using a fluorescence immunoassay (Neonatal TSH ELISA kit, PerkinElmer) on the Victor-2D system, according to the Thyrotropin Assay Kit Manual and GSP Operating Procedure. High-risk CH cases were defined as TSH >9 mIU/L. All high-risk newborns identified in the first screening underwent a repeat heel-prick sample at 1–2 weeks for second-step screening.

Diagnostic confirmation

High-risk newborns after initial or second screening underwent confirmatory testing. Venous blood samples were analyzed for TSH and free thyroxine (FT4) levels using an electrochemiluminescence immunoassay on the Cobas 6000 analyzer (Roche, Switzerland). CH was confirmed by elevated TSH and reduced FT4 levels, based on age-specific reference ranges.

Sample size and power

As a retrospective cohort, no *a priori* sample size was calculated. However, a post-hoc power analysis indicated that with 11,306 newborns and an observed incidence of 1:2,826 (0.035%), the study achieved >80% power to detect a prevalence difference of 0.02% at $\alpha = 0.05$.

Statistical analysis

Analyses were conducted using SPSS version 20.0 (IBM Corp., USA).

- ***Descriptive statistics*** were used to summarize prevalence, demographics, and screening outcomes.
- ***Diagnostic accuracy*** (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) was calculated for the first and second screenings.
- ***Chi-square tests*** assessed differences in the proportions of diagnosed cases across subgroups (gender, birth weight, geographical distribution).
- ***Multivariate logistic regression*** evaluated risk factors for CH (low birth weight, gender and topographical classification). Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

No adjustments for multiple testing were applied, given the exploratory nature and the small number of confirmed CH cases; results were interpreted with caution.

Ethical considerations

The Institutional Review Board of Ninh Binh Provincial Obstetric and Pediatric Hospital approved the study before commencement. Written informed consent was obtained from parents or legal guardians prior to participation.

Table 1. Prevalence of high-risk congenital hypothyroidism by gender and birth weight

Category	No. of newborns (N)	High-risk 1st screening	High-Risk 2nd screening	Confirmed CH (n)	Incidence (1:n)	*p*-value*
Gender						
Male	6,055	151	14	1	1/6,055	0.252
Female	5,251	120	12	3	1/1,750	
Birth weight						
≤2,500 g	1,025	17	5	2	1/512	**0.004**
>2,500 g	10,281	254	21	2	1/5,140	
Total	11,306	271	26	4	1/2,826	–

*Chi-square test comparing subgroups.
High-risk is defined as TSH >9 mIU/L.
Incidence was calculated as the total confirmed CH cases divided by the total number of newborns.

Table 2. Multivariate logistic regression analysis for the incidence of CH in neonates

Influencing Factors	β	SE	Wald χ^2	*p*-value	OR	95% CI
Sex	1.241	1.091	1.29	0.252	3.46	0.408–29.341
Birth weight	2.307	1.153	4.00	0.004	10.04	1.053–95.820
Topographical classification*	-0.192	1.000	0.04	0.841	0.83	0.116–5.870

*Transitional lowland and coastal delta region vs. hilly midland region

RESULTS

Prevalence of CH

A total of 11,306 newborns were screened for congenital hypothyroidism (CH) between 2019 and 2020. After the first screening, 271 newborns (2.40%) were identified as high risk, decreasing to 26 (0.23%) after the second screening. Four newborns were confirmed with CH, yielding an incidence of 1 in 2,826.

Table 1 shows the prevalence of high-risk CH cases by gender and birth weight. The incidence was higher in females (1/1,750) than in males (1/6,055), though the difference was not statistically significant ($p = 0.252$). Low birth weight infants (≤2,500 g) had a significantly greater risk of CH compared with normal weight infants (OR 10.04, 95% CI: 1.053–95.820, $p = 0.004$). Geographic and topographic subgroup analyses are presented in Supplementary Table S1, with no statistically significant differences observed.

Risk factors

In Table 2, multivariate logistic regression analysis was performed to evaluate factors associated with congenital hypothyroidism (CH) in 11,306 neonates, with results presented for sex, birth weight and topographical classification. For sex (female vs. male), the odds ratio (OR) was 3.46 (95% CI: 0.408–29.341, $p = 0.252$). For birth weight (Low Birth Weight vs. Normal Birth Weight), the OR was 10.04 (95% CI: 1.053–95.820, $p = 0.004$). Finally, for topographical classification (Transitional lowland and coastal delta region vs. hilly midland region), the OR was 0.83 (95% CI: 0.116–5.870, $p = 0.841$). Overall, low birth weight remained the only significant predictor of CH (OR 10.04, $p = 0.004$). Gender and topographical classification were not significantly associated with CH incidence.

Screening performance

The diagnostic accuracy of the screening program is summarized in Table 3 and illustrated in Figure 1. At first screening, sensitivity was 75.00%, specificity was 97.64%, PPV was 1.11% and NPV was 99.99%. After the second

Table 3. Performance of congenital hypothyroidism screening using TSH quantification

Parameter	Formula	Result (1st screening)	Result (2nd screening)
True positive	(a)	3	3
False positive	(b)	268	23
False negative	(c)	1	1
True negative	(d)	11,034	11,279
Sensitivity	a/(a + c) (%)	75.00	75.00
Specificity	d/(b + d) (%)	97.64	99.81
Positive predictive value	a/(a + b) (%)	1.11	11.54
Negative predictive value	d/(c + d) (%)	99.99	99.99

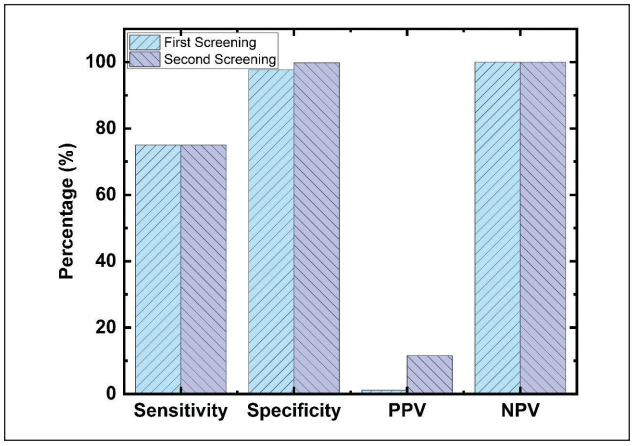


Figure 1. Comparison of screening performance between the first and second TSH-based screenings for congenital hypothyroidism (CH) in 11,306 newborns in Ninh Binh Province, Vietnam (2019–2020).

screening, sensitivity remained 75.00%, but specificity improved to 99.81% and PPV increased markedly to 11.54%, while NPV remained 99.99%. This demonstrates that the second screening substantially reduced false positives without increasing false negatives.

DISCUSSION

This study is the first evaluation of a two-step TSH-based screening program for congenital hypothyroidism (CH) in Vietnam. Conducted on 11,306 newborns in Ninh Binh Province during 2019–2020, it provides insights into prevalence, risk factors, and screening performance under real-world conditions in a resource-limited setting.

The incidence of confirmed CH was 1 in 2,826, which lies within the global range of 1:2,000–1:4,000 live births.[1,2,4,5] The relatively high proportion of initial high-risk results (2.40%) likely reflects transient TSH elevations and threshold effects, a phenomenon also noted in previous reports.[7,8] Low birth weight emerged as the only significant predictor, with an odds ratio of 10.04 (95% CI: 1.053–95.820, p = 0.004). Half of the confirmed CH cases were low birth weight infants, reinforcing findings from studies in Hainan and elsewhere that prematurity and reduced birth weight are associated with impaired thyroid function.[9] These results highlight the importance of tailored screening and follow-up for vulnerable subgroups.

A major contribution of this study is the demonstration that a repeat TSH test markedly improves diagnostic performance. Although sensitivity remained at 75.00%—with one false-negative case later diagnosed at ~3 months due to delayed growth, prolonged jaundice, constipation, and lethargy—specificity increased from 97.64% to 99.81%, and positive predictive value (PPV) rose more than tenfold (from 1.11% to 11.54%). This reduction in false positives (by >90%) is consistent with international recommendations that repeat testing minimizes unnecessary referrals and improves efficiency.[1] In the Vietnamese context, where abnormal first screens are usually referred directly to central hospitals, a second provincial-level screen can substantially reduce resource burdens while maintaining safety.

No statistically significant differences were observed across districts or topographic regions, either in univariate or multivariate analysis. These findings suggest that CH risk is not geographically clustered within Ninh Binh Province and support uniform province-wide screening policies.

The prevalence and screening performance observed here are broadly comparable to findings in other regions. Studies from China and Colombia have similarly highlighted the role of repeat or second-step testing in improving PPV.[9,10] Research in Kenya reported challenges with false positives and underdiagnosis in single-screen programs, underscoring the value of repeat testing.[11] Asia-Pacific regional reports also recommend two-step or tiered protocols to balance sensitivity with resource constraints (IAEA, 2005). Our findings add to this body of evidence and provide local data to guide newborn screening policies in Vietnam.

Several limitations should be acknowledged. First, confirmatory testing was restricted to high-risk newborns, raising the possibility of undetected CH cases and a true incidence higher than reported. Second, the small number of confirmed cases (n = 4) led to wide confidence intervals in logistic regression estimates, which should be interpreted with caution; future multicenter studies or extended follow-up periods are needed to improve statistical power. Third, maternal factors such as iodine deficiency and thyroid disease, which may influence neonatal TSH values, were not assessed. Finally, while the two-step method substantially reduced false positives, the persistence of false negatives indicates that clinical vigilance and follow-up remain essential.[10-12]

Overall, this study demonstrates that implementing a two-step TSH screening protocol is feasible and effective in reducing false positives in Vietnam. By reducing unnecessary referrals and focusing attention on true high-risk cases, this approach can optimize scarce healthcare resources while maintaining diagnostic accuracy. These findings provide a foundation for broader adoption of enhanced screening strategies in other provinces and similar resource-limited settings.

CONCLUSIONS

This study identified a high-risk prevalence of congenital hypothyroidism (CH) among newborns in Ninh Binh Province, Vietnam, of 2.40% (271/11,306), with four confirmed CH cases (incidence: 1:2,826), including one false-negative case diagnosed later through clinical manifestations. The two-step TSH-based screening program demonstrated high specificity (97.64% in the first screening, 99.81% in the second) and markedly improved positive predictive value (PPV) (11.54% vs. 1.11%), while maintaining sensitivity at 75.00%. Low birth weight infants had a significantly higher risk of CH (OR: 10.04, 95% CI: 1.053–95.820, p = 0.004), whereas sex, geography and topography showed no significant differences. These findings support the feasibility of two-step screening to reduce false positives, minimize unnecessary referrals, and optimize limited healthcare resources in Vietnam. However, the persistence of false negatives highlights the need for complementary clinical follow-up to ensure timely detection and intervention.

Acknowledgments
The authors sincerely thank the family members who participated in this study.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
NHV: Conceptualization, Methodology, Writing – original draft, Writing – review and editing, Supervision; **TKH:** Conceptualization, Methodology, Writing – original draft, Writing – review and editing, Supervision; **NBN:** Formal analysis, Investigation, Data curation; **BTB:** Formal analysis, Investigation, Data curation; **NAN:** Formal analysis, Investigation, Data curation; **VTT:** Conceptualization, Methodology, Writing – original draft, Writing – review and editing, Supervision.

Data Availability Statement
Data are available upon reasonable request from the corresponding author.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
This work was supported by the Ninh Binh Province Obstetrics and Pediatrics Hospital.

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Journal of the ASEAN Federation of Endocrine Societies

REVIEW ARTICLE

Living with Legacy: Outcomes and Future Implications for Offspring of Patients with MEN1

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Abstract

Background. Multiple endocrine neoplasia type 1 (MEN1) is a hereditary condition with an autosomal dominant inheritance, with a predisposition to both endocrine and non-endocrine tumours. MEN1-related tumours can appear as early as the age of five, with disease penetrance increasing with age. Offspring of a MEN1 parent shows a 50% probability of inheriting the MEN1-related gene mutation. A MEN1 diagnosis in a parent can lead to significant anxiety for both the diagnosed parent and their undiagnosed at-risk children. There is limited consensus specific for managing offspring of individuals diagnosed with MEN1.

Objectives. This review aims to evaluate the existing literature on the outcomes of MEN1 syndrome in the offspring of affected patients, to identify gaps in current protocols and to suggest possible improvements.

Methodology. A literature review was conducted to examine the outcomes and characteristics of the offspring of individuals diagnosed with MEN1.

Results. Predictive testing and screening for organ involvement in MEN1 aid early diagnosis and timely interventions. DNA testing is recommended for children within the first decade of life, and screening for organ involvement should ideally begin at age 5 years for all MEN1 mutation carriers. Manifestations of MEN1 in younger children are different from those of affected adults.

Conclusions. Standardised, internationally-accepted guidelines that provide specific recommendations for screening, diagnosis and treatment of offspring of adults diagnosed with MEN1 is a timely need. Furthermore, the absence of national and international data pooling across regions remains a serious limitation, impeding the ability to draw conclusions from larger, more representative patient populations.

Key words: MEN1, endocrine tumours, at-risk offspring, inheritance, genetic screening

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant hereditary tumour syndrome resulting from inactivating mutations in the tumour suppressor gene MEN1, and is distinguished by a predisposition to various endocrine and non-endocrine tumours.[1] The condition typically consists of hyperplasia and/or tumours originating from the parathyroid, duodeno-pancreatic and/or anterior pituitary glands, which are seen in 90%, 30–70%, and 30–40% of individuals, respectively, by the age of 40, but also includes other manifestations such as collagenomas and lipomas.[2,3] MEN1-associated neoplasms have been identified as early as at the first five years of life. However, most diagnoses occurred after age 10, with disease penetrance increasing with advancing age.[2] Despite advances in the diagnosis and management of MEN1-associated tumours, individuals with this disease still exhibit a reduced life expectancy relative to the general population, with a mean age of mortality ranging from 55 to 60 years.[4,5]

Screening for MEN1 presents with unique challenges, since the combination of affected glands can vary among members of the same family, and there is little genotype-phenotype correlation.[1] The precise age-related penetrance, which

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Muthukuda et al.
Received: July 27, 2025. Accepted: September 7, 2025.
Published online first: January 21, 2026.
https://doi.org/10.15605/jafes.041.01.5125

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refers to the proportion of carriers of the gene mutation who have shown symptoms or signs of the disease by a certain age, is still to be determined.[6] Moreover, a delayed diagnosis of MEN1 has been linked to increased morbidity, mostly associated with metastatic neuroendocrine tumours (NETs), as there is a median lag time of 3.5 years between the diagnosis of MEN1 in the index case and the genetic testing of family members for the condition.[7,8] In 50–70% of patients with MEN1, mortality is attributable to the disease itself.[9,10] Clinical practice guidelines for managing MEN1 were recently published in 2025 with modifications to the previous guidelines published in 2012.[3,11]

Why is it important to study the offspring of patients with MEN1 syndrome?

Psychological and social impact of early diagnosis of MEN1 in children

The diagnosis of MEN1 in a parent can significantly influence family dynamics. The parent already diagnosed with MEN1 as well as the yet-undiagnosed children may both suffer significant anxiety and concern regarding developing health risks associated with potential MEN1 in the offspring.[12,13] The chronic nature of the disorder, the need for long-term regular screening until a tumour(s) is detected, ongoing treatment for the diagnosed tumour (s), and the constant monitoring for risk of recurrence of a treated tumour(s) can significantly impact the quality of life for patients and their families. The presence of MEN1 in an individual or a family is a lifelong condition that a diagnosed individual and their family must live with. In addition to the psychological stress and anxiety associated with the disease, it also poses a significant financial burden associated with lifelong screening and monitoring, especially in resource poor settings. Early diagnosis of MEN1 in children can cause significant psychological and social impact on the child. The recommendation is to start screening children of affected parents at the age of 5, which is an age where they are unlikely to have an understanding of the disease condition and the need for frequent screening.[3] Frequent hospital visits, testing and treatment can lead to missed school days and childhood events with friends, leading to disappointment, which the child may find difficulty to understand. Affected children can experience anxiety from peer rejection and have difficulties fitting in.

Early screening strategies and psychological and social support for children and families with MEN1

Transparent discourse on illness and its ramifications is essential for the emotional welfare of such children and young adults. Providing education on MEN1, along with early screening and implementing a comprehensive follow-up plan, helps to alleviate anxiety in both parents and children of families affected with MEN1.[13] While coping mechanisms to unexpected new diagnosis and the effect of the disease on the children may differ in each family, there are patient groups or counselling services that offer a venue for exchanging experiences, sharing information regarding

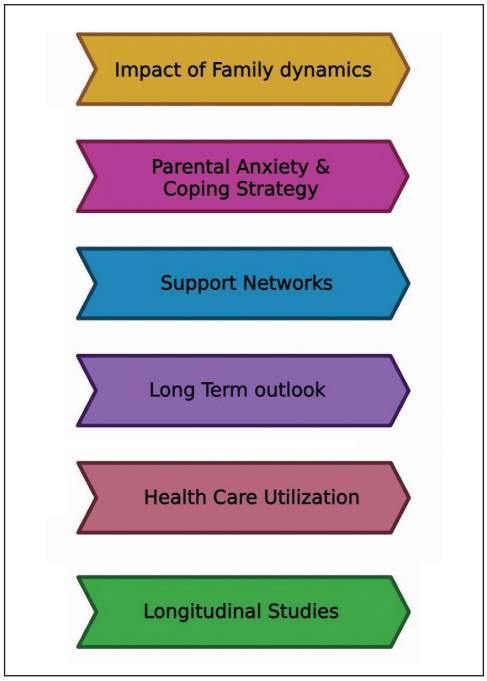


Figure 1. Key considerations in researching offspring of MEN1 patients.

MEN1 and providing some support to affected families.[13] Establishing a supportive environment in which children feel at ease expressing their fears and concerns is essential. These networks may encompass healthcare practitioners, counsellors and peer support groups, that can offer essential information and emotional assistance.[12] AMEND (*Association for Multiple Endocrine Neoplasia Disorders*) is a support group in the United Kingdom focused on individuals with MEN syndromes. They offer child-friendly guides and pamphlets, often in a cartoon or graphic form, aimed to explain and reassure.[14] The quality of life of the children of individuals with MEN1 may be influenced by the apprehension of developing the disorder, or the actual experience of living with a genetic illness. Longitudinal studies are essential for comprehending the impact of these factors on overall well-being.[15] This review aims to evaluate existing literature on the outcomes of MEN1 syndrome in the offspring, to identify gaps in current protocols, and to suggest possible improvements. (Figure 1)

METHODOLOGY

This narrative review on the offspring of individuals with Multiple Endocrine Neoplasia Type 1 (MEN1) entailed a systematic literature search across multiple databases, including PubMed, Embase, Scopus, and Google Scholar, employing keywords such as "MEN1 syndrome," "offspring" and "outcome." The inclusion criteria targeted studies on the progeny of MEN1 patients, including clinical studies, observational studies and case reports published in peer-reviewed publications over the past three decades. The exclusion criteria were papers that were not immediately pertinent to MEN1 or its implications for progeny, along with non-English literature lacking accessible abstracts.

Data extraction was done with a standardised form to collect essential information, including study design, demographics, clinical findings, screening processes and outcome.

Genetics and inheritance of MEN1

MEN1 syndrome is inherited in an autosomal dominant manner, and each offspring of an affected parent has a 50% chance of inheriting the mutation. The MEN1 gene is located on chromosome 11q13, and the related tumorigenesis is according to Knudson's 'two hit' hypothesis, indicating a gene inactivation. More than 1000 germline MEN1 mutations have been identified, of which 1% to 3% are large deletions. These mutations predict absent or truncated menin. Around 90% of individuals diagnosed with MEN1 have an affected parent, indicating a familial form of MEN1, defined as having at least one first-degree relative having one or more main endocrine tumours, or involvement if only one endocrine organ along with a MEN1-causing germline mutation. There are instances where a family history in familial MEN1 may not be identified because of either failure to recognise the disorder in an affected family member, early death of a parent before the onset of symptoms, or late onset of the disease in the affected parent. If the disease-causing MEN1 germline mutation identified in the proband is not identified in either parent, the possibilities are a germline mosaicism in a parent, or a *de novo* mutation in the proband. Simplex MEN1 due to *de novo* mutations, rather than familial MEN1, is seen in 10% of MEN1 cases. DNA testing detects MEN1 mutations in 80 to 90% probands with familial MEN1, and in 65% probands with simplex MEN1. When a known MEN1-causing mutation is not identified in an individual in a family with more than one affected family member in two generations, the next possible test would be linkage or haplotype analysis. Simplex MEN1 cases are less likely to be positive for a mutation than in familial cases, because some simplex cases are caused by somatic mosaicism.[16] One should also be aware of 'phenocopies' of MEN1 when there are incidentally two endocrine tumours identified in an individual who is clearly MEN1-mutation negative.

Genetic anticipation in successive generations

MEN1 mutations have a high penetrance of more than 95% including age-related penetrance. Genetic anticipation in MEN1 has been identified in some cases, but its mechanisms have not been fully explored and described. Genetic anticipation refers to the phenomenon of decreased age of disease onset or an increased severity in successive generations, indicating a higher mortality and morbidity from MEN1 in offspring and successive generations. Genetic anticipation has been well-described in heritable cancer syndromes such as dyskeratosis congenita, Lynch syndrome, Li-Fraumeni syndrome, Von Hippel-Lindau syndrome and hereditary breast and ovarian cancer syndrome. Three potential hypothesised mechanisms have been described in the literature for genetic anticipation in MEN1. The first speculated mechanism is progressive telomere shortening in successive generations, possibly owing to haploinsufficiency of the affected gene. The second hypothetical mechanism is the progressive accumulation of germline mutations prior to the loss of heterozygosity, due to microsatellite instability in germ cells passing on mutant alleles to offspring. The third possible mechanism is accumulation of DNA copy number variations in the context of haploinsufficiency.[17]

When is the best time to test offspring?

Predictive testing and screening for organ involvement helps with early diagnosis and facilitates interventions that reduce morbidity and mortality associated with MEN1. A DNA test identifying an individual as a MEN1 mutant gene carrier does not usually lead to immediate medical or surgical treatment, but it suggests the need for regular and frequent clinical screening. Identifying carriers also allows reproductive planning choices. However, predictive testing can have psychological ramifications, especially in asymptomatic individuals. Therefore, genetic counselling and patient education should precede carrier testing. Parents with MEN1 should have an initial consultation with a pediatric endocrinologist with or without the child, when the child is 5 years of age to discuss shared decision-making regarding screening and surveillance plans.[11] A DNA test for genetic testing of offspring in MEN1 is recommended to be offered to children within the first decade of life, as some tumours such as insulinomas and pituitary tumours are known to develop in children as early as at 5 years of age.[16] However, one always needs to bear in mind parental concerns regarding the impact of testing on the child, and possible implications regarding life insurance and mortgage applications in adulthood.

The current clinical practice guidelines recommend to start clinical screening for organ involvement manifestations from the age of 5 years in all MEN1 mutation carriers, and to further expand the screening with advancing age, with biochemical screening of asymptomatic children from 10 years.[3,11] In instances where molecular genetic testing is not possible or not informative, individuals at 50% risk of a MEN1 mutation, indicated by having first-degree relatives with MEN1 syndrome, should undergo routine biochemical and clinical evaluation.[16] The current MEN1 clinical practice guidelines recommend initiating clinical screening for pituitary tumours and insulinoma from 5 years of age, and regular biochemical assessments 10 years of age, with assessment for bronchial and thymic carcinoids at 15 years of age and gastrinomas at 20 years of age. Clinical, biochemical and imaging screening for MEN1-associated NETs is performed at regular intervals, generally annually. The frequency of screening investigations depends on the NET risk of occurrence and aggressiveness, with screening frequency increasing with advancing age.[3,11] Serum calcium levels should be tested every 1 to 3 years from the age of 10 years onwards to screen for primary hyperparathyroidism in children and adolescents (<19 years), and is increased

to annually in adults.[11] While physical examination for growth and pubertal development should be done in children with MEN1, asymptomatic children with normal growth and development should undergo biochemical screening for pituitary NETs with serum prolactin and insulin like growth factor -1 (IGF-1) from the age of 10 years, repeated every 1 to 3 years, compared to the previous recommendation of 5 years of age.[3,11] There is no consensus regarding testing gastrin level in children until they reach 18 years of age. Insulin level testing in children is done only if they develop symptomatic hypoglycaemia.[11] Although there is no consensus on the benefit of pituitary MRI screening in asymptomatic children with normal growth and development, if a decision for MRI pituitary is made by shared decision making, the age for first MRI pituitary is considered at 15 years, repeated every 3 to 5 years if negative.[11] The first MRI to screen for duodeno-pancreatic neuroendocrine tumours (DP-NETs) in asymptomatic children is recommended at 10 to 15 years of age, followed by repeat scans every 2 to 3 years if negative.[11] The 2012 guidelines recommended commencing thoracic imaging for thoracic NETs in asymptomatic individuals with MEN1 at age 15 years, but the recent 2025 guidelines have delayed this age to 20 to 25 years preferably with computed tomography (CT).[3,11]

Management of pre-symptomatic neuroendocrine tumours detected on screening

Asymptomatic children and adolescent or young adults (AYA) diagnosed with primary hyperparathyroidism without evidence of target organ involvement can undergo active surveillance. However, if they become symptomatic, develop end-organ involvement or have a total serum calcium level >1 mg/dL (>0.25 mmol/L) consistently above the upper limit of the normal range, subtotal (3 to 3.5 glands) parathyroidectomy with transcervical thymectomy is recommended. Early parathyroidectomy for primary hyperparathyroidism can be considered in the presence of concomitant symptomatic gastrinoma, as this would help with reducing gastrin hypersecretion and gastrinoma tumour growth.[11]

The treatment of clinically functional and symptomatic MEN1-associated NETs is surgical resection and additional medical management as needed. However, the optimal treatment strategy remains controversial for non-functional NETs or earlier detected NETs in their pre-symptomatic stage during screening. Upon detection of a non-functional NET in their pre-symptomatic stage, the decision regarding early intervention or active surveillance depends on the aggressiveness of the tumour, as indicated by its size and rate of growth. The risk of metastasis of NETs increases substantially when the tumour size exceeds 2 cm, with most smaller tumours running an indolent course. In MEN1 patients with stable non-functional pancreatic NETs ≤2 cm in size with growth rates <1 mm/year (for >1 year), active surveillance with serial imaging every 1 to 2 years is recommended.[11] Consideration of surgery is recommended for NETs larger than 1 cm.[3] However, this size criterion in decision-making cannot be applied to all NETS, especially in the absence of specific tumour biomarkers for aggressiveness. Bronchopulmonary NETs generally have a low growth rate and excellent overall survival compared to other MEN1-associated NETs. Serial imaging, preferably with non-contrast magnetic resonance imaging (MRI), given its low radiation exposure, is recommended to ascertain the rate of tumour growth. Given that occasionally small non-functional NETs <1 cm in size can also develop metastasis, ^{68}Gallium DOTATATE PET/CT may be of value in detecting occult metastatic disease. However, it has limited utility as a serial surveillance investigation due to its high ionising radiation exposure and expense. The risk of ionising radiation exposure with any of the aforementioned imaging modalities, when performed in regular intervals, is specifically harmful for growing children. Therefore, it is crucial to have specific strategies for children in surveillance of small, non-functional NETs.[18]

Differences in MEN1 manifestation in children with MEN1 compared to adults with MEN1

The frequency of MEN1-related tumours in children is different to that of adults. Primary hyperparathyroidism was the most common clinical manifestation of MEN1 in both children and adults; however the second most frequent manifestation in children is a pituitary tumour, followed by a gastro-entero-pancreatic neuroendocrine tumour. MEN1-related pituitary tumours are more frequent in adult females. There is a higher penetrance of non-functioning pituitary tumours (42%) than insulinomas (11%) in MEN1 patients aged 12 to 20 years. Cushing's disease is more common than adrenal Cushing's in childhood MEN1.[15]

Clinical studies conducted on the children of patients with MEN1

A study conducted in Japan discovered three asymptomatic mutant gene carriers (children of cases 1-3) and 12 non-carriers among first-degree relatives of sporadic patients with the MEN1 mutation. No non-carriers exhibited MEN1-related lesions.[19] Another case study in this research indicated that the parents did not possess the same mutation, implying a *de novo* mutation in the offspring. One of the proband's daughters was identified as an asymptomatic carrier of the mutation, and the patient's genotype aligned with the biological parentage of her mother and father. Haplotype analysis surrounding the MEN1 region indicated that the patient's mutant allele originated from her father, verifying that the detected mutation 893+1G-A was not *de novo*[19] (Table 1).

An Indian case study revealed that the proband's elder brother died due to a pituitary tumour, while his sister had nephrolithiasis associated with hyperparathyroidism, causing hypercalcaemia,which was treated with excision of a parathyroid adenoma.[20] His parents and his three children, the eldest being 13 years old, and his sister's two

Table 1. Global clinical studies on offspring of MEN1 patients: A comparative analysis

Country, Year Of Publication	Methodology	Results	Conclusion/Recommendation	Reference
Japan, 1999	10 cases of diagnosed Japanese MENl were included.	Identified 3 asymptomatic mutant gene carriers (children of cases 1-3) and 12 noncarriers among first-degree relatives of the sporadic patients with MENl	A patient who has been considered sporadic will become a proband of familial MEN1. If no offspring have inherited the mutant allele, or while offspring inheriting the mutant allele are too young to manifest symptoms, or if a family study is insufficient, the diagnosis will remain as sporadic MEN1.	18
India, 2008	A case study of an Indian family with MEN1 syndrome	The DNA sequencing of exon 4 of the patient's family members showed the presence of the same mutation in 7 of 8 cases examined. The father did not carry the mutation; the mother was the carrier. Apart from the proband, the daughter and 5 of 6 grandchildren were affected.	The genetic testing is shown to improve the quality of diagnosis and treatment in the proband and family members.	19
United Kingdom, 1996	Age related penetrance was Investigated. 709 people from 62 MEN1 families, and 36 non- familial MEN1 patients	Among 288 offspring of 101 affected parents, 129 were affected. The ages of conversion from an unaffected to affected phenotype were found in two individuals to be 20 and 21 years respectively, 2/162 carriers remain unaffected, thereby indicating a 98.8% penetrance of the MEN1 gene by the age of 53 years.	Screening should be initiated before 8 years of age.	6
Netherlands, 2020	Mutation Positive MEN1 families. A total of 10 families was included	The number of affected family members ranged from 11 to 29 per family. A total of 137 affected members (90.1%) showed 1 or more MEN1-related manifestations during follow-up. The median age at detection of the first encountered manifestation was 46 in the first generation, compared with 14 (range: 11–17 years) in the youngest generation. Furthermore, patients from younger generations encountered their first MEN1-related tumor significantly earlier in life.	Manifestations occurred significantly earlier in the lives of patients from successive generations. Even with the adjustments for the beneficial effect of surveillance programs, our results suggested the presence of genetic anticipation in MEN1.	16
France, 1997	Two branches of a MEN1 family were studied.	Clinically, generations IV and V were severely affected with the disease. In generation IV of the first branch, 5 siblings out of 7 were affected.	By comparing the age of presentation and the severity of the disease through each generation, there is evidence of anticipation phenomenon.	20
Tasmania, 2019	Retrospective cohort analysis of 341 children with a MEN1 positive (MEN1+) parent and n = 314 children with MEN1 negative (MEN1–) parents. The contemporary cohort included neonates (n = 52) of MEN1+ women (n = 21)	Historical cohort: compared with MEN1– parents, children of MEN1+ parents were more likely to die postpartum at 6 months of age). Excess mortality at 15 years of age was observed for children of MEN1+ mothers and fathers. Contemporary cohort: neonates of MEN1+ mothers were more likely to have low birth weight)	Children with a MEN1+ parent are disproportionately vulnerable postpartum. Neonates of MEN1+ mothers remain vulnerable despite contemporary care. The excess risk was not fully explained by maternal MEN1 or antenatal hypercalcemia.	21

children, remained asymptomatic. DNA sequencing of exon 4 in the patient's relatives revealed the identical mutation in 7 out of 8 tested cases. The mother was the carrier, while the father did not possess the mutation. In addition to the proband, the daughter and 5 of the 6 grandchildren were mutation-positive. The proband's eldest child was found to have elevated serum calcium and an insulinoma[20] (Table 1).

The implementation of standardised surveillance methods and clear criteria for MEN1 symptoms has improved follow-up for subsequent generations. However, older generations have benefited less from these techniques, leading to potential delays in diagnosis compared to more recent generations. In the family studied, the second and third generations showed no clinical signs of MEN1, while the fourth generation had eight affected individuals. The fifth generation had all 5 patients show at least one MEN1-related symptom before the age of 22[20] (Table 1).

Transition of care of adolescents and young adults with MEN1

MEN1 is a chronic disorder which requires lifelong surveillance and ongoing treatment. This requires a thorough understanding of the disease condition and is a major responsibility for the patient. Children with MEN1 are managed by a paediatric endocrinologist, and they are primarily cared for by their parents, who assume the principal responsibility for their follow-up care and decision-making. When transitioning an AYA with MEN1 to adult care, they need to gradually be helped to take responsibility for their care and decision-making. Unfortunately, individuals with rare endocrine disorders, including MEN1, have been shown to have a high drop-out rate during transition of care, leading to loss of follow-up and active surveillance. Transition of care must be done gradually over a period of time and should commence at an earlier age. This is to ensure that the AYA gets a better understanding of the disease, understands the responsibility

that comes with it, and develops confidence with self-care and independent decision-making. This transition process should include joint consultations with paediatric and adult endocrinologists, as well as the MEN1-affected child and their parents. Before the complete transition of care, the AYA's readiness for transition should be assessed. This can be done through validated checklists, such as the TRAQ (Transition Readiness Assessment Questionnaire) and TRAM (Transition Readiness and Appropriateness Measure). It is important to identify shortcomings early, so that patients have sufficient time to train all skills with any required support from the endocrinologist prior to transfer.[23] This is especially important as the AYA considers moving out of the parental home to attend college or university, when close parental supervision is no longer possible.

Pregnancy outcomes

Managing MEN1-related complications in pregnancy can be challenging. Primary hyperparathyroidism (PHPT) during pregnancy correlates with a significant risk of maternal, fetal and neonatal adverse effects, directly proportional to maternal calcium levels. This can result in intrauterine growth restriction, preterm delivery, intrauterine fetal demise, neonatal low birth weight and hypocalcaemia.[24,25]

Children with an MEN1-positive parent have historically been shown to experience an excess of mortality, with the risk most pronounced in the post-partum period.[22] In the contemporary context, offspring of MEN1-positive mothers experienced a high frequency of adverse events during the neonatal period, including low birth weight, prolonged length of hospital stay, increased admission to higher dependency nurseries and metabolic and infectious events. Antenatal hypercalcaemia alone did not significantly alter neonatal outcomes. Hypoglycaemia was highly prevalent in neonates of MEN1-positive mothers, and this may reflect an additive risk posed by increased incidence of low birth weight, preterm birth and antenatal diabetes.[22] MEN1 is associated with an increased risk of type 2 diabetes mellitus. The excess of childhood mortality in the historical cohort was not solely attributable to offspring of MEN1-positive mothers but was also apparent in offspring of MEN1-positive fathers.[22]

Key issues and debates in offspring of multiple endocrine neoplasia type 1

Inadequate protocols and guidelines

Existing Protocols and International guidelines, including the European Society of Endocrinology (ESE) guideline and the American Association of Clinical Endocrinologists (AACE) Clinical Practice Guideline relating to MEN1, have been created with an emphasis on managing adult patients diagnosed with the condition, including recommendations for the management of related tumours.[3] These guidelines advocate for the screening of pituitary tumours, parathyroid hyperplasia, and pancreatic neuroendocrine tumours at an early age, although they typically do not include explicit recommendations for the offspring of individuals affected with MEN1. This constitutes a significant limitation in guidelines, as MEN1 may manifest earlier in life, and unaddressed early symptoms in children could be more severe.

Adult MEN1 patients generally undergo screening beginning in their late teens or early twenties. However, there is no consensus on the optimal age to initiate screening for offspring, though evidence shows the benefit of initiating screening before the age of 8 years.[20] There is also no consensus on the specific treatments recommended for this population. This ambiguity arises partly from the diversity in disease manifestation and penetrance, which can significantly differ among individuals, even within the same family.[26]

Certain specialised institutions, such as neuroendocrine tumour centres (NET centres), have established different protocols for the management of MEN1 patients, potentially better suited to the unique requirements of at-risk children and adolescents.[27] These centres may do early genetic testing, increase surveillance frequency, and tailor therapies according to genetic results. Nonetheless, these procedures lack widespread adoption and standardisation, resulting in significant variations in institutional practices compared to larger international recommendations. As a result, there is a lack of a standardised method for offspring management, resulting in disparities in treatment and outcomes.

Data gaps and challenges

Owing to the lack of national or worldwide data pooling, MEN1 research remains fragmented and isolated. Researchers from various regions may face the challenges of working with limited sample sizes, which limits the generalisability and impact of their findings. Even if national data are obtained, many nations lack the legal frameworks and ethical principles required for the secure and standardised exchange of health data across borders. This limitation restricts the ability to aggregate MEN1 data internationally or regionally, which could improve research and inform clinical decision-making. The lack of longitudinal data on the emergence of MEN1 offspring impedes the establishment of effective management procedures. The majority of research concentrates on adults with established tumours, providing scant information on pre-symptomatic individuals or those diagnosed at a younger age.[3,11] Consequently, there is limited knowledge regarding the early natural history of MEN1 in infants and adolescents, as well as the potential effects of early therapies on disease progression.

Recommendations and future directions

Future guidelines for the management of offspring of individuals with MEN1 in developing countries should emphasise improving accessibility and support. Community-oriented genetic counselling should be imple-

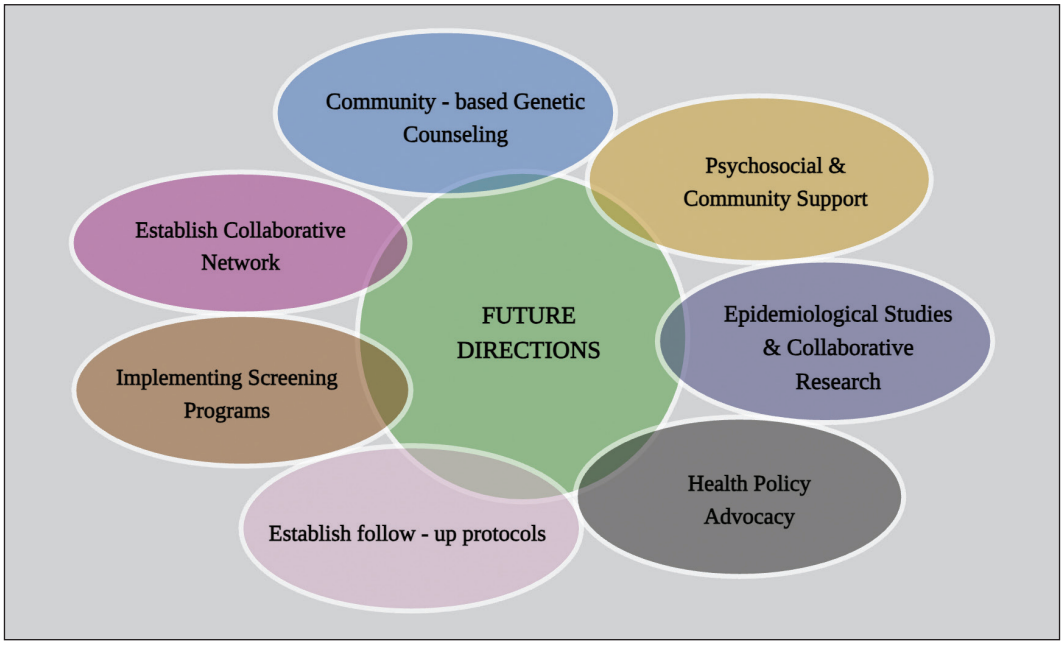


Figure 2. Key aspects for future research on offspring of MEN1 patients.

mented, with local healthcare professionals educated to deliver customised support and information. Enhancing access to affordable genetic testing is essential, possibly via subsidies and mobile health units that serve underserved regions. Comprehensive screening systems must be established, incorporating early detection techniques into current maternal and child healthcare. As psychosocial assistance is crucial, healthcare providers must undergo mental healthcare training, and local support networks should be established to promote community involvement. To enhance the management of offspring of patients with MEN1, it is imperative to establish a collaborative framework for data aggregation and the formulation of comprehensive clinical guidelines. Specialised institutions, such as Neuroendocrine Tumour (NET) Centres, play a vital role in enhancing therapeutic protocols for the management of MEN1. These centres serve as focal points for research, education, and the dissemination of best practices, ensuring that healthcare personnel possess the most updated knowledge and tools for patient management.

Moreover, the requirement for global collaboration and data exchange among academics and institutions is essential. Collaborative initiatives can enhance worldwide comprehension of MEN1, leading to improved clinical outcomes through the exchange of resources, expertise and data. Creating national databases that aggregate clinical, genetic and psychosocial data on MEN1 can increase understanding of the condition's prevalence and presentations across various groups. These databases should be structured to facilitate seamless access for healthcare professionals and researchers, thereby enhancing informed decision-making and evidence-based practice. Multiple domains necessitate further inquiry to improve our comprehension of MEN1, especially regarding its effects on offspring. Research should concentrate on the long-term health consequences for these individuals, the psychosocial impacts of residing with a hereditary illness, and the efficacy of early screening techniques. Furthermore, research on the genetic differences and environmental factors that affect MEN1 expression across diverse populations is essential. Promoting the incorporation of genetic disorders in national health strategies will guarantee the allocation of adequate resources. Management plans must be culturally relevant and tailored, taking into account the socio-economic circumstances of families. Ultimately, sustained health monitoring, possibly through telemedicine and digital platforms, can provide continuous assistance and early identification of potential MEN1-related illnesses, ensuring a holistic approach to the health and welfare of these individuals (Figure 2).

CONCLUSION

The study of the offspring of patients with MEN1 is an important area of research that has been largely under-explored, particularly in less developed nations. This review has identified major gaps in our understanding of MEN1 in children and adolescents, with a particular emphasis on the absence of comprehensive screening methods, standardised management practices and adequate psychosocial support for affected families. We emphasise the need for standardised, internationally accepted guidelines that not only address the clinical care of MEN1 in adults, but also provide clear recommendations for the screening, diagnosis and therapy of affected children. Furthermore, the lack of national and international data pooling remains a significant limitation, hindering our ability to draw conclusions from larger, more representative patient populations.

Statement of Authorship
All authors fulfilled ICMJE authorship criteria.

CRediT Author Statement

DTM: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **KPJ:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **GW:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **AG:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

Author Disclosure

The authors declared no conflict of interest.

Funding Source

None.

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Journal of the ASEAN Federation of Endocrine Societies

REVIEW ARTICLE

High Remnant Cholesterol Increased the Risk of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) or Non-Alcoholic Fatty Liver Disease (NAFLD): A Systematic Review and Meta-Analysis

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Abstract

Background. MAFLD is currently acknowledged as the most common chronic liver disease and is strongly associated with obesity, metabolic dysregulation and diabetes. MAFLD is defined by the accumulation of lipids within the liver due to impaired lipid metabolism.

Objective. The objective of this study is to assess the association between increased remnant cholesterol levels and the likelihood of developing MAFLD or NAFLD.

Methodology. A systematic review and meta-analysis were performed in accordance with PRISMA recommendations. Databases such as the Cochrane Library and PubMed were queried for relevant material through March 21, 2025, using specific keywords related to remnant cholesterol and fatty liver disorders. The inclusion criteria concentrated on research investigating the influence of remnant cholesterol on the incidence of NAFLD/MAFLD. Data extraction and quality evaluation were conducted utilizing the JBI Critical Appraisal Checklist for Cohort Studies and ROBINS-I instruments.

Results. Six studies were eventually included in our systematic review, including cross-sectional studies with a total of 45,821participants. The meta-analysis, conducted with Review Manager version 5.4, demonstrated a significant association between elevated remnant cholesterol levels and an increased risk of NAFLD/MAFLD, yielding a relative risk (RR) of 3.18 (95% CI 1.89-5.37; p <0.00001; I^2 = 99%). This indicates a robust link between remnant cholesterol and the prevalence of various hepatic disorders.

Conclusion. Remnant cholesterol is associated with MAFLD or NAFLD. Increased remnant cholesterol is a risk factor for MAFLD or NAFLD.

Key words: remnant cholesterol, insulin resistance, MAFLD, NAFLD

INTRODUCTION

Since the introduction of non-alcoholic fatty liver disease (NAFLD) in 1980, several trials have been conducted by various scientists and organizations to propose alternative nomenclature for the condition for diverse reasons.[1] In 2019, Eslam et al., recommended reclassifying classic NAFLD as metabolic dysfunction-associated liver disease (MAFLD).[2] The alteration of a single letter holds significant implications for researchers, physicians and patients. The authors articulated their perspective on a novel nomenclature by associating fatty liver with metabolic syndrome, the predominant and most severe cause of fatty liver illnesses, which is often inadequately assessed under the previous nomenclature. Furthermore, the revised nomenclature provides the healthcare community with an opportunity to mitigate the stigma associated with alcohol consumption, circumvent the negative connotations of NAFLD terminology and address trivialization.[3] The streamlined diagnostic criteria for MAFLD were established by consensus among an international panel of hepatologists in 2020.[4] These criteria facilitate the straightforward detection of fatty liver disorders due to their practical usefulness. The agreement defined MAFLD as the presence of steatosis, identified by imaging or histology, alongside either diabetes mellitus, obesity/overweight, or the presence of two of seven metabolic dysfunction criteria. The revised terminology and methodology elucidate the significance

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Biya et al.
Received: May 5, 2025. Accepted: June 20, 2025.
Published online first: April 24, 2026.
https://doi.org/10.15605/jafes.041.01.5159

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of metabolic dysfunctions in fatty liver disease, aligning the condition more closely with its etiology.

The novel nomenclature and its practical application invigorated researchers globally, leading to a significant increase in publications over the past two years. Recent studies have provided substantial evidence demonstrating the superiority of MAFLD criteria over NAFLD criteria. Numerous studies throughout various global regions, involving substantial patient populations in the United States, Europe, and Asia,, have shown that the efficacy of MAFLD criteria exceeds that of NAFLD criteria in multiple facets of fatty liver disease.

Among the significant findings, MAFLD criteria demonstrated superior efficacy in identifying individuals at risk of liver fibrosis compared with NAFLD criteria within the American population.[5] The fatty liver index showed a high diagnostic capability in identifying steatosis in individuals with MAFLD.[6] The Fibrosis-4 index and NAFLD fibrosis score can reliably exclude advanced fibrosis in individuals with MAFLD who are overweight, obese, or extremely obese.[7] MAFLD correlates with an increased incidence of hepatocellular carcinoma.[8] MAFLD, as opposed to NAFLD, is a predictor of extrahepatic malignancy.[8] MAFLD outperformed NAFLD in identifying individuals at elevated risk of renal disease.[9] A recent meta-analysis indicated that MAFLD correlates with heightened severity of COVID-19.[10] Renaming to MAFLD enhances awareness of the condition among primary care providers and clinicians in other specialties.[11] Alterations to MAFLD positively influence clinical trials. MAFLD assesses the severity of the coexistence of fatty liver disease with other hepatic disorders.[12–15]

As of the publication of this paper, the two prominent hepatology associations, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, have not yet adopted the new name. The discourse among these communities mostly concentrated on the untimeliness of transformation.[16] A primary discussion centers on non-metabolic or lean NAFLD. Evidence indicates that the non-metabolic NAFLD group appears equivalent to individuals without fatty liver for cardiovascular-related mortality and overall mortality. Furthermore, the non-metabolic NAFLD cohort appears to possess a low risk of fibrosis (0.8%).[17] Another issue pertained to pediatric non-alcoholic fatty liver disease (NAFLD). A recent study of 1,446 adolescents in the US aged 12 to 18 years from the National Health and Nutrition Examination Survey III found that the majority fit the criteria for MAFLD, supported by elastographic evidence of steatosis.[18] Further discussion pertained to clinical studies. A newly published report by a group of academics asserts that the new nomenclature and methodology with affirmative inclusion criteria facilitate patient recruitment and are more likely to yield favorable outcomes.[19] In the era of evidence-based medicine, we assert that an evidence-based discussion is essential. The MAFLD conceptual framework eliminates the notion of alcohol absence, connects liver disease frequently associated with metabolic dysregulation to its systemic effects, and enhances patient identification, risk stratification, disease awareness and collaboration with metabolic disease specialists.[20,21]

Metabolic dysfunction-associated fatty liver disease (MAFLD), the most prevalent chronic liver disease previously classified as nonalcoholic fatty liver disease (NAFLD), has been shown to impact roughly 33% of the global population, according to a recent meta-analysis involving approximately 9,808,677 individuals.[22,23] The rising incidence of MAFLD and its associated consequences coincides with the epidemics of obesity, systemic metabolic dysfunction and diabetes.[24] A diverse array of histological alterations contributes to the advancement of MAFLD, encompassing hepatic steatosis, fibrosis, cirrhosis and liver failure.[25] Moreover, it significantly contributes to the worldwide incidence of hepatocellular carcinoma.[26] MAFLD is a significant contributor to liver transplantation.[27] Examining risk factors for MAFLD can help identify high-risk groups and enhance management strategies by addressing the lack of targeted pharmaceutical treatments.[28]

MAFLD is defined by the accumulation of lipids within the liver due to impaired lipid metabolism.[29] The lipid profile associated with dyslipidemia in MAFLD is characterized by hypertriglyceridemia, decreased high-density lipoprotein (HDL) cholesterol levels and elevated low-density lipoprotein (LDL) cholesterol concentrations.[30] Recent analyses from a longitudinal study reveal that remnant cholesterol, defined as the cholesterol level in triglyceride-rich lipoproteins, is independently associated with NAFLD, particularly in males.[31,32] Remnant cholesterol has been recognized as an independent predictor of the occurrence of atherosclerotic cardiovascular disease.[33] A cohort research revealed that elevated remnant cholesterol levels are significantly linked to the incidence of ischemic stroke in the general population.[34] A recent investigation indicated that elevated remnant cholesterol correlates with the incidence and long-term mortality of patients with MAFLD; however, the potential linear or non-linear association remains unexamined.[35]

METHODOLOGY

Search strategy

This systematic review was registered in the Prospective Register of systematic Reviews (PROSPERO) under registration number: **CRD420251029326**. It is important to note that adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was ensured throughout the process of conducting and recording this meta-analysis. Cochrane Library and PubMed databases were utilized in order to carry out an exhaustive search of the available literature up until March 21st, 2025. When doing the literature

search, the keywords that were specified for use were "((("remnant"[All Fields] OR "remnants"[All Fields]) AND ("cholesterol"[Supplementary Concept] OR "cholesterol"[All Fields] OR "cholesterol"[MeSH Terms] OR "cholesterols"[All Fields] OR "cholesterole"[All Fields] OR "cholesterols"[All Fields])) OR (("remnant"[All Fields] OR "remnant s"[All Fields] OR "remnants"[All Fields]) AND ("lipoprotein s"[All Fields] OR "lipoproteine"[All Fields] OR "lipoproteins"[Supplementary Concept] OR "lipoproteins"[All Fields] OR "lipoprotein"[All Fields] OR "lipoproteins"[MeSH Terms]))) AND ("Non-alcoholic fatty liver disease"[All Fields] OR ("naflds"[All Fields] OR "Non-alcoholic fatty liver disease"[MeSH Terms] OR ("non alcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "Non-alcoholic fatty liver disease"[All Fields] OR "nafld"[All Fields]) OR "Metabolic dysfunction-associated fatty liver disease"[All Fields] OR "MAFLD"[All Fields])". Articles that have titles and abstracts that are pertinent to the topic at hand will be included to facilitate a comprehensive review and subsequent qualitative and quantitative analysis.

Inclusion and exclusion criteria

The inclusion criteria were structured according to the PICO framework. The population of interest were healthy individuals without known liver disease. The exposure was defined as high levels of remnant cholesterol, while the comparator group consisted of individuals with low levels of remnant cholesterol. The primary outcome was the prevalence of non-alcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated fatty liver disease (MAFLD). Studies were excluded if full-text articles were unavailable or if the study design, exposure, or outcomes did not match the inclusion criteria. Detailed information on the search methods used in the study is presented in Figure 1. The definition of "high" versus "low" remnant cholesterol levels varied slightly across the included studies, depending on their respective population norms and analytical thresholds. In general, most studies dichotomized participants based on either quartiles, population medians, or predefined cut-off values derived from local clinical guidelines.

Data extraction and risk of bias assessment

After that, all authors began to retrieve data from the publications that we had selected. All authors independently screened the titles and abstracts for eligibility, followed by full-text assessment. Data extraction and quality appraisal were also conducted independently by two reviewers using a standardized form. Any disagreements during study selection or data extraction were resolved through discussion and consensus, with a third reviewer consulted when necessary. The JBI Critical Appraisal Checklist for Cohort Studies was used by all authors to assess the quality of the articles in accordance with the research methodology of the publications that were included in the review. The evaluation of quality was carried out in a collaborative

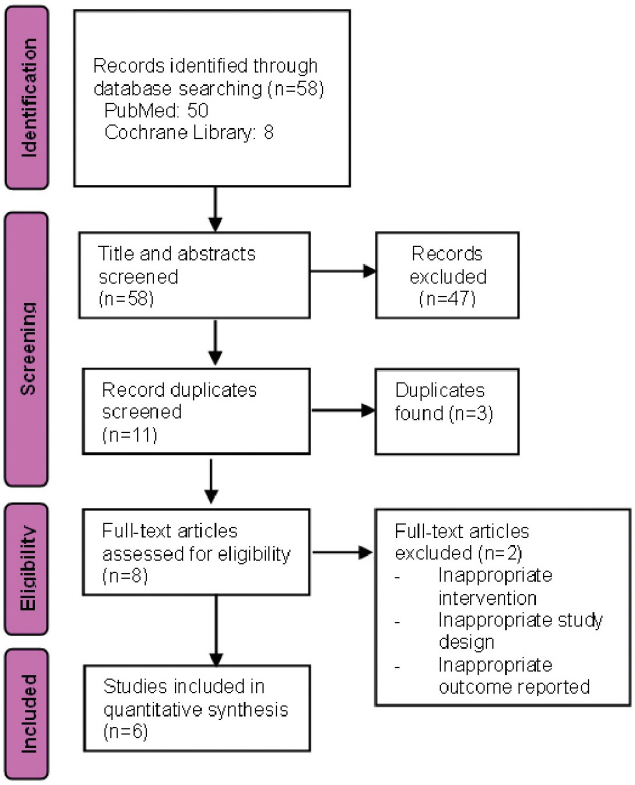


Figure 1. Diagram flow of literature search strategy for this meta-analysis.

manner by all of the reviewers until an agreement was reached. The ROBINS-I, which was provided by Cochrane for the type of study that was being evaluated, was utilized in order to carry out the assessment of the potential for bias.

Statistical analysis

A meta-analysis was carried out with the assistance of Review Manager version 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). The relative risk (RR) and its confidence interval (CI) with a 95% level of certainty were chosen as the standard metrics to evaluate the effect that the exposure had on the primary outcome. The use of random-effects models allowed for the consolidation of effect estimates, which was necessary due to the predicted clinical heterogeneity. If the p-value is less than 0.05, the results of the analysis are regarded as being statistically significant. The Higgins I-squared (I2) statistical model was utilized in order to evaluate the heterogeneity of the data. Heterogeneity was evaluated and categorized as: Minimal (0-25%) Low (25-50%), Moderate (50-75%), or High o(greater than 75%).

The overall certainty of evidence for the primary outcome was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. Factors such as risk of bias, inconsistency, indirectness, imprecision and potential publication bias were considered to qualitatively assess the strength of the findings.

Table 1. Characteristics and results of the included studies

Author	Year	Exposure	Control	Exposure (n)	Control (n)	Outcome measure	Prevalence of NAFLD/MAFLD	
							Exposure	Control
Hao, et al.	2025	High remnant cholesterol	Low remnant cholesterol	863	1018	Prevalence of MAFLD	495	153
Miao, et al.	2023	High remnant cholesterol	Low remnant cholesterol	5445	5346	Prevalence of NAFLD	1195	438
Zou, et al.	2021	High remnant cholesterol	Low remnant cholesterol	2851	2850	Prevalence of NAFLD	1271	77
Huang, et al.	2023	High remnant cholesterol	Low remnant cholesterol	1498	1536	Prevalence of NAFLD	986	357
Jia, et al.	2023	High remnant cholesterol	Low remnant cholesterol	2455	2458	Prevalence of NAFLD	1454	825
Pastori, et al.	2018	High remnant cholesterol	Low remnant cholesterol	399	399	Prevalence of NAFLD	356	276

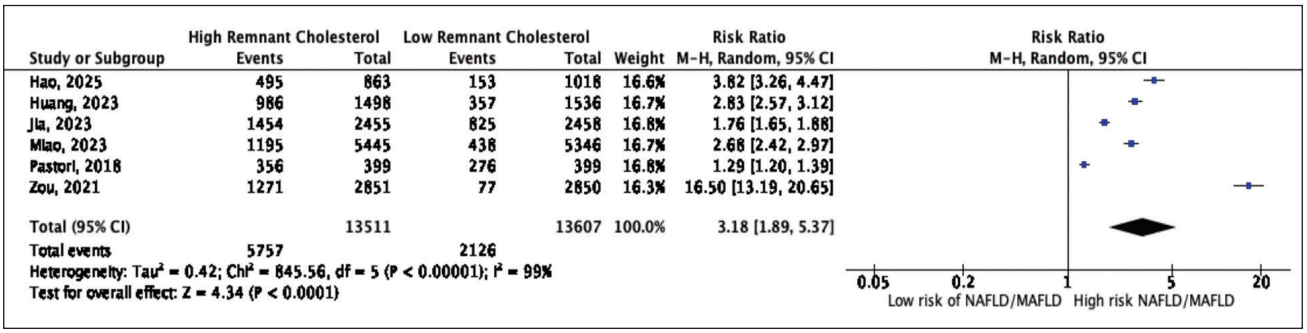


Figure 2. Pooled results for the risk of NAFLD/MAFLD in high remnant cholesterol level.

RESULTS

Six cross-sectional studies were eventually included in our systematic review (Table 1), and total participants included was 45,821. Our meta-analysis showed that high level of remnant cholesterol is associated with a significantly higher risk of NAFLD/MAFLD with an RR of 3.18 (95%CI 1.89-5.37; p <0,00001; I^2 = 99%) (Figure 2).

A sensitivity analysis was conducted by excluding the study of Zou et al. (2021), which visually appeared as an outlier in the funnel plot. However, the pooled analysis still demonstrated high heterogeneity (I^2 = 99%), indicating that no single study accounted for the observed variability. Subgroup analyses were not feasible due to the lack of consistently reported stratified data across studies. Therefore, a random-effects model was applied to account for this heterogeneity resulting to a more conservative estimate of the pooled association.

A funnel plot was generated to assess potential publication bias among the included studies (Figure 3). The plot demonstrated a degree of asymmetry, suggesting the possibility of publication bias. However, given the small number of studies included (<10), formal statistical tests such as Egger's regression test were not conducted, in accordance with current methodological guidance.

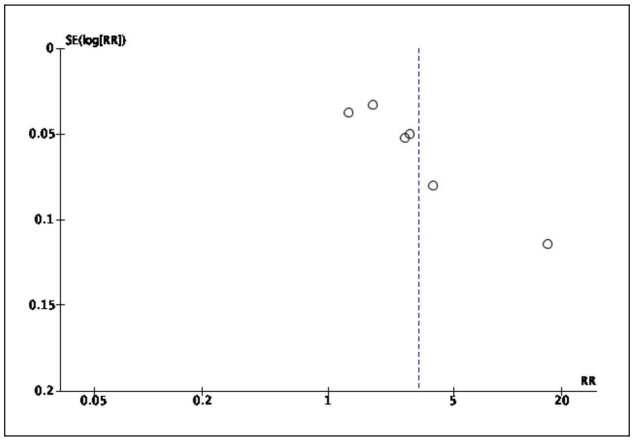


Figure 3. Funnel plot for the results of the included studies, indicating that the high heterogeneity was mainly caused by one outlier reported by the included study.

DISCUSSION

The correlation between MAFLD and residual cholesterol has been previously documented. The results of a longitudinal cohort research with 5,156 patients indicated that remnant cholesterol had an independent correlation with the incidence of MAFLD.[35] A notable association was identified between increased remnant cholesterol levels and the occurrence of MAFLD in a study by Wang et al.[36] MAFLD is defined by the abnormal accumulation of lipids in hepatocytes.[37] Recently, elevated remnant cholesterol has been hypothesized to have a role in the residual risk following effective LDL cholesterol primary prevention.[33,38] The remnant cholesterol, seen in triglyceride-rich lipoproteins, includes chylomicron remnants during the non-fasting state and intermediate- and very low-density lipoproteins during the fasting state.[39] Participants with MAFLD had elevated levels of remnant cholesterol. The pathophysiological processes behind remnant cholesterol-induced MAFLD are little elucidated. Insulin resistance, a prevalent underlying pathology, may elucidate the

association between remnant cholesterol and MAFLD. A recent study indicated that individuals with MAFLD had elevated HOMA-IR values, which are favorably correlated with remnant cholesterol levels.[36] These findings corroborated the hypothesis that insulin resistance may be crucial in the association between remnant cholesterol and MAFLD. Consistent with prior studies, the current study also shown a strong positive correlation between insulin resistance and MAFLD. The prevalent underlying pathophysiological anomaly in Type 2 Diabetes Mellitus (T2DM) and metabolic syndrome is insulin resistance, with Metabolic Associated Fatty Liver Disease (MAFLD) seen as a hepatic manifestation of systemic insulin resistance.[40] Hepatic steatosis is strongly correlated with insulin resistance in the liver and peripheral tissues, such as skeletal muscle and adipose tissue.[41] The insulin-resistant condition in the liver leads to inadequate inhibition of lipolysis in adipose tissue, resulting in increased free fatty acid influx to the liver, alongside heightened lipogenesis and enhanced ApoB production.[30] As a result, the synthesis of extremely low-density lipoproteins rises, shown by a rise in remnant cholesterol.[42]

Dyslipidemia is an established pathogenic component in NAFLD, as corroborated by several epidemiological and genetic research.[30,43] The elevation of intrahepatic triglycerides associated with insulin resistance is a significant trait.[44,45] Nevertheless, newer investigations have suggested alternative causes. In a research done by Yamaguchi et al., it was shown that TG does not appear to be lipotoxic and resembles an inert lipid.[46] The etiology of NAFLD may be intricately linked to the buildup of free cholesterol in the liver and the disruption of cholesterol homeostasis within the liver.[47–49] Nuño-Lámbarri et al., described that an imbalance in hepatic cholesterol exacerbates the buildup of free cholesterol in the liver.[50] Furthermore, Ducheix et al. indicated that excessive cholesterol buildup in cells activates the liver X receptor, which subsequently promotes or exacerbates hepatic steatosis.[51] Atherogenic dyslipidemia in peripheral blood may signify cholesterol buildup in hepatocytes and an increased risk of NAFLD.

Remnant cholesterol is a triglyceride-rich lipoprotein abundant in cholesterol, including chylomicron remnants, intermediate-density lipoprotein, and very-low-density lipoprotein.[52] It can incorporate many atherosclerotic consequences, such as monocyte activation, elevation of proinflammatory cytokines and heightened production of thrombogenic factors.[52,53] Recent findings have shown the association between RC and NAFLD. In 2018, Pastori et al., discovered for the first time that elevated levels of RC were independently and positively connected with NAFLD in patients with cardiac metabolic disorders, while Chin et al., identified a similar connection in teenagers.[54,55] This study confirmed the conclusion, and its findings endorse the function of RC as an independent risk factor for NAFLD in the general population. Consequently, another study revealed that the predictive capacity of RC for NAFLD was much superior to that of other lipid markers in males. Furthermore, a recent study by Campanella et al. examined 237 individuals with metabolic syndrome included in a randomized controlled trial and identified an association between RC and the severity of NAFLD.[56] This discovery indicates that RC may be of significant use in tracking the onset and progression of NAFLD.

A longitudinal cohort published by Cheng, et al. reported a data on the role of triglycerides (TG) in non-alcoholic fatty liver disease (NAFLD), indicating that elevated blood TG concentrations were linked to an increased risk of NAFLD over time.[57] The characterisation of the pathogenic pathways of NAFLD identifies the 'first strike' as initiated by lipid buildup in hepatocytes, whereby excessive fat consumption and insulin resistance are significant contributors.[58] While NAFLD correlates with elevated triglycerides in the liver, recent research indicates that free fatty acids (FFAs), rather than triglycerides, accumulate in lipid droplets, leading to inflammatory liver injury in nonalcoholic steatohepatitis. The hepatic metabolism of free fatty acids results in the generation of hazardous metabolites, primarily accountable for oxidative stress, inflammation, and damage to liver parenchyma.[59,60] The accumulation of triglycerides in the liver is presently regarded as a non-toxic and safer method of lipid storage, serving as an epiphenomenon that indicates alterations in the balance of free fatty acid flux and cellular stress; thus, steatosis can be identified as an initial adaptive response to hepatocyte stress due to heightened caloric intake.[61] During this process, potentially lipotoxic free fatty acids (FFAs) are converted into comparatively benign intracellular triglyceride (TG) molecules.[62] Numerous studies have identified insulin resistance as the predominant and prevalent possible factor contributing to the buildup of free fatty acids in the liver. The prevailing concept is that insulin resistance results in dyslipidemia.

Remnant-C is the by product of TRL metabolism, including chylomicron remnants during the non-fasting state and VLDL and intermediate-density lipoproteins during the fasting state. Prior research indicated that remnant-C was linked to an elevated risk of major adverse cardiovascular events (MACEs); however, the longitudinal association between serum remnant-C levels and the incidence of NAFLD has not been investigated.[63] A research conducted in Italian hospitals involving 798 individuals with cardio-metabolic disorders, showed that 79.2% exhibited NAFLD, indicated a link between circulating remnant-C levels and the severity of liver disease in NAFLD patients.[54] In accordance with this, adolescents exhibiting elevated remnant-C levels demonstrated more hepatic fat accumulation than those with reduced remnant-C levels in the Raine Study.[55]

A notable limitation of this meta-analysis is the presence of substantial heterogeneity among the included studies, as indicated by an I^2 value of 99%. This high degree of heterogeneity reflects considerable variability in study results and warrants cautious interpretation of the pooled effect estimate. In an attempt to explore and reduce this variability, we conducted a sensitivity analysis by excluding

the Zou et al., study, which initially appeared to be a visual outlier. However, the heterogeneity remained markedly high (I^2 = 99%), indicating that no single study was solely responsible for the overall inconsistency across effect sizes.

Subgroup analysis, which is a conventional method to explore sources of heterogeneity, was deemed infeasible due to limitations in the available data. Specifically, the included studies did not consistently report subgroup-specific outcomes based on key stratifying variables such as age, sex, ethnicity or study setting. Moreover, although some studies focused on MAFLD and others on NAFLD, the definitions and diagnostic criteria used were often overlapping or insufficiently detailed to permit meaningful categorization. As a result, formal subgroup stratification could not be implemented without risking misclassification bias or introducing further uncertainty into the analysis.

Despite these challenges, we addressed the observed heterogeneity through the application of a random-effects model, which is more appropriate than a fixed-effects model under conditions of high between-study variance. The random-effects model accounts for both within-study and between-study variability, thereby yielding a more conservative and generalizable estimate of the association between remnant cholesterol and fatty liver disease. The persistent heterogeneity may stem from differences in population characteristics (e.g., metabolic profiles, baseline cardiovascular risk), variations in the cut-off values used to define "high" remnant cholesterol, and inconsistencies in the diagnostic methods employed for NAFLD and MAFLD across studies. Furthermore, regional differences in lifestyle, diet and genetic predisposition may also have contributed to the observed effect size variability. While this limits the precision of the pooled estimate, the directionality of association remained consistent, reinforcing the overall conclusion of a significant link between elevated remnant cholesterol and fatty liver disease.

The possibility of publication bias was examined using a funnel plot, which appeared moderately asymmetric. This may suggest a tendency for smaller studies with negative or null findings to remain unpublished or excluded. However, with fewer than ten studies included in the meta-analysis, the power of such visual assessments is limited, and statistical tests such as Egger's or Begg's test are generally discouraged due to high false-positive and false-negative rates in small samples. Nonetheless, the observed asymmetry calls for cautious interpretation of the pooled effect estimate, as it may reflect selective publication of studies reporting stronger associations. Future systematic reviews incorporating a larger body of evidence would benefit from formal quantitative assessments of publication bias.

Based on the GRADE criteria, the certainty of the evidence was judged to be moderate. Although the analysis included observational studies, the large and consistent direction of the effect across different studies provided some confidence in the association. However, the very high heterogeneity (I^2 = 99%) and possible risk of publication bias limited the overall certainty. No major concerns were identified regarding indirectness or imprecision. Consequently, while the pooled result likely reflects a true association between remnant cholesterol and NAFLD/MAFLD, further well-designed studies are needed to confirm these findings and explore sources of heterogeneity.

CONCLUSION

This systematic review and meta-analysis highlight the substantial correlation between raised remnant cholesterol levels and the heightened risk of metabolic dysfunction-associated fatty liver disease (MAFLD) or non-alcoholic fatty liver disease (NAFLD). The results indicate that elevated remnant cholesterol is significantly associated with liver disorders, with a relative risk of 3.18, signifying a considerable effect on disease prevalence. The research emphasizes the significance of residual cholesterol as a pivotal factor in the pathogenesis of MAFLD or NAFLD, especially regarding its correlation with insulin resistance and dyslipidemia. These discoveries underscore the necessity for tailored therapies aimed at decreasing remnant cholesterol levels to reduce the incidence and development of fatty liver disorders. The findings further endorses the growing terminology and diagnostic criteria of MAFLD, which more accurately reflect the metabolic foundations of these liver illnesses, hence improving patient identification and therapy approaches.

Acknowledgments
This systematic review and meta-analysis was supported by Internal Medicine Department, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
TB: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **HS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision; **AMA:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Supervision.

Data Availability Statement
Datasets analyzed in the study are under license and not publicly available for sharing.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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REVIEW ARTICLE

Liver Enzyme Biomarkers Before or in Early Pregnancy as Predictors for Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Background. Liver enzymes may reflect early metabolic disturbances and insulin resistance preceding gestational diabetes mellitus (GDM). This systematic review and meta-analysis evaluated whether liver enzyme biomarkers measured before or in early pregnancy are associated with subsequent development of GDM.

Methodology. PubMed, Cochrane, EBSCOHost, and SCOPUS databases were searched through May 2025 for observational studies or trials assessing pre- or early pregnancy liver enzymes in relation to GDM development. Pooled mean differences (MD) and odds ratios (OR) with 95% confidence intervals (CI) were calculated using a random-effects model. Risk of bias was assessed using RoB 2.0 and ROBINS-E; certainty of evidence was evaluated using GRADE.

Results. Twenty-seven studies were included in the analyses. GDM was associated with higher AST (MD 0.97 U/L; OR 1.42), ALT (MD 2.38 U/L; OR 1.69), GGT (MD 3.77 U/L; OR 2.57), and hepatic steatosis index (HSI) (MD 2.82; OR 2.19). ALP showed no significant mean difference but an elevated GDM risk (OR 1.47). Substantial heterogeneity was observed with very low certainty of evidence across outcomes.

Conclusion. Elevated liver enzymes, especially GGT and HSI, are associated with increased GDM risk at a population level. However, high heterogeneity and very low certainty of evidence limit current clinical applicability, warranting further prospective validation.

Key words: liver enzymes, gestational diabetes mellitus, pregnancy, meta-analysis, odds ratio

INTRODUCTION

Gestational diabetes mellitus (GDM) refers to glucose intolerance diagnosed for the first time during pregnancy.[1] It is one of the most common metabolic disturbances during pregnancy. Around 16.7% of live births are complicated by diabetes during pregnancy, and of these, 84% are diagnosed with GDM, bringing notable health risks for both the mother and fetus.[2] Gestational diabetes mellitus is shown to have an association with preeclampsia, macrosomia, and long-term risk of type 2 diabetes mellitus for both mother and offspring.[3] Early diagnosis of GDM in pregnancy is necessary for opportune intervention to improve pregnancy outcomes and decrease the risk of further metabolic complications.[4]

The diagnostic criteria for GDM have grown significantly in recent decades and vary internationally. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) suggested new diagnostic points based on data from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, which revealed a constant association between mother glucose levels and unfavorable perinatal outcomes. These recommendations were later adopted by the World Health Organization (WHO) in 2013 and have since been implemented in various countries.[5] In Indonesia, the Indonesian Endocrinology Society advocated these WHO/IADPSG criteria in their national guidelines, suggesting a one-step 75-gram oral glucose tolerance test (OGTT) examined at 24–28 weeks of gestation. According to these standards, GDM is diagnosed when one or more of the following blood glucose thresholds are met or exceeded: fasting ≥92 mg/dL, 1-hour ≥180 mg/dL, or 2-hour ≥153 mg/dL.[6] There are also other guidelines, such as the American Diabetes Association (ADA) and the American College of Obstetricians and Gynecologists (ACOG), which differ in screening approach, glucose load, number of abnormal values required for diagnosis, and diagnostic thresholds. Nonetheless, diagnosing GDM at this stage decreases the possibility of early preventive steps. Identifying steadfast

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Pratama et al.
Received: December 28, 2025. Accepted: February 2, 2026.
Published online first: April 26, 2026.
https://doi.org/10.15605/jafes.041.01.5807

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biomarkers in the preconception phase or early pregnancy could ameliorate risk assessment and encourage an earlier implementation of lifestyle or therapeutic interventions.[7]

Liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), have been acknowledged as indicators of hepatic function and insulin resistance. Increased levels of these indicators have been linked to metabolic syndrome, type 2 diabetes mellitus (T2DM), and metabolic dysfunction-associated fatty liver disease (MAFLD) in the general population.[8] In line with type 2 diabetes mellitus, the core mechanism of GDM is insulin resistance. Therefore, liver enzyme levels may serve as early markers of metabolic disturbances that precede the onset of the condition.[9]

Several studies have analyzed whether liver enzyme levels measured prior to or early in pregnancy are associated with the risk of developing GDM, but the findings have been conflicting. Therefore, this systematic review and meta-analysis seeks to assess and quantitatively analyze the significance of liver enzymes as biomarkers to predict the occurrence of GDM.

METHODOLOGY

Search strategy

A systematic search of four databases (i.e., PubMed, Cochrane, EBSCOHost, and SCOPUS) was conducted to gather available literature concerning the predictive value of liver enzymes measured before or in early pregnancy towards GDM. The keywords listed in Table 1 were utilized for the search. There were no restrictions on language or on publication time frame. Additional references were manually searched to locate more literature. Duplicates in the initial results were subsequently eliminated, and then the titles and abstracts were screened. Comprehensive reviews were performed to further identify suitable studies for inclusion in the data analysis. The process of searching and screening was carried out separately by four investigators with any disagreements resolved by discussion. This systematic review has been registered in PROSPERO with identification code CRD420251077120.

Study eligibility criteria

The inclusion criteria for a study to be included in the analysis were the following: 1) Clinical trials, cohort, or case control studies; 2) Human female subjects aged 18 years old or above as the subjects; 3) No history of Type 2 Diabetes Mellitus (T2DM) or known liver diseases among the subjects; and 4) The liver enzymes were measured before pregnancy or during early pregnancy (before 24 weeks of gestation). A study was excluded if there were any of these following criteria: 1) Other types of articles (e.g., reviews, commentary, etc.); 2) Single arm study (with no control group); 3) The liver enzymes were measured at the time of GDM testing; 4) Subjects with history of T2DM or liver diseases; and 5) No full text available.

Data extraction and risk of bias assessment

The data extraction was done independently by four reviewers. The following data were extracted from each included study: 1) First author and publication year; 2) Study characteristics, including study location, study design, time of marker measurement, time of GDM diagnosis, and GDM diagnosis criteria used; 3) Characteristics of GDM and non-GDM group, including sample size, age, pre-gravid body mass index (BMI), and the percentage of GDM subjects for cohort study; and 4) Study outcomes, including Mean Differences (MDs) of measured liver enzymes and odd ratio for increased markers between GDM and non-GDM group. The liver enzymes of interest included serum AST, ALT, GGT, and ALP level. Additional data of AST/ALT ratio and Hepatic Steatosis Index (HSI) were also extracted and analysed if reported. HSI is typically used to assess fatty liver disease and can be calculated by using AST, ALT, and BMI of the subject.[10] The odds ratio was calculated using the number of events and non-events in subjects with high and normal liver enzymes. Definitions

Table 1. Keywords used in each database

Database	Keywords
Pubmed	("Liver Function Tests"[Mesh] OR "liver enzymes"[tiab] OR "ALT"[tiab] OR "AST"[tiab] OR "GGT"[tiab] OR "alanine aminotransferase"[tiab] OR "aspartate aminotransferase"[tiab] OR "gamma-glutamyl transferase"[tiab]) AND ("Diabetes, Gestational"[Mesh] OR "gestational diabetes"[tiab] OR "GDM"[tiab] OR "pregnancy-induced diabetes"[tiab]) AND ("clinical trial"[Publication Type] OR "observational study"[tiab] OR "systematic review"[tiab] OR "meta-analysis"[Publication Type])
Cochrane Library	#1 MeSH descriptor: [Diabetes, Gestational] explode all trees #2 "Liver enzyme" OR "Liver Biomarker" #3 "ALT" OR "Alanine transaminase" OR "SGPT" OR "Serum Glutamic Pyruvic Transaminase" #4 "AST" OR "Aspartate transminase" OR "SGOT" OR "Serum Glutamic Oxaloacetic Transaminase" #5 "ALP" OR "Alkaline Phosphatase" #6 "GGT" OR "Gamma-Glutamyl Transferase" #7 #1 AND (#2 OR #3 OR #4 OR #5 OR #6)
EBSCOHost	("Gestasional diabetes mellitus" OR "GDM" OR "Gestasional diabetes") AND (("Liver enzyme" OR "Liver Biomarker") OR ("ALT" OR "Alanine transaminase" OR "SGPT" OR "Serum Glutamic Pyruvic Transaminase") OR ("AST" OR "Aspartate transminase" OR " SGOT" OR "Serum Glutamic Oxaloacetic Transaminase") OR ("GGT" OR "Gamma-Glutamyl Transferase") OR ("ALP" OR "Alkaline Phosphatase"))
SCOPUS	("Gestasional diabetes mellitus" OR "GDM" OR "Gestasional diabetes") AND (("Liver enzyme" OR "Liver Biomarker") OR ("ALT" OR "Alanine transaminase" OR "SGPT" OR "Serum Glutamic Pyruvic Transaminase") OR ("AST" OR "Aspartate transminase" OR " SGOT" OR "Serum Glutamic Oxaloacetic Transaminase") OR ("GGT" OR "Gamma-Glutamyl Transferase") OR ("ALP" OR "Alkaline Phosphatase"))

of elevated liver enzyme levels varied across studies. Most studies categorized liver enzyme concentrations using relative thresholds within each cohort, commonly defining "high" levels as values in the upper quartile or highest percentile category. Because absolute laboratory cut-offs were not standardized across populations or pregnancy stages, relative categorization was used to enable within-study risk comparisons. These comparisons therefore represent relative exposure contrasts rather than pathological liver dysfunction. Subjects with liver enzymes included in the upper fourth quartile among other subjects, were considered as high or elevated.

The risk of bias for each study was assessed using the appropriate tools. Cohort and case control studies were assessed using the Cochrane risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E) tool, whereas randomized trials were assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool.[11,12] The risk of bias assessment was done independently, with any discrepancies among the investigators were resolved by discussion. The summary of the assessment is presented as plots generated using the Robvis tool.[13]

Data synthesis and statistical analysis

The extracted data was compiled into tables and summarized descriptively. The variations in enzyme levels and the occurrences of GDM for both the exposed and unexposed groups were computed for quantitative analysis. The evaluation was conducted utilizing Review Manager 5.4 (Cochrane). The extracted dichotomous data were examined using the Mantel-Haenszel statistical method with a random effects analysis model. For continuous outcomes, pooled MDs with 95% confidence intervals were calculated using the inverse-variance method under a random-effects model. The odds ratio (OR) was computed to assess the comparative impact of the intervention against the control. A p-value of less than 0.05 was deemed statistically significant, 95% confidence intervals were used to estimate precision, and heterogeneity analysis computed I^2 as the measure. An I^2 of <50% signified no notable heterogeneity, 50-70% signified substantial heterogeneity, 70-90% signified high heterogeneity, and >90% signified very high heterogeneity. The pooled results were converted into forest plots for enhanced data visualization. Publication bias was assessed using funnel plots for each outcome of interest.

The results are presented according to the PRISMA 2020 guideline for systematic review and meta-analysis.[14] The certainty of evidence for each outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. The GRADE domains include risk of bias, inconsistency, indirectness, imprecision, and publication bias.[15] Each outcome was rated as having high, moderate, low, or very low certainty based on these domains. The assessments were performed independently by four reviewers, and discrepancies were resolved through discussion.

Ethical approval

Due to the nature and design of this study, no ethical approval was needed.

RESULTS

Study selection

The study selection process was done according to the PRISMA guideline and is reported as the PRISMA flow chart in Figure 1. The initial search was done on May 15, 2025, across four databases and resulted in 2,916 hits. Duplicates were removed and the remaining records underwent title and abstract screening. The full text review was performed to 50 records, with another 3 records added from manual searching. A total of 26 records were excluded due to reasons stated in Figure 1. Findings are presented using quantitative meta-analytic methods. One study was excluded from the quantitative synthesis due to exclusively reported data as median (interquatile range) without sufficient information for the mean-difference meta-analyses. Other results are described narratively where meta-analysis was not feasible.

Study characteristics and risk of bias

There are 27 studies included in the analyses with characteristics summarized in Table 2.[9,16–41] They were published between 2014 and 2024, mostly from Asian countries, particularly China. The included studies consist of 17 prospective cohort studies, 6 retrospective cohort studies, 3 case control studies, and 1 pilot RCT study. Pre-pregnancy marker measurements were done in 5 studies, while the others measured the liver marker during 4-20 weeks of pregnancy. The GDM diagnosis was mostly done during the 24-28 weeks of gestation period using various diagnosis criteria, but the majority were using the IADPSG criteria. The total subjects included in the GDM group are 61,858 subjects and 1,018,947 subjects in the non-GDM group. The pilot RCT and prospective studies reported a wide range of GDM incidence among their cohorts, ranging from 5.9-56.3%. The incidence was lower in studies that only included insulin-treated GDM, ranging from 0.6-2.74%. In addition, almost all studies reported that subjects in the GDM group were older and had higher pre-gravid BMI when compared with the non-GDM group. Other information regarding each study (e.g., funding, ethnicity, socioeconomic status) were highly variable and are not discussed in this manuscript.

The risk of bias assessment was done using the RoB 2.0 tool for 1 pilot RCT study by Maitland et al., showing some concerns within the study (Figure 2). The remaining 26 cohort or case-control studies were assessed using the ROBINS-E tool, showing that 17 out of 26 studies also had some concerns regarding the risk of bias (Figure 3A and Figure 3B).

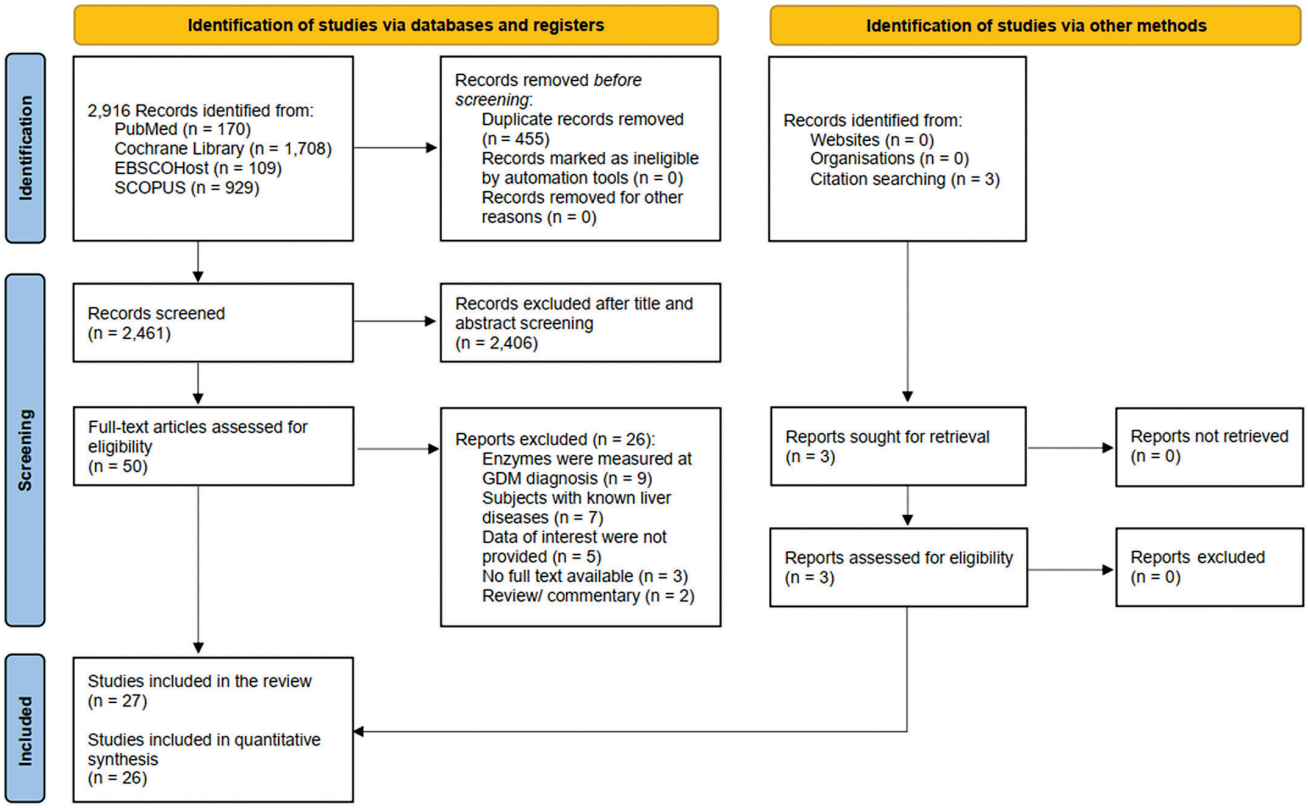


Figure 1. PRISMA flow diagram of this systematic review.

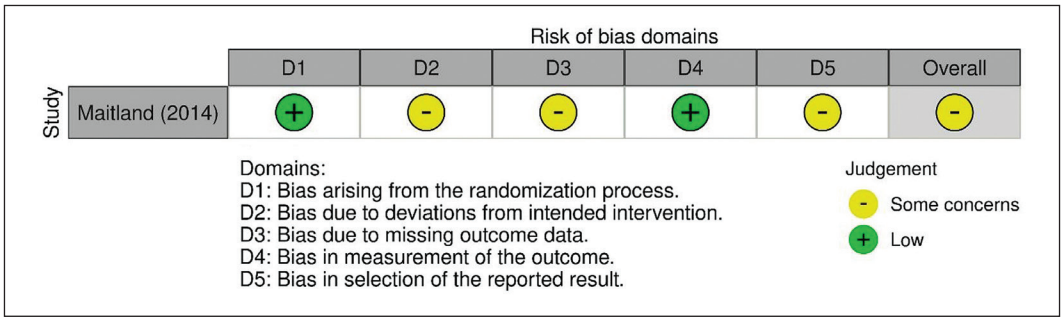


Figure 2. The risk of bias assessment using the RoB 2.0 tool.

Study outcomes

The study outcomes from the included studies are extracted and summarized in Table 3. Data of interest were collected from the included studies to be analyzed quantitatively. It is noteworthy that most of the studies compared the event of GDM between subjects who had elevated liver markers (i.e., upper 4th quartile) to those with lower liver markers (i.e., lower 1st quartile) to calculate their odds ratio.

Serum AST level

There are 15 studies that compare the AST level between GDM and non-GDM groups (Figure 4A). The quantitative analysis showed that subjects in the GDM group had higher levels of AST prior to the diagnosis compared with subjects without GDM, with a mean difference of 0.97 U/L (95% CI 0.29-1.64; p <0.005). The result analysis from 5 studies showed that subjects with higher AST levels had significantly higher odds of developing GDM (OR 1.42, 95% CI 1.24-1.62; p <0.0001), as shown in Figure 4B. The heterogeneity analysis showed substantial heterogeneities among these studies. The funnel plots for both the mean difference and odds ratio showed a symmetric distribution of studies, suggesting a low risk of publication bias (Supplementary Figure S1A-B).

Serum ALT level

The analysis on serum ALT levels can be seen in Figure 5A and 5B. The level of pre-gravid or early pregnancy serum ALT was also shown to be higher in the GDM group compared to the non-GDM group, with a mean difference of 2.38 U/L (95% CI 0.97-3.79; p = 0.001). The increased serum ALT level was also shown to increase the odds of GDM occurrence in pregnant subjects (OR 1.69, 95% CI 1.17-2.45; p = 0.005). A substantial heterogeneity was also shown in the analysis, suggesting notable variability among

Table 2. The characteristics of included studies

Author	Year published	Study location	Study design	Marker measurement timing (wog)	Definition of elevated liver enzyme [a]	GDM diagnosis timing (wog)
Maitland et al	2014	UK	Pilot RCT	16-18	Study-defined percentile categories	27-28
Sridhar et al	2014	USA	Case Control	Pre-pregnancy	Highest (Q4) vs lowest (Q1) quartile	27-28
Zhao et al	2016	China	Prospective Cohort	8-12	Not dichotomized	24-28
White et al	2016	UK	Prospective Cohort	15-18	Not dichotomized	24-33
Leng et al	2016	China	Prospective Cohort	4-12	Highest (Q4) vs lowest (Q1) quartile	24-28
Yarrington et al	2016	USA	Prospective Cohort	Mean: 10.4	ALT <19 U/L vs ≥19 U/L	24
Kong et al	2018	China	Prospective Cohort	14-18	GGT <26.9 U/L vs ≥26.9 U/L	24-28
Zhu et al	2018	USA	Prospective Cohort	10-13	Highest (Q4) vs lowest (Q1) quartile	24-28
Xiong et al	2019	China	Prospective Cohort	<20	Highest (Q4) vs lowest (Q1) quartile	24-28
Correa et al	2019	Chile	Case Control	<14	Not dichotomized	24-28
Lee et al	2019	South Korea	Prospective Cohort	10-14	High-risk HIS (>36) vs ≤36	24-28
Gao et al	2020	China	Prospective Cohort	<12	Study-defined percentile categories	24-28
Lee et al	2020	South Korea	Retrospective Cohort	4-20	ALT >95th percentile vs ≤95th percentile	24-28
Park et al [d]	2021	South Korea	Retrospective Cohort	Pre-pregnancy	Highest (Q4) vs lowest (Q1) quartile	24-28
Zhao et al	2021	China	Prospective Cohort	8-12	Study-defined percentile categories	24-28
Kim et al [d]	2021	South Korea	Retrospective Cohort	Pre-pregnancy	Highest (Q4) vs lowest (Q1) quartile	24-28
Sang et al [d]	2021	South Korea	Retrospective Cohort	Pre-pregnancy	Highest (Q4) vs lowest (Q1) quartile	24-28
Wang et al	2021	China	Case Control	12	Highest (Q4) vs lowest (Q1) quartile	24-28
Shuoning et al	2021	China	Prospective Cohort	6-12	Highest (Q4) vs lowest (Q1) quartile	24-28
Shuoning et al	2022	China	Prospective Cohort	6-12	Highest (Q4) vs lowest (Q1) quartile	24-28
Rongjing et al	2022	China	Prospective Cohort	10-14	Study-defined percentile categories	24-28
Quotah et al	2022	UK	Prospective Cohort	15-18	Not dichotomized	23-30
Duo et al	2023	China	Prospective Cohort	6-12	AST/ALT ratio ≥0.825 vs <0.825	24-28
Wu et al	2023	China	Prospective Cohort	6-15	Highest (Q4) vs lowest (Q1) quartile	24-28
Lee et al [d]	2023	South Korea	Retrospective Cohort	Pre-pregnancy	Serum GGT ≥20 vs <10 U/L	24-28
Zhen et al	2024	China	Prospective Cohort	<14	Highest (Q4) vs lowest (Q1) quartile	24-28
Liu et al	2024	China	Retrospective Cohort	8-14	Highest (Q4) vs lowest (Q1) quartile	24-28

Abbreviations: GDM, Gestational Diabetes Mellitus; WOG, Weeks of Gestations; BMI, Body Mass Index; RCT, Randomized Controlled Trial; IADPSG, International Association of the Diabetes Pregnancy Study Groups; ACOG, American College of Obstetricians and Gynecologist; ADA, American Diabetes Association; UK, United Kingdom; USA, United States of America; N/A, Not Applicable.

Data for continuous variables with normal distribution are presented as mean (standard deviation) or as median (interquartile range) if the distribution is abnormal.

[a] Elevated liver enzyme levels for dichotomized analyses were defined using study-specific relative thresholds due to heterogeneity in laboratory reference ranges and timing of measurement during pregnancy.

[b] Only applicable for RCT or cohort studies.

[c] Statistically significant in difference from the GDM group (p <0.05).

[d] Data from the insulin treated group was used

studies. The shape of the funnel plots for ALT analysis appeared symmetrical, indicating no significant evidence of publication bias (Supplementary Figure S2A–B).

Serum GGT level

Based on the findings from 10 studies, the meta-analysis revealed a significantly higher mean GGT level in the GDM group compared to the non-GDM group, with a mean difference of 3.77 U/L (95% CI 1.97-5.58; p <0.0001). Furthermore, the results from 8 studies indicate that women with high GGT levels had 2.57 times higher odds of developing GDM compared to those with lower GGT levels (OR 2.57, 95% CI 2.07-3.20; p <0.0001). Heterogeneity was also found to be substantial in these studies. The forest plot can be observed in Figure 6A and 6B. Funnel plots for GGT were visually symmetrical, reflecting minimal small-study effects or reporting bias (Supplementary Figure S3A–B).

Serum ALP level

The forest plots based on analyses of serum ALP level can be seen in Figure 7A and 7B. There was no significant difference in mean ALP levels between women with and without GDM (mean difference 0.86 U/L, 95% CI -1.22-2.95; p = 0.42) and also moderate heterogeneity was present

GDM diagnosis criteria	GDM group			% of gdm[b]	Non-GDM group		
	Sample size	Age (Years)	Pre-gravid BMI		Sample size	Age (Years)	Pre-gravid BMI
IADPSG	29	34 (31-36)	35.27 (3.60)	27.4	77	31 (26-34)[c]	36.11 (4.95)
ACOG	256	28.2 (5.5)	26.0 (6.5)	N/A	497	28.4 (5.2)	23.7 (4.6)[c]
ADA	725	32 (29-35)	21.7 (19.9-24.0)	56.3	935	31 (28-34)[c]	20.7 (19.2-22.6)[c]
IADPSG	337	32 (4.9)	36.2 (33.1-39.9)	25.85	966	30.3 (5.5)[c]	34.7 (32.7-38.1)[c]
IADPSG	1,332	29.5 (3.1)	24.1 (3.9)	7.67	16,027	28.4 (2.8)[c]	22.1 (3.3)[c]
Carpenter-Coustan Criteria	83	34 (5)	29.7 (6.6)	25.15	247	32 (6)[c]	29.2 (6.6)
IADPSG	122	29.4 (3.4)	21.8 (3)	8.1	1,309	27.9 (3.1)[c]	20.7 (2.5)[c]
Carpenter-Coustan Criteria	117	Age range 18-24: 5 (4.3%) 25-29: 24 (20.5%) 30-34: 56 (47.9%) ≥35: 32 (27.4%)	BMI range <18.5: 1 (0.9%) 18.5-24.9: 20 (17.1%) 25.0-29.9: 36 (30.8%) ≥30.0: 32 (27.4%)	33.52	232	Age range 18-24: 16 (6.9%) 25-29: 51 (22%) 30-34: 114 (49.1%) ≥35: 51 (22%)	BMI range [c] <18.5: 6 (2.6%) 18.5-24.9: 100 (43.1%) 25.0-29.9: 56 (24.1%) ≥30.0: 70 (30.2%)
IADPSG	169	Categorized according to serum ALP quartiles		8.15	1,904	Categorized according to serum ALP quartiles	
IADPSG	16	32.63 (6.36)	26.55 (6.29)	N/A	80	32.63 (6.36)	24.9 (4.2)
ADA	36	33.0 (31.0-34.0)	26.4 (23.0-29.0)	5.9	572	33.0 (30.0-34.0)	21.7 (19.8-23.8)[c]
IADPSG	1,485	29.6 (3.2)	24.2 (3.9)	7.68	17,846	28.4 (2.9)[c]	22.1 (3.3)[c]
IADPSG	160	Categorized according to serum ALT level		6.8	2,162	Categorized according to serum ALT level	
ACOG	119	33.04 (3.60)	23.41 (4.28)	2.74	3,860	31.22 (3.65)[c]	21.18 (2.8)[c]
IADPSG	49,611	29.33 (4.88)	20.8 (19.1-23.0)	26.47	137,821	28.34 (4.45)[c]	20.1 (18.7-22.0)[c]
ACOG	2,614	33.13 (4.19)	23.79 (4.13)	1.1	219,937	30.28 (3.83)[c]	21.05 (2.86)[c]
Insulin prescription	1,984	Categorized according to the fatty liver index score		0.6	306,111	Categorized according to the fatty liver index score	
IADPSG	202	31 (28-34)	23.7 (30.4-26.4)	N/A	516	30 (28-33)[c]	22.7 (20.5-24.5)[c]
IADPSG	239	31.40 (3.92)	23.13 (3.53)	22.09	843	30.08 (3.93)[c]	21.68 (2.81)[c]
IADPSG	249	31.43 (3.91)	22.8 (20.4-25.5)	22.07	879	30.11 (3.93)[c]	21.5 (19.7-23.2)[c]
IADPSG	94	31.93 (4.69)	22.00 (2.82)	14.1	572	29.15 (3.92)[c]	20.44 (2.50)[c]
IADPSG	119	32.6 (4.3)	36.7 (33.8-40.4)	7.6	112	33.6 (5.3)	36.9 (34.0-41.3)
IADPSG	272	32 (29-34)	22.9 (21.3-25.0)	21.1	1,017	30 (28-32)[c]	21 (19.5-22.5)[c]
IADPSG	492	28 (25-31)	21.8 (19.9-24.1)	7.2	6,368	26 (24-29)[c]	20.4 (18.9-22.3)[c]
Insulin prescription	2,024	Age range <25: 29 (1.4%) 25-29: 447 (22.1%) 30-34: 946 (46.7%) ≥35: 602 (29.7%)	BMI range <18.5: 124 (6.1%) 18.5-22.9: 952 (47.0%) 23-24.9: 355 (17.5%) 25-29.9: 443 (21.9%) ≥30: 150 (7.4%)	0.69	290,024	Age range [c] <25: 14,395 (5%) 25-29: 115,476 (39.8%) 30-34: 126,465 (43.6%) ≥35: 33,688 (11.6%)	BMI range [c] <18.5: 45,073 (15.5%) 18.5-22.9: 190,175 (65.6%) 23-24.9: 30,109 (10.4%) 25-29.9: 21,056 (7.3%) ≥30: 3611 (1.3%)
ACOG	37	Categorized according to the ALT/HDL-C ratio		6.27	553	Categorized according to the ALT/HDL-C ratio	
IADPSG	1,668	30 (27-34)	21.9 (19.9-24.5)	18.2	7,480	28 (26-31)[c]	20.8 (19.2-22.8)[c]

(I^2 = 69%) among the studies. However, the odds ratio analysis showed that women with high ALP levels had 47% higher odds of developing GDM (OR 1.47, 95% CI 1.26-1.72; p <0.00001) with acceptable consistency between studies. Although some dispersion was observed, the overall distribution remained balanced, with no substantial asymmetry (Supplementary Figure S4A–B).

AST/ALT ratio

The analyses on AST/ALT ratio are visualized in Figure 8A and 8B. There was no meaningful difference in AST/ALT ratio between the two groups on average (mean difference 0.01, 95% CI -0.16-0.17; p = 0.94). The heterogeneity was found to be substantial among these studies. However, the odds ratio analysis showed that individuals with a higher AST/ALT ratio had 26% lower odds of having GDM compared to those with a lower AST/ALT ratio. This association was statistically significant, even though only one study provided data for this analysis (OR 0.74, 95% CI 0.64-0.84; p <0.00001). The funnel plots showed consistent symmetry, suggesting that the results are unlikely to be influenced by publication bias (Supplementary Figure S5A–B).

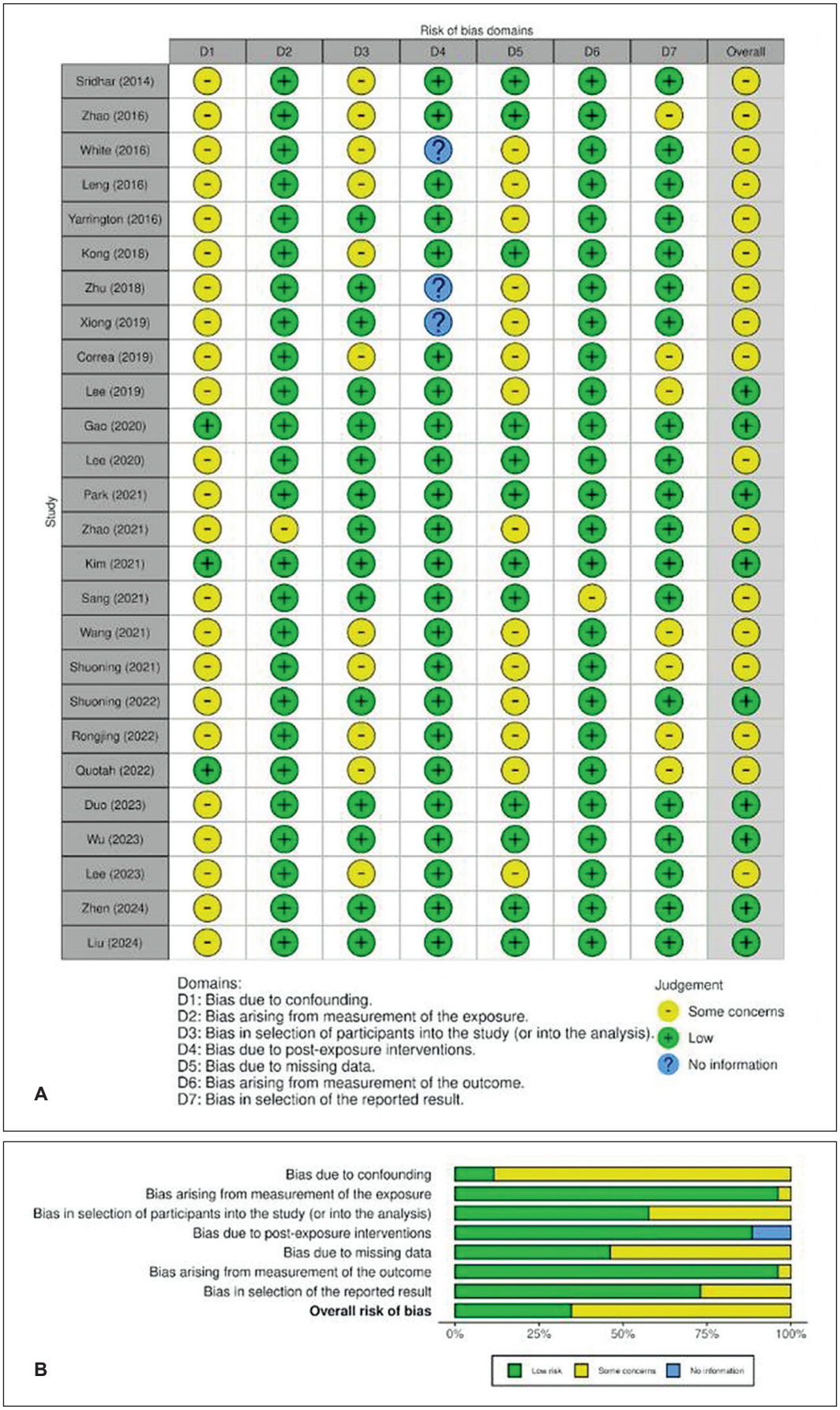


Figure 3. (A) The risk of bias assessment using the ROBINS-E tool for each study. **(B)** The summary for risk of bias assessment using the ROBINS-E tool.

Table 3. The outcomes of included studies

Study (year published)	Reported outcomes, GDM vs Non GDM group					
	Serum AST, U/L	**Serum ALT, U/L**	**Serum GGT, U/L**	**Serum ALP, U/L**	**AST/ALT ratio**	**HSI**
Maitland et al (2014)	30.63 (1.53) vs 25.07 (1.41); *p* = 0.11 OR (95% CI) 1.17 (0.96-1.43); *p* = 0.11	21.41 (1.79) vs 19.00 (1.57); *p* = 0.42 OR (95% CI) 1.12 (0.84-1.50); *p* = 0.42	ND	ND	ND	ND
Sridhar et al (2014)	13.9 (25.3) vs 11.8 (6.6); *p* = 0.18 Crude OR (95% CI) 0.84 (0.48-1.45)	8.5 (9.5) vs 6.7 (3.8); *p* <0.001 Crude OR (95% CI) 1.55 (0.92-2.59)	28.0 (21.7) vs 22.4 (16.6); *p* <0.001 Crude OR (95% CI) 2.91 (1.77-4.77)	ND	ND	ND
Zhao et al (2016)	Median (IQR) 41 (26-43) vs 41 (23-43); *p* = 0.588	Median (IQR) 18 (12-30) vs 16 (11-26); *p* = 0.004	ND	ND	ND	ND
White et al (2016)	4.5 (0.5) vs 4.5 (0.5); *p* = 0.10	4.2 (0.7) vs 4.1 (0.8); *p* = 0.32	4.0 (1.0) vs 3.6 (1.0); *p* <0.001	ND	ND	ND
Leng et al (2016)	ND	18 (13-26) vs 15 (11-21); *p* <0.001 Univariate OR (95% CI) 2.03 (1.60-2.56); *p* <0.001 Multivariate OR (95% CI) 1.62 (1.31-2); *p* <0.001	ND	ND	ND	ND
Yarrington et al (2016)	ND	15 (12-19) vs 13 (11-18); *p* = 0.07 Crude OR (95% CI) 1.50 (0.88-2.55) Adjusted OR (95% CI) 1.37 (0.73-2.59)	ND	ND	ND	ND
Kong et al (2018)	27.3 (24.1) vs 25.3 (23.0); *p* = 0.229	23.7 (16.2) vs 22.9 (14.0); *p* = 0.082	18.7 (13.0) vs 14.5 (7.0); *p* <0.001 Crude RR (95% CI) 5.81 (3.72-9.08)	ND	ND	ND
Zhu et al (2018)	ND	15.5 (1.0) vs 13.5 (0.8); *p* = 0.04 Crude OR (95% CI) 2.05 (1.06-3.99); *p* <0.035 (for trend)	17 (1.5) vs 12 (1.0); *p* <0.001 Crude OR (95% CI) 3.78 (1.93-7.39); *p* <0.001 (for trend)	ND	ND	ND
Xiong et al (2019)	ND	ND	ND	Mean ALP level for all cohort = 44.87 (9.66) Crude OR (95% CI) 2.62 (1.63-4.21); *p* <0.001 (for trend)	ND	ND
Correa et al (2019)	19.5 (16.5-22.5) vs 20 (18.25-21.75); *p* = 0.22	29.5 (20.25-38.75) vs 26.5 (21.75-31.25); *p* = 0.437	ND	71.5 (60.5-82.5) vs 66.5 (55-78); *p* = 0.371	ND	ND
Lee et al (2019)	18 (15-22) vs 16 (15-22); *p* = 0.047	16 (10-27) vs 11 (8-14); *p* = 0.001	17 (11–24) vs 12 (10–15); *p* = 0.001	ND	ND	35.5 (32.0–39.5) vs 29.0 (26.8–32.5); *p* <0.001 Crude OR (95% CI) 1.23 (1.16, 1.31)
Gao et al (2020)	ND	Log Transferred 1.29 (0.23) vs 1.22 (0.21); *p* <0.001 OR (95% CI) 1.73 (1.10-2.71) *p* = 0.024	ND	ND	ND	ND
Lee et al (2020)	ND	Adjusted OR 1.795 (1.002-3.217); *p* <0.05	ND	ND	ND	ND
Park et al (2021)	19.69 (18.49–20.98) vs 18.52 (18.35–18.68); *p* = 0.019 Crude OR (95% CI) 1.349 (0.677-2.691)	17.33 (15.79–19.02) vs 13.67 (13.47–13.87); *p* <0.001 Crude OR (95% CI) 2.714 (1.308-5.633)	18.16 (16.62–19.83) vs 14.59 (14.39–14.8); *p* <0.001 Crude OR (95% CI) 2.126 (1.098-4.114)	ND	ND	ND
Zhao et al (2021)	16.20 (14–20) vs 16.10 (14–20); *p* = 0.282 Crude OR (95% CI) 1.04 (1.01–1.07)	14 (10.90–20) vs 14 (10.70–19.50); *p* <0.001 Crude OR (95% CI) 1.06 (1.04–1.08)	ND	ND	ND	ND

Table 3. The outcomes of included studies *(continued)*

Study (year published)	Reported outcomes, GDM vs Non GDM group					
	Serum AST, U/L	**Serum ALT, U/L**	**Serum GGT, U/L**	**Serum ALP, U/L**	**AST/ALT ratio**	**HSI**
Kim et al (2021)	20 (19.71-20.29) vs 18.22 (18.19-18.24); *p* <0.001 Crude OR (95% CI) 1.294 (1.137-1.473)	17.95 (17.55-18.36) vs 13.34 (13.32-13.36); *p* <0.001 Crude OR (95% CI) 2.205 (1.913-2.541)	19.21(18.79-19.63) vs 14.12(14.1-14.15); *p* <0.001 Crude OR (95% CI) 2.748 (2.337-3.232)	ND	ND	ND
Sang et al (2021)	ND	ND	Adjusted OR (95% CI); 2.78 (2.54-3.04)	ND	ND	ND
Wang et al (2021)	18.67 (6.57) vs 18.97 (8.70); *p* >0.05	20.39 (13.33) vs 17.69 (13.07); *p* >0.05 Crude OR (95% CI) 1.02 (1.01 - 1.03); *p* <0.05	ND	ND	ND	ND
Shuoning et al (2021)	16.17 (14.00-19.00) vs 16 (14-18.8); *p* = 0.406	15.28 (11-20.8) vs 12.56 (10-17.7); *p* <0.001	ND	ND	ND	30.67 (27.2 - 35.1) vs 27.98 (25.7-30.82); *p* <0.001 Crude OR (95% CI) 3.166 (2.069-4.845)
Shuoning et al (2022)	ND	ND	ND	ND	0.92 (0.75-1.18) vs 0.80 (0.65-1.02); *p* <0.001 Crude OR (95% CI) 2.143 (1.500 - 3.061); *p* <0.001	ND
Rongjing et al (2022)	15.88 (17.9 - 21.9) vs 17.7 (14.1 - 20.1); *p* = 0.054	18 (13.1 - 25.93) vs 14.3 (10.3 - 18.6); *p* <0.001	ND	ND	0.96 (0.79 - 1.21) vs 1.18 (1.02 - 1.49); *p* <0.001 RR (95% CI) 0.228 (0.107-0.488); *p* <0.001	ND
Quotah et al (2022)	Median (IQR) 23.7 (19.2 -29.2) vs 21.8 (17.8 - 27.9); *p* value not reported	Median (IQR) 16.9 (12.5 - 24.2) vs 15.7 (11.9-22.6); *p* value not reported	21.7 (17.73) vs 16.2 (12.19); *p* value not reported	ND	ND	ND
Duo et al (2023)	16 (14-18.1) vs 16 (14-18.2); *p* = 0.634	15 (11-19.6) vs 12.1 (9.8-16.4); *p* <0.001	ND	ND	0.9 (0.8-1.2) vs 0.8 (0.6-0.9); *p* <0.001 Univariate OR (95% CI) 6.310 (3.968-10.036); *p* <0.001 Multivariate OR (95% CI) 3.345 (1.969-5.683); *p* <0.001	ND
Wu et al (2023)	19 (16-23) vs 18 (16-22); *p* <0.001 Crude OR (95% CI) 1.75 (1.36-2.25); *p* <0.001	19 (14-23) vs 16 (12-24); *p* <0.001 Crude OR (95% CI) 2.39 (1.84-3.11); *p* <0.001	16 (12-24) vs 13 (10-18); *p* <0.001 Crude OR (95% CI) 2.15 (1.66-2.79); *p* <0.001	49 (31-58) vs 46 (40-54); *p* <0.001 Crude OR (95% CI) 1.65 (1.28-2.13); *p* <0.001	ND	32.3 (29-36) vs 29.9 (27.4-33.2); *p* <0.001 Crude OR (95% CI) 3.45 (2.59-4.59); *p* <0.001
Lee et al (2023)	ND	ND	Univariate OR (95% CI) 4.24 (3.50-5.14) Multivariate OR (95% CI) 2.17 (1.78-2.65)	ND	ND	ND
Zhen et al (2024)	Median for all cohort: 16 (14-20) OR (95% CI) 1.02 (0.99-1.05); *p* = 0.138	Median for all cohort: 11.00 (8-15) OR (95% CI) 1.04 (1.01-1.06); *p* = 0.002	Median for all cohort: 12 (10-15) OR (95% CI) 1.04 (1.01-1.07); *p* = 0.002	ND	ND	ND
Liu et al (2024)	17 (15-20) vs 17 (14-19); *p* >0.05 Adjusted OR (95% CI) 1.25 (1.06-1.48)	14 (11-21) vs 13 (10-19); *p* <0.001 Adjusted OR (95% CI) 1.29 (1.11-1.51)	12 (10-17) vs 11 (9-15); *p* <0.001 Adjusted OR (95% CI) 1.33 (1.13-1.56)	51 (44-59) vs 49 (43-57); *p* <0.001 Adjusted OR (95% CI) 1.39 (1.19-1.63)	1.1 (0.9-1.4) vs 1.2 (0.9-1.5); *p* <0.001 Adjusted OR (95% CI) 0.72 (0.61-0.84)	31.3 (28.3-35.4) vs 29.7 (27.3-32.8); *p* <0.001 Adjusted OR (95% CI) 1.91 (1.55-2.36)

Abbreviations: GDM, Gestational Diabetes Mellitus; AST, Aspartate Transaminase; ALT, Alanine Transaminase; GGT, Gamma-Glutamyl Transferase; ALP, Alkaline Phosphatase; HSI, Hepatic Steatosis Index; OR, Odd Ratio; RR, Relative Risk; CI, Confidence Interval; ND, No Data.

Data for continuous variables with normal distribution are presented as mean (standard deviation) or as median (interquartile range) if the distribution is abnormal.

HSI

On average, GDM patients had significantly higher HSI compared to non-GDM counterparts (mean difference of 2.82, 95% CI 1.89-3.76; p <0.00001), suggesting a stronger degree of hepatic lipid accumulation or metabolic dysfunction (Figure 9A). The odds ratio analysis showed that the odds of developing GDM were significantly increased in patients with high HSI before or in early pregnancy (OR 2.19, 95% CI 2.00-2.40; p <0.00001). Even though the heterogeneity was high in the mean difference analysis, it was minimal in the odds ratio analysis (Figure 9B). The funnel plots were generally symmetrical, further supporting the robustness of the findings (Supplementary Figure S6A–B).

Certainty of evidence

Using the GRADE framework, the certainty of evidence for all outcomes was rated as very low. As most included studies were observational, the initial certainty of evidence was low. Further downgrading was applied due to serious inconsistency, reflected by substantial heterogeneity across studies, and concerns regarding risk of bias. Consequently, the overall certainty of evidence was judged to be very low for all liver enzyme outcomes. A summary of the GRADE ratings is presented in Table 4.

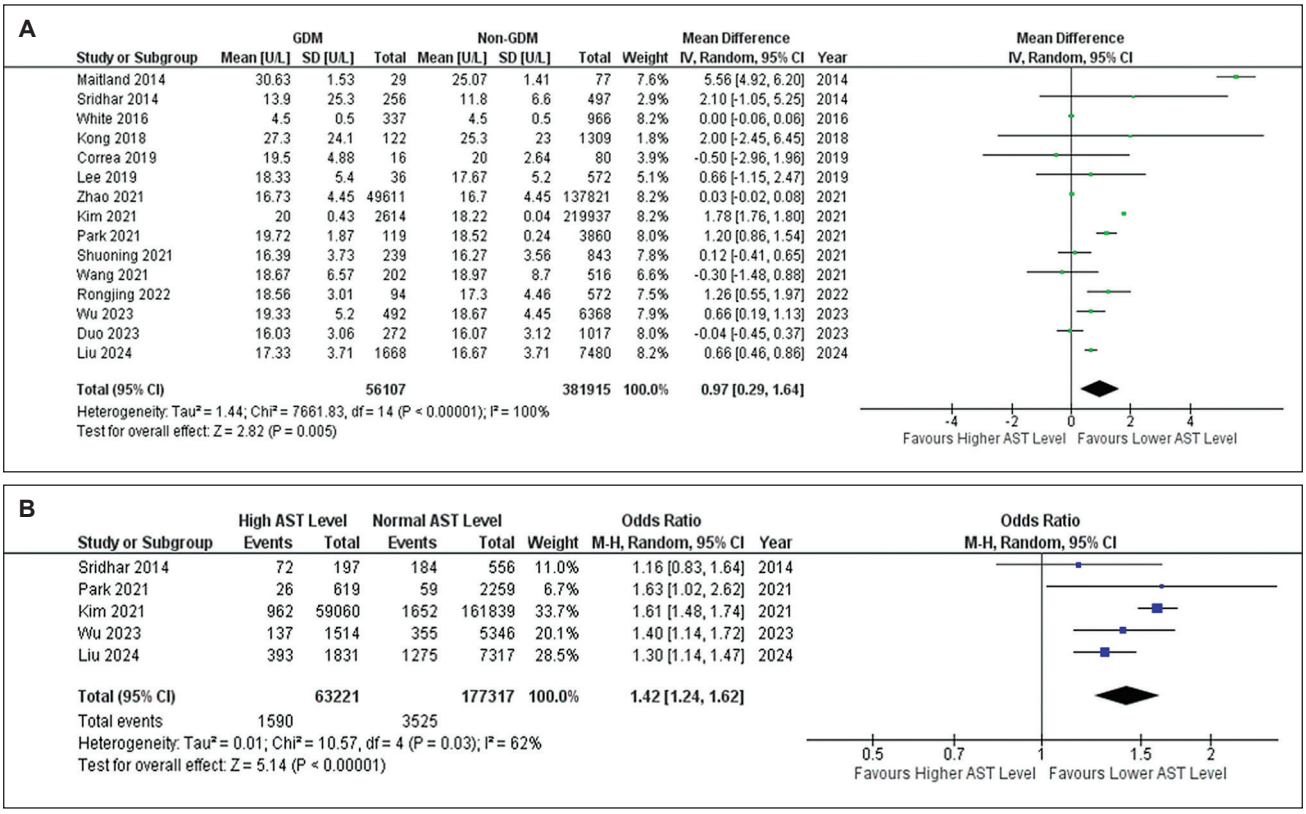


Figure 4. (A) The mean difference in pre- or early pregnancy serum AST level between GDM and non-GDM groups. **(B)** The odds ratio of GDM in subjects with higher AST level.

Table 4. The Summary of Findings using GRADE approach

Outcome	Number of studies	Participants	Effect estimate (MD)	Effect estimate (OR)	Certainty of evidence	Reasons for downgrade
AST	15 (MD), 5 (OR)	MD: 438,022 OR: 240,538	0.97 U/L (95% CI 0.29–1.64)	1.42 (95% CI 1.24–1.62)	Very low	Inconsistency and risk of bias
ALT	18 (MD), 8 (OR)	MD: 456,060 OR: 282,522	2.38 U/L (95% CI 0.97–3.79)	1.69 (95% CI 1.17–2.45)	Very low	Inconsistency and risk of bias
GGT	10 (MD), 8 (OR)	MD: 247,213 OR: 845,681	3.77 U/L (95% CI 1.97–5.58)	2.57 (95% CI 2.07–3.20)	Very low	Inconsistency and risk of bias
ALP	5 (MD), 3 (OR)	MD: 16,104 OR: 18,081	0.86 U/L (95% CI -1.22–2.95)	1.47 (95% CI 1.26–1.72)	Very low	Imprecision and inconsistency
AST/ALT Ratio	3 (MD), 1 (OR)	MD: 12,231 OR: 9,148	0.01 (95% CI -0.16–0.17)	0.74 (95% CI 0.64–0.84)	Very low	Limited data and imprecision
HSI	6 (MD), 4 (OR)	MD: 17,698 OR: 17,090	2.82 (95% CI 1.89–3.76)	2.19 (95% CI 2.00–2.40)	Very low	Inconsistency and risk of bias

Glutamyl Transferase; ALP, Alkaline Phosphatase; HSI, Hepatic Steatosis Index; MD, Mean Difference; OR, Odd Ratio; CI, Confidence Interval.

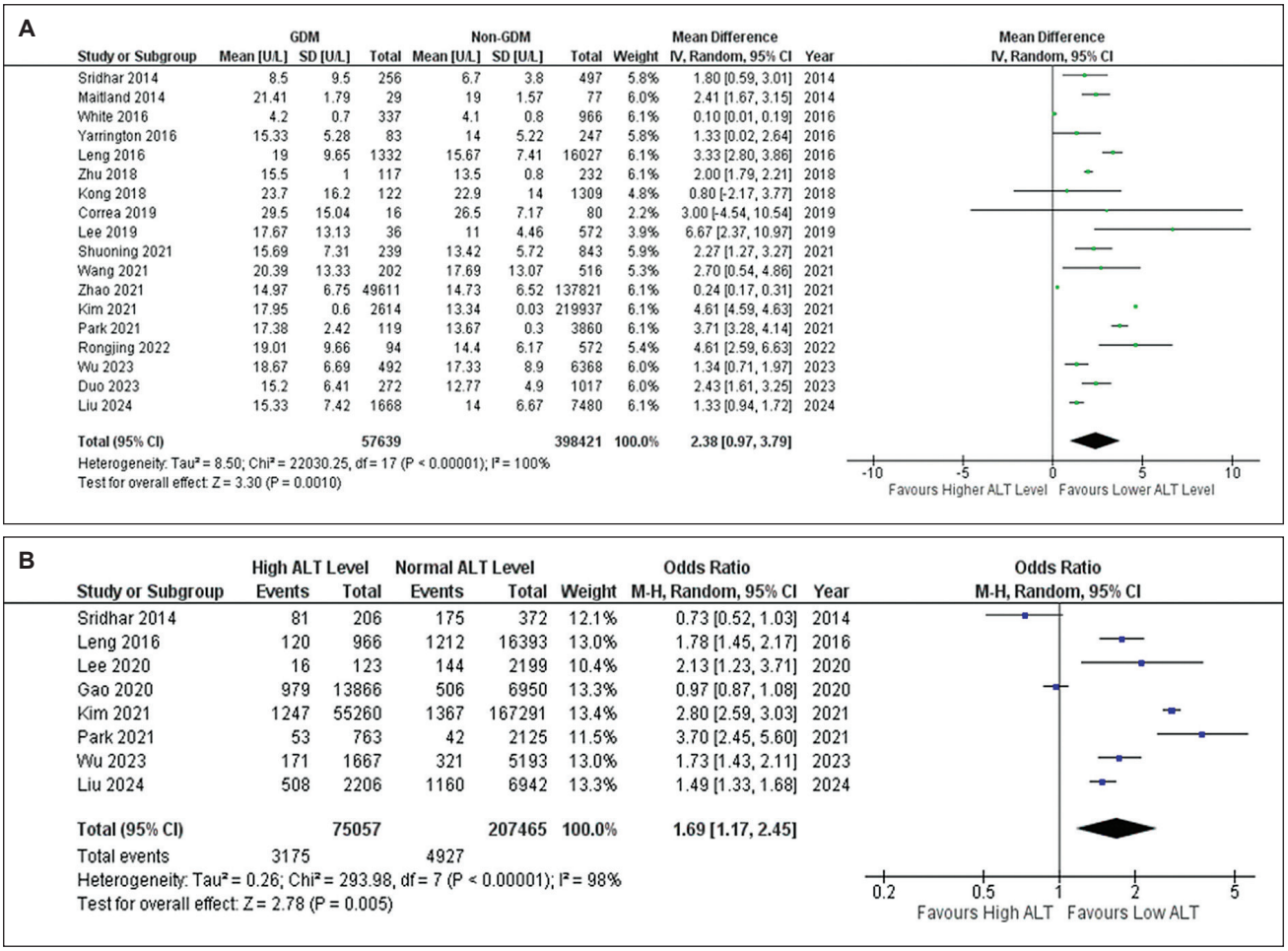


Figure 5. (A) The mean difference in pre- or early pregnancy serum ALT level between GDM and non-GDM groups. **(B)** The odds ratio of GDM in subjects with higher ALT level.

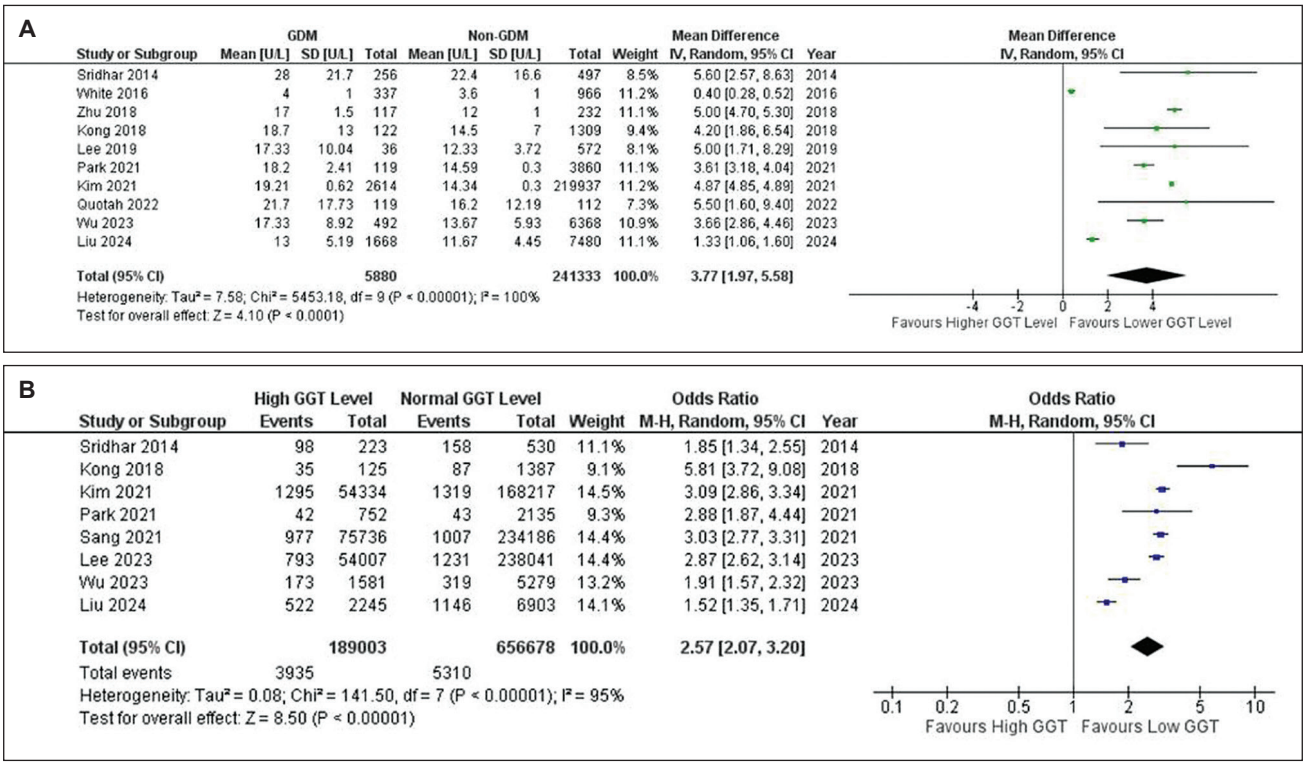


Figure 6. (A) The mean difference in pre- or early pregnancy serum GGT level between GDM and non-GDM groups. **(B)** The odds ratio of GDM in subjects with higher GGT level.

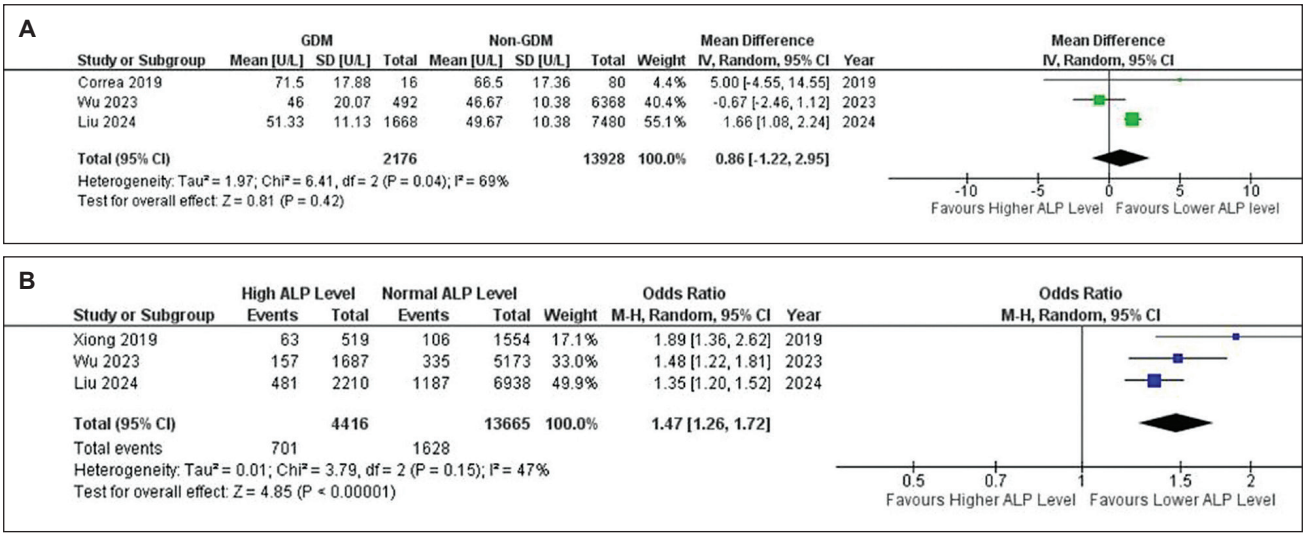


Figure 7. (A) The mean difference in pre- or early pregnancy serum ALP level between GDM and non-GDM groups. **(B)** The odds ratio of GDM in subjects with higher ALP level.

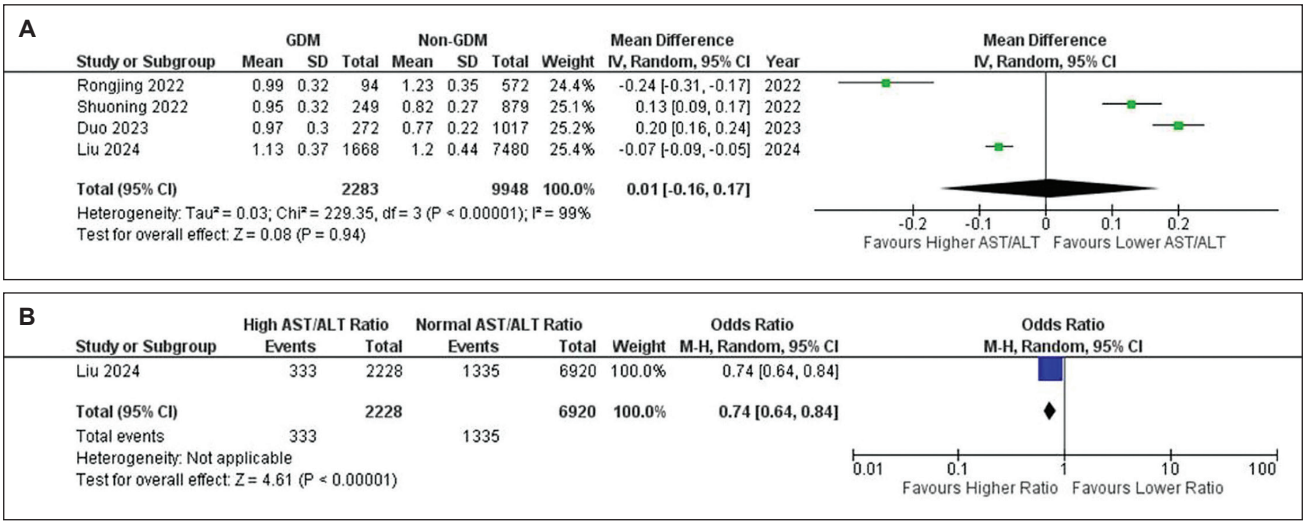


Figure 8. (A) The mean difference in pre- or early pregnancy AST/ALT ratio between GDM and non-GDM groups. **(B)** The odds ratio of GDM in subjects with higher ALP level.

DISCUSSION

The meta-analysis aimed to determine the correlation between various liver function markers and the risk of developing GDM. In a review of 27 studies, our main findings indicate that higher levels of liver enzymes, especially AST, ALT, and GGT, along with HSI, are significantly linked to a greater likelihood of GDM occurring during pregnancy. Among these factors, GGT exhibited the most significant correlation, with an OR value of 2.57. Similarly, the HSI was also associated with higher odds of GDM (OR 2.19). A significant correlation between ALT and AST was also found to increase the risk of GDM, with a slightly smaller effect size (OR 1.69 and 1.42, respectively). On the other hand, although no significant mean difference in serum ALP levels was observed between groups, the odds ratio of GDM was still marginally higher in individuals with high ALP levels, with an OR of 1.47. These findings imply that while average ALP levels may not differ dramatically, elevated ALP may still serve as a risk indicator for GDM when elevated above the normal level. AST/ALT ratio findings were inconsistent, with limited evidence supporting its utility as a predictive marker. These findings highlight the potential utility of liver enzyme biomarkers as early screening tools for GDM risk.

The subjects with GDM had a higher mean level of serum AST, ALT, GGT, and higher HIS. However, the pooled mean differences observed for AST, ALT, and GGT were numerically small and may fall within accepted laboratory variability at the individual level. It can be explained by the fact that mean differences represent population-level averages and do not capture risk concentration among individuals with higher enzyme levels. In contrast, dichotomized analyses compared women in the highest exposure categories—typically the upper quartile—against

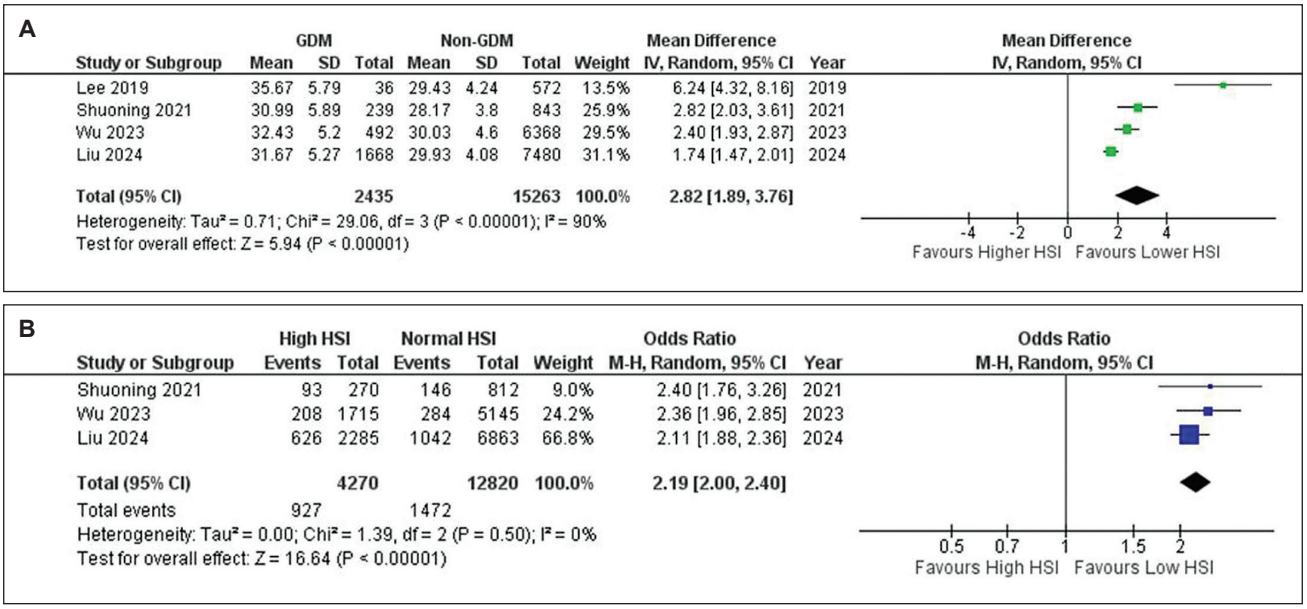


Figure 9. (A) The mean difference in pre- or early pregnancy HSI between GDM and non-GDM groups. **(B)** The odds ratio of GDM in subjects with higher HSI level.

those with lower levels. This approach identifies subgroups with disproportionate metabolic risk with both groups generally remained within clinically normal enzyme ranges. Consequently, small shifts in population means can coexist with significantly increased odds of GDM among women with relatively elevated liver enzyme levels.

The resulting odds ratios should therefore not be interpreted as comparing women with overtly abnormal liver function to those with normal function, but rather as reflecting risk gradients within the normal distribution of liver enzymes. In this context, relatively higher enzyme levels may serve as markers of subclinical metabolic dysfunction or hepatic insulin resistance rather than biochemical liver injury. This distinction explains how small absolute mean differences can coexist with sizable relative odds ratios.

Futhermore, given the small absolute mean differences observed for AST, ALT, and GGT, these biomarkers are unlikely to be clinically useful as standalone indicators for categorizing individual patients into high- or low-risk groups for gestational diabetes mellitus. However, liver enzyme abnormalities may reflect underlying hepatic insulin resistance or metabolic dysfunction and could potentially serve as adjunctive variables within existing multivariable GDM risk prediction models.

Substantial heterogeneity was observed across most pooled analyses, which is not unexpected given the diversity of study designs and populations included. Several factors likely contributed to this heterogeneity. First, population characteristics varied considerably, particularly with respect to ethnicity and pre-pregnancy body mass index, both of which are known to influence baseline liver enzyme levels, insulin resistance, and gestational diabetes risk. Second, the timing of biomarker measurement ranged from the pre-conception period to as late as 20 weeks of gestation, during which physiological changes in hepatic metabolism and insulin sensitivity may differentially affect enzyme concentrations. Third, diagnostic criteria for gestational diabetes mellitus were not uniform across studies, with the use of IADPSG, ACOG, ADA, and insulin-treatment–based definitions, each capturing different clinical phenotypes and disease severity. Finally, variation in covariate adjustment, particularly for age, BMI, and parity, may have further contributed to between-study variability in effect estimates. Collectively, these methodological and biological differences plausibly explain the high heterogeneity observed and underscore the need for cautious interpretation of pooled estimates.

Liver transaminase values are known to vary across laboratories and populations due to differences in assay methods and reference ranges. In the present review, this variability was mitigated by focusing on within-study comparisons rather than absolute enzyme concentrations. Mean differences compared GDM and non-GDM groups measured within the same laboratory context, while dichotomized analyses relied on study-specific relative thresholds such as quartiles or validated indices. As a result, inter-laboratory differences in normal reference values are unlikely to fully account for the observed associations, although they may have contributed to between-study heterogeneity. Given the heterogeneity of included studies, lack of standardized laboratory reference ranges, and very low certainty of evidence, we do not propose specific liver enzyme cut-off values for clinical use.

In the third trimester, particularly beyond 26 weeks of gestation, the placenta secretes a range of hormones (including estrogen, progesterone, cortisol, and human placental lactogen) that exert anti-insulin effects, thereby

inducing a state of progressive insulin resistance. This physiological adaptation facilitates increased maternal glucose availability to support optimal fetal growth and development. To maintain euglycemia, maternal pancreatic β-cells must compensate through enhanced insulin secretion. GDM develops when this compensatory response is inadequate, resulting in maternal hyperglycemia due to insufficient insulin production or heightened peripheral insulin resistance.[42] In Indonesia, GDM is still a major problem affecting up to 4% of all pregnancies.[43]

Our findings align with prior studies linking liver dysfunction and insulin resistance to metabolic diseases, including GDM. The liver plays a crucial role in maintaining glucose homeostasis, insulin clearance, and the production of inflammatory cytokines. Various liver conditions have been associated with diabetes, which is reflected by alterations in liver parameters. Elevated GGT levels are proposed as markers of oxidative stress and liver dysfunction, contributing to the development of GDM or T2DM.[44] A previous systematic review and meta-analysis by Zhao et al. in 2019 also reported a significant association between GGT levels and risk of GDM (OR 2.10, 95% CI 1.14-3.86), though fewer studies and participants were included.[45] Increased AST and ALT levels are associated with liver inflammation or injury, particularly in MAFLD. The HSI is a composite marker reflecting hepatic fat accumulation in conditions such as MAFLD as well. Insulin resistance has been implicated in the pathogenesis of MAFLD by promoting glucotoxicity and lipotoxicity. Likewise, populations with MAFLD have a twofold higher risk of developing T2DM than those without MAFLD and are often associated with a worse cardiometabolic profile.[46]

Elevated ALP levels can be influenced by liver inflammation, biliary dysfunction, or bone metabolism changes. During pregnancy, ALP levels will progressively increase due to placental production and typically reach their highest concentration in the third trimester. This explained the insignificant mean difference between the groups.[47] Notably, consistent with this meta-analysis result, a prospective cohort study by Xiong et al in 2019 reported a higher risk of GDM with higher early maternal ALP level (OR 2.47, 95% CI 1.47-4.15).[24]

When GDM is not properly managed, it can lead to higher rates of illness and death for both the mother and the baby. Women who have experienced GDM are at a greater long-term risk of developing T2DM. More than 50% of women diagnosed with GDM will progress to T2DM within 20 years postpartum.[48] Recent studies by Peramaki et al, in 2023, reported the risk for T2DM was 11 times higher in women with than without a history of GDM. Alongside an elevated risk of developing T2DM, women with a prior history of GDM also exhibit increased predisposition to metabolic syndrome and cerebrovascular disease.[49] Furthermore, the offspring of mothers with GDM are also at elevated long-term risk for metabolic dysregulation, including impaired glucose tolerance and obesity, as well as increased susceptibility to endocrine disorders, adverse neurodevelopmental outcomes, and neuropsychiatric morbidities.[48]

The Indonesian Endocrinologist Society has published its guideline for GDM in 2021, encouraging OGTT to be done in populations with moderate or high risk for GDM combined with blood glucose level at the first antenatal visit. The mentioned criteria for risk stratification include obesity, personal history of T2DM or history of T2DM among first-degree relatives, history of macrosomia, presence of glycosuria, and certain high-risk ethnicities. Unfortunately, the screening and diagnosis of GDM are rarely done due to limited resources and a lack of urgency. In addition, the guideline also includes the management of GDM, which generally consists of medical nutrition therapy, physical activity or exercise, self-blood glucose monitoring, weight monitoring, and pharmacological treatment if needed.[6] Given the widespread availability and affordability of liver function tests, integrating them into first-trimester or preconception risk assessments could provide a cost-effective strategy for early intervention among the Indonesian population.

There are several limitations in this study. This study is limited by substantial between-study heterogeneity, which reduced the certainty of pooled estimates and precluded robust subgroup or threshold analyses. Variability in laboratory assays and reference ranges across studies may have contributed to heterogeneity, although the use of within-study comparisons likely reduced systematic bias. The very low certainty of evidence underscores that the observed associations should be interpreted cautiously and viewed as hypothesis-generating rather than confirmatory. Although the funnel plots suggest minimal publication bias, most included studies were observational in nature, which may introduce residual confounding. Subgroup analyses based on diagnostic criteria or population characteristics would be informative. However, inconsistent reporting and limited data availability across studies precluded statistically robust subgroup analyses. Lastly, not all studies adjusted for key confounders such as age, BMI, and parity, limiting the internal validity of pooled estimates.

While we conducted a comprehensive database search and followed rigorous inclusion criteria, gray literature was not included, which may have led to the omission of relevant unpublished studies. Furthermore, the inclusion of studies with heterogeneous methods and reporting styles limited the ability to conduct subgroup and sensitivity analyses, particularly for cut-off thresholds of liver enzyme elevation. That being said, no studies were rated as having high risk of bias, reducing the necessity of excluding studies to test robustness. Future prospective studies should aim to establish standardized thresholds, explore causality, and evaluate whether early lifestyle or pharmacologic interventions based on elevated liver enzymes can reduce GDM incidence and improve maternal-fetal outcomes. Further exploration of composite scores like HSI may offer

enhanced predictive power, particularly in populations with high metabolic risk. Lastly, future models may consider incorporating liver enzymes as continuous predictors alongside established risk factors such as maternal age, pre-pregnancy BMI, ethnicity, family history of diabetes, and prior obstetric outcomes. Importantly, such integration would require prospective validation to determine whether inclusion of liver enzymes meaningfully improves model discrimination, calibration, or clinical decision-making.

CONCLUSION

Relatively higher liver enzyme biomarkers, particularly GGT, ALT, AST, and the HSI measured before or during early pregnancy are associated with an increased risk of developing GDM. These associations support the potential role of liver enzyme abnormalities as population-level markers of metabolic risk preceding GDM. However, substantial heterogeneity among studies and the very low certainty of evidence limit their immediate clinical applicability as individual screening tools. The observed associations should therefore be interpreted within a population and risk-stratification framework rather than as indicators of clinically meaningful differences in absolute enzyme values for individual patients. Further prospective studies are needed to confirm these associations, establish diagnostic thresholds, and evaluate the impact of early preventive strategies guided by liver enzyme profiles.

Acknowledgment
The authors would like to acknowledge the authors of the included studies who have provided the data needed to generate this manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
SP: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft preparation; **RDA:** Formal analysis, Investigation, Writing – original draft preparation; **IJ:** Formal analysis, Investigation, Writing – original draft preparation; **BCL:** Writing – review and editing, Visualization.

Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

REVIEW ARTICLE

Addressing Unmet Needs in the Management of Diabetes in Asia and Enhancing Diabetes Care Through the Use of Digital Technology: An Expert Opinion

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Abstract

Background. Asia faces a growing diabetes burden compounded by low awareness, limited access, affordability concerns, and heterogeneous care practices. These challenges hinder consistent management across the region.

Methodology. An expert panel representing India, Japan, South Korea, the Philippines, Singapore, Australia and Austria reviewed regional barriers, compared national practices, and proposed feasible strategies for improvement.

Results. Key gaps included healthcare access, affordability, limited workforce capacity, poor adherence to guidelines, cultural influences and underuse of digital tools. Experts examined region-specific approaches, highlighting effective models from Singapore, India, Japan, the Philippines, China, Malaysia, Indonesia, Thailand and South Korea.

Discussion. Synthesised insights yielded policy-oriented and practical recommendations, focusing on insurance expansion, digital and AI-enabled care, workforce strengthening, and community-based programs to enhance diabetes care delivery.

Conclusion: Tailored, region-specific and technology-enabled strategies addressing systemic and economic barriers are vital to strengthen diabetes management across Asia.

Key words: Asia, telemedicine; diabetes mellitus type 2, integrated healthcare, mhealth, artificial intelligence, diabetes monitoring, healthcare policies

INTRODUCTION

Diabetes has emerged as one of the most urgent health concerns in Asia, home to nearly 60% of the global diabetes burden.[1] The prevalence of diabetes has surged in recent decades, driven by rapid urbanisation, sedentary lifestyles, unhealthy dietary habits, and genetic predisposition. The International Diabetes Federation (IDF) estimates that by 2045, in Southeast Asia alone, the number of adults living with diabetes, which was approximately 90 million in 2021, is projected to reach around 152 million by 2045.[2]

Despite advancements in diabetes care, the region continues to face significant healthcare disparities. Most low- and middle-income countries (LMICs) are in Asia, where diabetes care is fragmented, leading to inconsistent treatment approaches.[3,4] Healthcare systems are often overburdened, with limited access to diabetes specialists and endocrinologists, particularly in rural and remote areas.[5] A large proportion of people with diabetes (PwD) remain undiagnosed, mainly due to inadequate screening programmes, low health literacy, and financial constraints.[6–8] As a result, many individuals receive a

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Gardner et al.
Received: August 19, 2025. Accepted: October 10, 2025.
Published online first: February 25, 2026.
https://doi.org/10.15605/jafes.041.01.5209

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diagnosis only after complications have developed, leading to a higher incidence of diabetes-related complications, including cardiovascular disease, diabetic retinopathy (DR), nephropathy and neuropathy.[9]

Economic barriers further limit access to essential medications and glucose monitoring devices. Many PwD in LMICs rely on out-of-pocket payments, making long-term diabetes management unaffordable.[10] Additionally, cultural factors play a critical role in healthcare-seeking behaviour.[11–13] In several Asian countries, many PwD turn to alternative and complementary medicine, which can contribute to poor glycaemic control or pose additional health risks.[14]

The rapid advancement of digital health technologies presents an opportunity to transform diabetes care across the region. The widespread adoption of smartphones, telemedicine platforms and mobile health (mHealth) applications offers new avenues for early detection, remote monitoring and patient education.[15,16] Innovations such as artificial intelligence (AI)-driven diagnostics, continuous glucose monitoring (CGM), and electronic health records (EHRs) have shown promise in improving clinical outcomes.[17–19] However, technological literacy gaps, regulatory hurdles and data security concerns hinder the widespread adoption of digital solutions.[20]

METHODOLOGY

Eight diabetes experts from seven countries (India, Japan, South Korea, the Philippines, Singapore, Australia, and Austria) were onboarded to identify key challenges and unmet needs for diabetes care in this region, exploring how technology and policies may be leveraged to bridge these gaps. These experts were selected based on their recognised expertise in diabetes care, clinical research and policy engagement in their respective countries. The panel included endocrinologists, nurse practitioners and diabetes educators affiliated with medical institutions and organisations with expertise in diabetes care, research, and policy development. The focus was (i) to highlight the barriers and unmet needs in diabetes care in Asia; (ii) to examine the evolving policy landscape; and (iii) to improve the standard of care through digital technology and policy changes within the continuum of diabetes care. Challenges in the current care pathways were identified and prioritised via email through a combination of literature reviews and expert consultations. Subsequently, experts provided independent input based on their national and regional experiences in clinical practice and healthcare delivery. This feedback was then consolidated to identify common themes and key barriers to effective healthcare delivery.

A focused review of published literature on PubMed and Google Scholar was undertaken to validate and supplement expert insights. Search terms included "diabetes management," "Asia," "digital health," "telemedicine," "healthcare access," and "real-world practice." Publications from 2010 to 2025, including regional guidelines, implementation studies, and digital health reports, were considered.

The process was exploratory and iterative, aimed at identifying and contextualising barriers, and discussing potential approaches to strengthen diabetes care in Asia. It was intended to generate expert perspectives and thematic insights.

The following sections discuss the key barriers to diabetes management in Asia, region-specific strategies in digital diabetes management, and future directions and policy recommendations by experts.

RESULTS

Key barriers to diabetes management in Asia

Despite growing awareness of the diabetes burden in Asia, effective management remains a significant challenge due to a range of systemic, socioeconomic and cultural factors. The region's diverse healthcare landscapes, particularly in LMICs, struggle with infrastructural limitations, financial constraints, and gaps in policy implementation. These barriers not only impede timely diagnosis and treatment but also undermine the continuity and quality of care for PwD. The following subsections explore the multifaceted challenges that hinder optimal diabetes management throughout the region.

Limited healthcare infrastructure and workforce shortages

One of the most pressing challenges in diabetes management is the shortage of trained healthcare professionals (HCPs) and the underdeveloped healthcare infrastructure in Asia.[3,21] Specialised diabetes care is often limited to urban centres, leading to limited access to timely diagnosis and treatment for those in rural areas.[5,12]

Fragmented care pathways

Healthcare delivery in Asia remains largely unstructured, particularly in LMICs.[3] The common practice of consulting multiple providers among PwD often results in uncoordinated management.[22] Furthermore, inadequately maintained patient registries and limited collaboration between primary and secondary care impair continuity of care, hindering effective disease management. Additionally, inefficient referral systems between primary care facilities and specialised diabetes centres contribute to delays in accessing advanced treatment.[3] Geographic factors further exacerbate these challenges in rural and resource-limited settings where access to care remains limited.[22]

Absence or poor implementation of national diabetes guidelines

Another challenge is the lack of or poor implementation of standardised national diabetes guidelines, leading to wide variations in treatment approaches.[3,23] HCPs may not consistently adhere to local guidelines due to

a lack of awareness or time constraints.[22] As a result, less than one-tenth of PwD in Asian LMICs receive diabetes treatment aligned with World Health Organisation (WHO) guidelines.[4]

Financial barriers and cost of care

Diabetes management places a significant financial burden on PwD in Asia, where public health insurance coverage is often inadequate.[8,22,24] High costs of medications and insulin contribute to poor disease control and an increased risk of complications.[5,25] Economic constraints also drive nonadherence to self-management practices. The financial impact of diabetes-related complications not only affects PwD but also places a growing burden on healthcare systems.[13]

Low awareness and lack of diabetes education

Lower levels of awareness about diabetes and its complications continue to be a major barrier to effective self-management practices among PwD.[12] Low health literacy, inadequate educational materials and insufficient patient counselling affect adherence to treatment among PwD.[22,26] Many PwDs lack a clear understanding of disease progression, the importance of glycaemic control and the long-term risks associated with uncontrolled diabetes. These challenges are exacerbated by overburdened healthcare systems, where limited appointment times and poor communication between health providers and PwD hinder the delivery of comprehensive diabetes education.[9,12,22] Furthermore, inconsistencies in healthcare provider training affect diabetes care quality across different healthcare clusters. In India, for instance, primary care HCPs often lack sufficient training in diabetes management.[5]

Poor screening rates for diabetes and complications

Diabetes screening in Asia is fraught with challenges, particularly in low-resource settings, where many cases go undetected in the early stages. The absence of clear global guidelines for screening in many countries contributes to low rates of early diagnosis. Commonly used screening tools, such as glycated haemoglobin (HbA1c) and oral glucose tolerance tests, may be unavailable to identify at-risk individuals.[12] Further, the uptake of diabetes screening among PwD may be limited by low awareness, reluctance to seek testing, apprehension about a potential diagnosis and the lifestyle adjustments it may require.[27]

Cultural barriers and preference for alternative medicine

Traditional diets and cultural factors can present additional challenges, as significant dietary modifications may be necessary for effective diabetes control.[12] The growing shift toward high-carbohydrate diets and increasingly sedentary lifestyles highlights the need for targeted interventions.[12,13] Compounding these challenges, many PwD opt for complementary and alternative medicine (CAM) alongside prescribed treatments. HCPs are often unaware of CAM use by patients, raising concerns about safety, potential drug interactions, and treatment efficacy.[14]

Limited adoption of digital tools

Digital health innovations have great potential to transform diabetes care, resulting in improved management and increased accessibility. However, their widespread adoption remains limited due to gaps in technological literacy, regulatory barriers and privacy concerns.[28,29] Many digital solutions fail to cater to the specific needs of PwD, particularly older adults, resulting in poor usability and engagement.[27] Without user-centric designs and more substantial policy support, these tools risk remaining underutilised, limiting their impact on improving diabetes management.

Region-specific strategies for addressing barriers in digital diabetes management

Asia is a highly diverse region, characterized by significant variations in economic development, health systems and the adoption of digital health technologies. Several countries have adopted distinct approaches to digital diabetes management, leveraging their unique healthcare landscapes and technological capacities. While Singapore has set a benchmark for AI-powered smart healthcare, India and Indonesia have leveraged telemedicine and national insurance integration to expand diabetes care. On the other hand, Japan has advanced AI-driven personalised medicine, tailoring treatments to individual patient needs.

Digital health solutions have revolutionised diabetes management, enabling remote care, AI-driven diagnostics, mobile health (mHealth) interventions, and centralised EHRs.[30,31,17] Several pioneering digital diabetes programmes have been implemented in Singapore, India, Japan, the Philippines, China, Malaysia, Indonesia, and Thailand. Examining these initiatives and successful international models from Europe, North America and Australia provides valuable insights into best practices and areas for improvement. A comparative analysis of these initiatives and successful international models from Germany, the United Kingdom (UK) and Canada offers valuable insights into best practices, scalability and future advancements in diabetes care.

Singapore: A global leader in smart health technologies

Singapore has emerged as a global benchmark for digital diabetes care, leading the way in healthcare solutions, centralised data systems and public-private collaborations. The country's strong digital infrastructure and government-backed initiatives have ensured high accessibility and efficiency in diabetes management.

The Singapore flagship initiative, the HealthHub platform, serves as a centralised digital health ecosystem, integrating EHRs, teleconsultations, AI-driven lifestyle coaching, and big data analytics. The key advantage of HealthHub is its ability to provide real-time access to patient data, enabling doctors, patients and caregivers to track glucose levels, medication adherence and lifestyle modifications seamlessly. Unlike traditional models that rely on fragmented

paper-based records, HealthHub ensures treatment continuity, particularly for patients with multiple healthcare providers.[32]

Singapore has also pioneered AI-based DR screening through the Singapore Eye Research Institute. This automated AI system detects diabetic eye complications with over 90% accuracy, significantly reducing screening time while increasing early detection rates and risk stratification. This programme overcomes the shortage of trained ophthalmologists in primary healthcare settings.[33]

A critical component of Singapore's success is the Smart Nation Healthcare Initiative, which utilizes big data analytics to predict diabetes trends, optimise resource allocation, and personalise intervention strategies.[32] This initiative helps prevent diabetes progression, thereby reducing long-term healthcare costs. Its studies on AI-based insulin dosing algorithms showed real-time glucose management, improving glycaemic control without the need for frequent doctor visits.[34]

Comparison with global models: Singapore's model is comparable to Denmark's National Health Data Network, which integrates EHRs across hospitals and primary care facilities, improving treatment coordination.[35,36]

Singapore's comprehensive digital infrastructure has addressed major barriers in diabetes management. By integrating AI-driven diagnostics, the country has significantly reduced its dependence on specialists, making diabetes screening more accessible to the general population. The introduction of centralised EHRs has ensured seamless data continuity, allowing physicians to track patient history efficiently and adjust treatment plans accordingly.

India: Expanding telemedicine and diabetes care

India has one of the largest diabetes populations globally, with disparities in care due to geographical barriers, limited specialist availability, and financial constraints. The country has leveraged telemedicine, AI-powered diagnostics, and mobile-based health interventions to expand diabetes care.

The e-Sanjeevani Telemedicine Platform,[37] launched by the Ministry of Health, provides virtual consultations, connecting PwD in remote areas with diabetes specialists, general practitioners, and nutritionists. This overcomes the shortage of endocrinologists, particularly in rural states where specialised care is scarce. The mDiabetes Programme, a WHO-Indian Council of Medical Research initiative, delivers short message service (SMS)-based diabetes education in multiple regional languages, ensuring accessibility for low-literacy populations. This programme has been instrumental in improving awareness, medication adherence, and self-care behaviours.[38] The Ayushman Bharat Digital Mission integrates EHRs across hospitals and clinics, ensuring seamless patient data access and improving treatment continuity and follow-ups.[39] This model is more extensive due to its multi-language mobile diabetes interventions, making them more inclusive for diverse populations.

In parallel, technology-driven innovations, such as tele-ophthalmology networks and AI-enabled smartphone-based retinal screening, have proven effective in detecting advanced DR. A multicentre study across 35 diabetes care centres demonstrated that tele-ophthalmology using Fundus on Phone devices enabled centralised grading by retina specialists and effectively identified sight-threatening DR (STDR), with 7.3% of screened individuals requiring referral.[40] Similarly, AI-assisted analysis of smartphone fundus images has shown very high sensitivity and specificity for detecting DR and STDR, providing a scalable solution for mass retinal screening.[41]

Comparison with global models: India's telemedicine model is similar to Canada's Ontario Telemedicine Network, which has successfully expanded access to specialists in remote regions. However, India's model is more extensive due to its multi-language mobile diabetes interventions, making them more inclusive for diverse populations.

India's digital interventions have addressed several systemic barriers in diabetes care. Telemedicine networks have expanded access to specialised diabetes care in rural areas, reducing healthcare inequities. AI-powered diagnostics have enhanced early detection of complications, preventing avoidable blindness and amputations. Mobile-based education programmes have also empowered patients with better self-management skills, improving long-term health outcomes.

Japan: Personalised diabetes management

Japan has focused extensively on AI-driven predictive analytics and patient-centred digital therapeutics to improve diabetes care. The Diabetes Digital Registry System, developed by the Japan Diabetes Society, allows real-time tracking of patient data across hospitals, ensuring timely intervention and coordinated care.[42]

A key innovation is Fujitsu's Healthy Living, a cloud-based data platform,[43] that aggregates and standardises patient health information. It aims to support AI-enabled personalised healthcare by analysing real-time patient data to inform clinical decision-making and individual care.

Japan has also pioneered AI-integrated insulin pumps integrated with CGM, allowing automated insulin dose adjustments based on real-time glucose readings.[44] Japan's real-time AI-powered insulin adjustments make it one of the most advanced diabetes management systems globally.

Comparison with global models: Japan's AI-driven predictive healthcare is similar to the UK's National Diabetes Prevention Programme, which also integrates behavioural AI coaching.[45]

Japan's AI-driven healthcare solutions have transformed diabetes management by making treatment highly personalised and data-driven. The nationwide digital diabetes registry ensures continuous patient monitoring, while machine learning-based predictive analytics help doctors optimise medication dosages and provide lifestyle recommendations.

The Philippines: Expanding telemedicine and remote monitoring

In the Philippines, access to diabetes care is uneven, particularly in rural areas where healthcare infrastructure remains limited. The Philippines' eHealth Strategic Framework was introduced to expand digital health platforms and integrate diabetes management into the national health system. The Diabetes Telemedicine Programme, a government initiative led by the Department of Health, has played a crucial role in linking PwD with endocrinologists and general practitioners through teleconsultations.[46]

In addition to government-led programmes, private-sector initiatives offering home-based consultations, such as the AIDE Mobile App,[47] have enhanced diabetes care. They also provide diagnostic services and medication delivery, reducing the need for hospital visits and ensuring continuity of care for patients with limited mobility or transportation constraints.

Comparison with global models: The Philippines' telehealth model, similar to Canada's Ontario Telemedicine Network,[48] focuses on mHealth solutions, making diabetes care more accessible to low-income populations.

The Philippines has tackled healthcare accessibility challenges by leveraging telemedicine and mHealth solutions to connect rural communities with specialised care.

China: Diabetes diagnostics and smart wearables

China has taken a data-driven approach to diabetes care, integrating big data analytics and smart wearable technology to enhance early diagnosis, prevention and long-term management.[49]

Additionally, AI-powered glucose monitoring devices are widely used for continuous diabetes tracking, providing real-time alerts for abnormal blood sugar levels.[50] This has been particularly effective in preventing severe diabetes-related complications in the elderly and high-risk populations.

Comparison with global models: China's big data-driven diabetes care is comparable to the UK's National Diabetes Prevention Programme, which also employs risk assessment models to identify high-risk individuals and intervene early.[45]

China's big data integration and AI-driven monitoring systems have addressed the challenge of fragmented patient data and inconsistent diabetes management protocols. By leveraging nationwide digital registries, China has ensured that PwD receive evidence-based treatment tailored to their specific needs.[51] The government's partnerships with private AI companies have also accelerated technological innovation, making diabetes care more efficient.

Malaysia: Digital health integration into primary care

Malaysia has made significant strides in incorporating digital health solutions into its primary healthcare system to improve diabetes management. The MyDiabetes App, developed by the Ministry of Health Malaysia, provides an AI-driven self-management platform that enables PwD to track blood sugar levels, monitor diet, receive personalised treatment recommendations, and access educational resources. Unlike traditional diabetes management approaches, this app enables real-time intervention and remote monitoring, promoting better adherence to treatment plans.[52]

Government initiatives, such as the Diabetes Medication Therapy Adherence Clinics in Malaysian hospitals, integrate pharmacists into diabetes care teams to provide structured education on medication use, lifestyle modifications, and self-monitoring techniques.[53]

The National eHealth Strategy (2019–2025) focuses on integrating EHRs across healthcare facilities to create a unified patient data system, making treatment history accessible across different healthcare settings. This initiative reduces the risk of fragmented care and medication errors, ensuring PwD receive consistent and well-informed medical support.[54]

Comparison with global models: Malaysia's mHealth strategies are similar to Germany's regional diabetes care programmes. However, Malaysia's mobile clinics extend healthcare access to underserved regions, ensuring proactive intervention rather than reactive treatment.

Malaysia's digital health integration addresses major barriers such as limited access to specialists, a lack of structured diabetes education, and poor follow-up care. Through government-backed initiatives and mHealth interventions, the country has made diabetes management more inclusive and patient-centred. By integrating EHRs into primary care, Malaysia ensures continuity of care.

Indonesia: National insurance and digital diabetes solutions

Indonesia has taken a national policy-driven approach to digital diabetes care, integrating telemedicine and digital monitoring into its universal health insurance system. The Kesehatan Digital Health Framework, launched by the Indonesian National Health Insurance Agency, allows PwD to access subsidised CGM devices, participate in remote consultations, and receive AI-driven medication adjustments through a government-backed mobile application.[55]

Comparison with global models: Indonesia's community-driven diabetes programmes resemble Canada's remote diabetes management initiatives. However, Indonesia's large-scale integration into a national insurance model minimises financial constraints, making the approach more inclusive and sustainable.

By integrating digital diabetes monitoring into its national insurance framework, Indonesia has significantly reduced financial barriers to advanced diabetes care. The use of AI-powered predictive models has allowed for earlier detection of diabetes, reducing long-term complications. The training of village health workers in mobile diabetes monitoring has ensured that care reaches rural populations, eliminating the geographical barriers traditionally associated with specialist-led diabetes treatment.

Thailand: Nationwide digital diabetes monitoring

AI-based hospital screening programs have been deployed in Thailand's major public hospitals, where AI-assisted DR screening tools have reduced waiting times and increased early detection rates. These programs are particularly impactful in rural areas, where specialist ophthalmologists are limited.[56] Additionally, Thailand's Ministry of Public Health has launched an innovative telemedicine service known as the 'Health Station' to improve healthcare access and reduce hospital congestion.[57]

Comparison with global models: Thailand's national diabetes monitoring system is comparable to Germany's digital model, which promotes AI-assisted monitoring tools (e.g., Esysta) that support diabetes self-management.[58]

Thailand's comprehensive digital diabetes strategy has tackled barriers such as fragmented care, specialist shortages and a lack of structured patient monitoring. The country ensures timely intervention and long-term disease control by integrating national registries with AI-based monitoring. Implementing hospital-based AI screenings has significantly reduced undiagnosed diabetic complications, ensuring earlier, targeted and more effective interventions.

South Korea: Telemedicine and online glycaemic monitoring platforms

The Korean Diabetes Association supports the integration of telemedicine, enabling remote consultations.[59] It also fosters collaborations for exploring AI-driven treatment protocols and innovative management strategies. Seoul National University Bundang Hospital spearheads government-funded initiatives for research networks and advancing AI-driven healthcare software.[60] Korea-exclusive platforms (e.g., Diaconn Web) provide free online glycaemic monitoring solutions, allowing users to seamlessly integrate CGMs, glucose meters, and insulin pumps (automated insulin delivery and continuous subcutaneous insulin infusion therapy) with diabetes therapy for more effective disease management.[61]

Comparison with global models: Korea's telemedicine concept is comparable to Australia's, where telemedicine plays a significant role in diabetes management, particularly in remote areas. Initiatives such as Diabetes Western Australia's telehealth clinics offer free, personalised consultations with certified diabetes educators.[62]

The various strategies illustrated from different countries and continents emphasise that technology-driven interventions can bridge gaps in diabetes management, offering scalable models for other regions facing similar challenges. However, continued investment, policy support, and regional collaborations will ensure the long-term success and expansion of digital diabetes care across Asia.

DISCUSSION

Future directions and policy recommendations

The future of diabetes care in Asia hinges on the successful integration of digital health solutions, policy reforms and enhanced healthcare infrastructure. As diabetes prevalence rises, governments, healthcare institutions and private-sector stakeholders must collaborate to implement sustainable, patient-centric solutions. Several key areas must be prioritised to ensure equitable and effective diabetes management across the region.

Strengthening national diabetes policies and guidelines

One of the foremost challenges in diabetes management is the lack of standardised national guidelines across many Asian countries.[23] Policymakers must focus on developing and implementing region-specific diabetes management frameworks that consider local healthcare capacities, socioeconomic factors and cultural behaviours.[23] Strengthening national diabetes action plans with clear targets for screening, treatment adherence and complication prevention is essential to reducing the disease burden.[23,63]

Expanding public and private health insurance coverage

Affordability remains a critical issue in diabetes care, particularly in LMICs where many PwD are unable to afford long-term treatment.[13,22] Governments should consider expanding public health insurance schemes to cover essential diabetes medications, CGMs and telemedicine consultations.[64,65] Innovative financing models, including microinsurance for diabetes,[66] and public-private partnerships, can play a pivotal role in reducing the financial burden on patients.[67] Expanding public health insurance programmes, subsidising diabetes medications, and introducing value-based pricing models can help reduce economic barriers and improve treatment adherence.[65,68,69]

Advancing digital health and telemedicine adoption

While digital health solutions have demonstrated efficacy in improving diabetes management, widespread adoption remains a challenge due to regulatory fragmentation and

a lack of integration into existing healthcare systems.[20,30] Policymakers must establish clear regulatory frameworks to standardise telemedicine practices, ensure data security and promote interoperability between digital health tools and EHRs.[19] Governments can also invest in digital literacy programmes to train HCPs and PwD on the effective use of mHealth applications, wearable devices, and AI-powered diagnostics.[70,71] Community health workers (CHWs) can be incentivised to adopt digital diabetes tools for routine diabetes screenings in underserved areas.[72]

Leveraging artificial intelligence for personalised care

AI-driven solutions have the potential to revolutionise diabetes management by enabling early detection, predictive analytics and personalised treatment regimens.[30] Machine-learning algorithms can analyse real-time patient data to provide tailored recommendations for glycaemic control, dietary habits and medication adjustments.[17,34] AI-assisted DR screening programmes have already shown promise in countries like Singapore and India, reducing the burden on ophthalmologists and improving early intervention rates.[33,71] Studies from India have demonstrated that AI-based assessment using smartphone fundus photography has high sensitivity for detecting severe DR.

Strengthening healthcare workforce and task-shifting strategies

Addressing the shortage of diabetes specialists in Asia requires a shift towards task-sharing models where trained nurses, pharmacists, and CHWs take on expanded roles in diabetes education and screening.[73,74] Community-based diabetes programmes that empower non-physician healthcare providers have been effective in countries like India and the Philippines.[75,76] Digital tools, such as mobile-based decision-support systems, can further enhance the capabilities of frontline health workers in managing diabetes.[74] Task-shifting strategies, such as training nurses, pharmacists, and CHWs, can expand service delivery, while telemedicine can facilitate remote consultations for underserved regions.[73,77,78]

Establishing regional collaborations and knowledge-sharing platforms

Regional cooperation between nations can facilitate knowledge exchange, policy harmonisation and the scaling of successful diabetes interventions. Organisations such as the Asian Diabetes Prevention Initiative and the IDF work towards creating shared platforms for research collaboration, best practice dissemination, and joint public health initiatives.[79] Establishing localised diabetes guidelines and continuous training programmes for healthcare providers can ensure standardised care delivery.[80]

Investing in research and development for innovative therapies

In addition to digital health solutions, continued investment in research and development is crucial for advancing novel diabetes therapies, including precision medicine approaches.[4,81] Governments and private-sector partners should increase funding for diabetes research for Asian populations. Table 1 summarises the key barriers and potential solutions to addressing them.

Table 1. Challenges and facilitators in diabetes management

Challenges / Barriers	Facilitators / Enablers
Limited healthcare infrastructure and workforce shortages	• Train nurses, pharmacists, and CHWs to manage diabetes. • Expand telemedicine services for remote access.
Fragmented care pathways	• Establish EHRs and diabetes registries for seamless care coordination.
Absence or poor implementation of national diabetes guidelines	• Develop region-specific guidelines and ensure effective implementation. • Conduct training programmes for healthcare providers.
Financial barriers and cost of care	• Expand public health insurance and subsidise medication programmes. • Introduce value-based pricing models for diabetes care.
Low awareness and a lack of diabetes education	• Implement community-based diabetes education and mobile screening units. • Integrate blood glucose testing into routine health checkups.
Cultural barriers and preference for alternative medicine	• Regulate alternative treatments while integrating culturally adapted diabetes interventions. • Integrating discussions about CAM use into routine consultations could improve patient-provider communication and ensure safer, more effective diabetes management.
Limited adoption of digital health tools	• Enhance digital literacy and train healthcare workers on diabetes technology. • Strengthen data security for digital solutions.
High cost of advanced diabetes tools (CGMs, AI-driven screening, etc.)	• Provide subsidies and government incentives for digital diabetes tools. • Promote public-private partnerships for broader access.

AI: Artificial intelligence; CAM: Complementary and alternative medicine; CGM: Continuous glucose monitoring; CHW: Community health worker; EHR: Electronic health record.

CONCLUSION

A comprehensive, multi-sectoral approach integrating policy reforms, financial mechanisms, digital innovations and community-based strategies is essential to tackle the growing diabetes crisis in Asia. By leveraging emerging technologies, improving healthcare accessibility, and fostering regional collaborations, Asia-Pacific countries can build resilient and inclusive diabetes care ecosystems. Continued investment in healthcare infrastructure, digital transformation and workforce development will be critical in ensuring long-term, sustainable improvements in diabetes management across the region.

Acknowledgements

Medical writing and editorial assistance were provided by BioQuest Solutions Pvt. Ltd, funded by Becton Dickinson.

Statement of Authorship

All authors fulfilled ICMJE authorship criteria.

CRediT Author Statement

DSLG, JKM, SK: Conceptualization, Writing – original draft preparation, Writing – review and editing; **IK, BS, KS, SB**: Writing – review and editing; **MLV:** Writing – review and editing, Funding acquisition.

Data Availability

No datasets were generated or analysed for this study.

Author Disclosure

DSLG received speaker fees and honorariums from Roche, Sanofi, BD/Embecta, Abbott Diabetes Care, Medtronic, and Novo Nordisk. Received advisory fees from BD/Embecta, DKSH, and Novo Nordisk. **JKM** is a member of the advisory boards of Abbott Diabetes Care, Becton-Dickinson/Embecta, Dexcom, Biomea, Eli Lilly, Medtronic, MyLife, Novo Nordisk, Pharmasens, Roche Diabetes Care, Sanofi, Tandem, Viatris, received speaker honoraria from Abbott Diabetes Care, A. Menarini Diagnostics, Becton-Dickinson/Embecta, Dexcom, Eli Lilly, MedTrust, Novo Nordisk, Roche Diabetes Care, Sanofi, Ypsomed and is a shareholder of decide Clinical Software GmbH, elyte Diagnostics. **SK** received speaker fees from Boehringer Ingelheim, Novo Nordisk, and Sanofi. **MLV** received speaker fees and an honorarium from Bayer. **SB** is an employee and stockholder of BD/Embecta (formerly BD Diabetes Care), a manufacturer of a range of insulin delivery devices. No other potential conflict of interest relevant to this article was reported by the rest of the authors.

Funding Source

Medical writing and editorial support were funded by Becton Dickinson/Embecta (formerly BD Diabetes Care), Singapore, a manufacturer of a range of insulin delivery devices, in accordance with GPP 2022 guidelines (https://www.ismpp.org/gpp-2022).

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CASE REPORT

The Lingering Battle of Persistent Hypoaldosteronism Following Adrenalectomy for Primary Aldosteronism: A Case Report

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Abstract

Persistent hypoaldosteronism post-adrenalectomy for unilateral primary aldosteronism is not uncommon and should be anticipated in patients with risk factors for development of such condition. Most cases of hypoaldosteronism post-adrenalectomy are transient. However, persistent hypoaldosteronism may occur as a result of delayed recovery of contralateral zona glomerulosa suppression, requiring mineralocorticoid replacement for the prevention or treatment of life-threatening hyperkalemia.

Key words: hypoaldosteronism, post-adrenalectomy, unilateral primary aldosteronism, hyperkalemia

INTRODUCTION

Incidence of persistent hypoaldosteronism post-adrenalectomy for unilateral primary aldosteronism is reported to be between 5%-7.3% of adrenalectomized patients.[1-3] Management is challenging due to the lack of clear guidelines or expert consensus to recommend the best practice or follow-up for such cases.

We report a case of persistent hypoaldosteronism that was diagnosed nearly 5 years post-adrenalectomy with the first onset of hyperkalemia occurring at 10 months post-operatively. Hypoaldosteronism was not readily recognized due to the concomitant use of potassium supplement and renin-angiotensin-system (RAS) inhibitors post-operatively and the competing differential diagnosis of type 4 renal tubular acidosis (RTA) secondary to diabetic nephropathy.

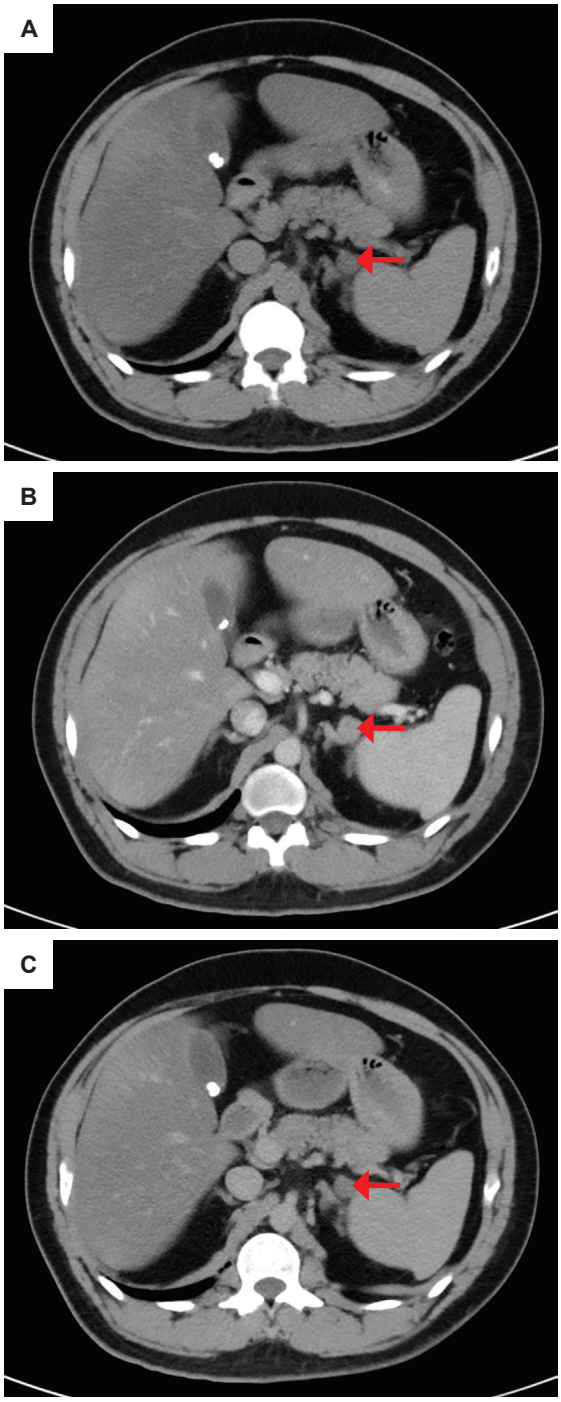
CASE

A 58-year-old Malay male was diagnosed with primary aldosteronism in 2016. His primary symptom was an 11-year history of hypertension. At initial presentation, he required three antihypertensive agents, excluding diuretics, with spontaneous hypokalemia requiring potassium supplementation. His plasma aldosterone was 859.4 pmol/L (normal upright: 102.5-1196.6) and direct renin 3.7 mU/L (normal upright: 5.3-99.1), giving an aldosterone renin ratio of 232 pmol/L:mU/L (positive >35) while on non-interfering medications. Plasma aldosterone was not suppressible on a seated saline infusion test, 340.1 pmol/L (normal <170 pmol/L). CT adrenal showed a well-defined homogenous mass abutting the body and lateral limb of the left adrenal gland (Figures 1 and 2), measuring 1.6 cm x 1.7 cm x 1.2 cm. The average attenuation of the adrenal lesion on non-enhanced CT was 8 HU, 70 HU on venous phase and 34 HU on delayed phase, giving an absolute washout of 58.1% and relative washout of 51.4%. Overall, features were suggestive of a left adrenal lipid-rich adenoma. The right adrenal gland was normal in appearance. He underwent continuous cosyntropin infusion with sequential bilateral adrenal venous sampling (AVS) which demonstrated left-sided lateralization; left adrenal vein aldosterone cortisol ratio to right adrenal vein aldosterone cortisol ratio of 9:1 (cortisol-corrected aldosterone ratio from high-side to low-side of more than 4:1 indicates unilateral aldosterone excess).[4] Both adrenal veins were successfully cannulated with the left and right adrenal vein to peripheral vein cortisol ratio respectively being more than 5:1 (adrenal/peripheral vein cortisol ratio more than 5:1 confirms successful catheterization).[4] The contralateral suppression index was 0.33, indicating that the aldosterone-cortisol ratio in the contralateral adrenal vein was no higher than the peripheral, again confirming contralateral suppression.[4] Due to his initial reluctance for operation, he was started on spironolactone. However, at a dose of 50 mg daily he developed gynecomastia and spironolactone was stopped after less than a year of use. His other comorbidities included severe obstructive sleep apnea and Type 2 Diabetes Mellitus (T2DM). He was also overweight with a BMI of 27 kg/m^2. Of note, his renal profile was normal, creatinine 89 μmol/L and there was presence of microalbuminuria.

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Tan et al.
Received: August 12, 2025. Accepted: September 9, 2025.
Published online first: April 27, 2026.
https://doi.org/10.15605/jafes.041.01.5151

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$$\text{Absolute Washout} \quad \frac{(70-34)}{(70-8)} \times 100 = \frac{36}{62} \times 100 \approx 58.06\%$$

$$\text{Relative Washout} \quad \frac{(70-34)}{70} \times 100 = \frac{36}{70} \times 100 \approx 51.43\%$$

Figure 1. A well-defined homogenous mass *(red arrow)* seen abutting the body and lateral limb of the left adrenal gland, measuring 1.6 cm x 1.7 cm x 1.2 cm. The average attenuation was 8 HU on non-enhanced CT **(A)**, 70 HU on venous phase **(B)** and 34 HU on delayed phase **(C)**, with washout characteristics suggestive of left adrenal lipid-rich adenoma.

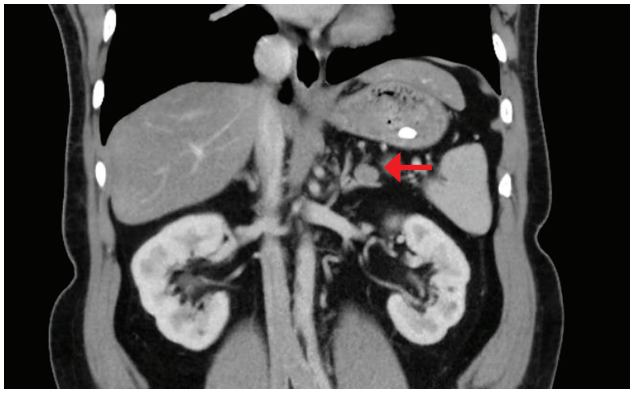


Figure 2. Left adrenal nodule *(red arrow)* as seen on CT adrenal in coronal view.

Three years after the diagnosis of PA, he underwent laparoscopic left adrenalectomy with histology confirming a benign adrenocortical adenoma and the adrenal nodule size was 2.0 cm x 2.0 cm x 1.5 cm on pathology. Post-operatively, he was kept on a reduced dose of potassium supplement and maintained on perindopril 4 mg daily, bisoprolol 2.5 mg daily and amlodipine 10 mg daily. Potassium level at day 2 post-operation was 3.9 mmol/L (Table 1). Two months later, he was seen in the clinic with a blood pressure of 126/80 mmHg and laboratory results showing potassium level 5.0 mmol/L (3.5-5.1), sodium 136 mmol/L (136-145) and creatinine 98 μmol/L (64-104). He was taken off bisoprolol and potassium supplement while perindopril and amlodipine were both continued.

Ten months after adrenalectomy, he was hospitalized and required emergency treatment for severe hyperkalemia (potassium level 6.3 mmol/L) which entailed a lytic cocktail (consisting of intravenous calcium gluconate, dextrose infusion and intravenous insulin). During his subsequent clinic visits, his potassium level ranged from 4.8 mmol/L to 5.7 mmol/L, coinciding with an increment in his serum creatinine, between 124 μmol/L to 143 μmol/L. He was advised dietary potassium restriction and perindopril was withheld 2 years later. In spite of this, hyperkalemia continued to recur at subsequent clinic visits, culminating in another admission in which lytic cocktail again was given for a potassium of 6.4 mmol/L, followed by a short course of oral calcium polystyrene sulfonate upon discharge.

Type 4 RTA was considered as a cause of the hyperkalemia in view of his background T2DM with microalbuminuria pre-operatively but a normal direct renin level (20.70 mU/L) and resolution of microalbuminuria after adrenalectomy made this diagnosis unlikely.

At 57 months post-adrenalectomy, he remained hyperkalemic (potassium 5.5 mmol/L), with sodium 139 mmol/L and creatinine 140 μmol/L. He was normotensive (blood pressure 135/88 mmHg) on single agent of felodipine 10 mg daily. Fludrocortisone 0.05 mg daily was prescribed empirically for the probable diagnosis of persistent hypoaldosteronism after blood was taken for plasma renin

Table 1. Laboratory results after adrenalectomy and prior to fludrocortisone replacement

Test	Reference range	Post-op Day 2	Jan-2020	Jun-2020	Oct-2020	Jan-2021	Sep-2021	Jan-2022	Sep-2022	Jan-2023	May-2023	Oct-2023	Jan-2024	Aug-2024
Sodium, mmol/L	136 - 145	143	136	NA	133	137	137	137	138	140	138	138	135	139
Potassium, mmol/L	3.5 - 5.1	3.9	5	4.6	6.3	5.1	4.8	5.5	5.4	5.8	6.5	5.6	4.9	5.5
Urea, mmol/L	3 - 9.2	5.1	7.2	NA	8.6	6.5	6.9	7.5	7.1	9.7	11.7	6.4	5.6	7.1
Creatinine, µmol/L	64 - 104	93	98	124	143	125	118	128	131	171	184	151	126	140

N/A – Not available

and aldosterone levels. Upon review in the clinic two months after initiated on fludrocortisone, potassium level had normalized to 4.7 mmol/L, sodium 142 mmol/L and creatinine stabilized at 125 µmol/L. Blood investigations prior to mineralocorticoid replacement revealed direct renin concentration to be normal at 39 mU/L (normal upright: 5.3-99.1) whereas plasma aldosterone was undetectable at less than 103 pmol/L.

Five months after fludrocortisone, blood pressure was 138/83 mmHg with potassium 5.1 mmol/L, sodium 136 mmol/L and creatinine at 129 µmol/L. He did not require further admission following the commencement of fludrocortisone. However, due to the presence of pedal edema, dosage of fludrocortisone was not escalated and oral furosemide was added. Follow-up visit 1 year after the initiation of fludrocortisone, his edema improved on the loop diuretic and he remained normokalemic with latest creatinine level at 109 µmol/L.

DISCUSSION

Surgery is the definitive treatment for unilateral primary aldosteronism, offering biochemical and/or clinical successes in the majority of cases. In unilateral primary aldosteronism, excess autonomous aldosterone production from the hypersecreting aldosterone-producing adenoma (APA) suppresses renal renin release, resulting in the suppression of the contralateral zona glomerulosa function.[3] With adrenalectomy, aldosterone level falls acutely creating a state of hypoaldosteronism as the contralateral zona glomerulosa may take one to four months for functional recovery.[3] Patients are at risk for hyperkalemia secondary to hypoaldosteronism made worse by the reduced glomerular filtration rate (GFR) brought about by the reversal of aldosterone-mediated hyperfiltration after surgical intervention.[3] The usual recovery of the renin-angiotensin-aldosterone system (RAAS) after unilateral adrenalectomy is relatively rapid, therefore avoiding the need for mineralocorticoid replacement. Reasons for such reversibility are attributed to the presence of other key regulators of aldosterone secretion namely potassium and ACTH which control the contralateral aldosterone production and thus preserve some degree of functional activities in the contralateral adrenal gland.[1,5] Interestingly, a prospective study by Livia et al., following up on cases of post APA adrenalectomy found that aldosterone took longer than renin to recover (60 vs. 15 days; p <0.02) and patients with higher aldosterone of ≥1442.6 pmol/L at diagnosis, had later recovery (p = 0.03), indicating that renin and aldosterone recoveries did not occur at the same rates.[6] The same study also demonstrated that despite the hypoaldosteronism, ACTH and cortisol levels were unaffected post adrenalectomy.[6]

The term "zona glomerulosa insufficiency" was coined by Fischer et al., and is defined as a state of hypoaldosteronism with undetectable plasma aldosterone level (<35 ng/L or 67.1 pmol/L) in the presence of hyperkalemia, potassium more than 5.0 mmol/L after adrenalectomy.[1] Hyperkalemia occurring postoperatively can be transient or persistent with the latter being defined as hyperkalemia lasting more than three months and has to be treated medically.[1]

Onset of hyperkalemia is described to occur as early as one week to as late as three months post adrenalectomy. In this case, hyperkalemia was detected at 10 months post adrenalectomy while he was still on angiotensin-converting enzyme inhibitor (ACEI), necessitating hospitalization for emergency treatment and correction of hyperkalemia. The occurrence of hyperkalemia was also associated with a sharp rise in creatinine, making acute kidney injury an important consideration as the cause of hyperkalemia. Acute kidney injury can develop from decreased intravascular volume associated with hypoaldosteronism and this can usually be treated with isotonic fluid resuscitation.[7]

The use of perindopril could give rise to type 4 hyperkalemic RTA, in which ACEI decreases the production of aldosterone by inhibiting the conversion of angiotensin I to angiotensin II, giving a normal-to-high renin level and low aldosterone levels. However, stopping perindopril did not appear to resolve the issue of hyperkalemia which made type 4 RTA secondary to perindopril unlikely to be the culprit.

With the persistent hyperkalemia, another plausible differential diagnosis included type 4 RTA secondary to diabetic nephropathy, a condition characterized by hyporeninemic hypoaldosteronism that is mediated by the destruction of the juxtaglomerular apparatus due to vascular hyalinosis.[8] As his direct renin concentration was not low on follow-up and given that his T2DM was well-controlled (HbA1c 6.4%) on single oral glucose-lowering agent with lack of other target organ damage, type 4 RTA caused by diabetic nephropathy was considered to be less likely. Diagnosis of persistent hypoaldosteronism was made much later at 57 months post-adrenalectomy and this was supported by an undetectable plasma aldosterone level with a normal upright renin level in the presence of hyperkalemia.

The etiology of persistent hypoaldosteronism post adrenalectomy for unilateral primary aldosteronism has not been clear-cut. Among the possible mechanisms include decreased contralateral adrenal mass or atrophy of the zona glomerulosa cells due to chronic renin suppression, stunting of the contralateral adrenal gland from severe and prolonged disease duration, and that the sustained hypokalemia before adrenalectomy may have suppressed the aldosterone synthesis in the zona glomerulosa and prolonged the duration of hypoaldosteronism.[3,9,10] Both hyporeninemic and hyperreninemic hypoaldosteronism have been described in patients with persistent post-operative hypoaldosteronism.[1] Irreversible damage to the juxtaglomerular apparatus from hypertension and/or other detrimental renal effects of aldosterone excess have been postulated to explain the hyporeninemic state post-adrenalectomy.[1] Nevertheless, renin deficiency was not the cause of sustained hypoaldosteronism in this case vignette where aldosterone production was still suppressed despite normalization of renin level. The dissociated renin and aldosterone levels reflected the underlying problem perhaps stemmed from defect in the synthetic capability of the contralateral adrenal gland. A study by Wada et al., also showed that renin concentration post-adrenalectomy was not significantly different between the persistent hypoaldosteronism group versus the group without this condition.[11] It is unknown how long persistent hypoaldosteronism may last given the limited longitudinal studies done on such patients, although in one of the literatures hyperkalemia was reported to occur even up to 46 months post-adrenalectomy.[1]

Predictors of hyperkalemia post-adrenalectomy include older age, longer duration of hypertension, impaired renal function pre- and post-adrenalectomy, presence of micro-albuminuria post-adrenalectomy, larger adrenal mass size on pathology and higher pre-operative aldosterone level.[1-3,12] This patient had longstanding hypertension of 14 years prior to adrenalectomy, to which Park et al., found that duration of hypertension greater than 9.5 years was associated with 10.5 times higher risk of developing hyperkalemia.[2] This patient was 52 years old at the time of operation which was approximate to the older age cut-off of 53 years old as demonstrated by the same authors to pose higher risk for hyperkalemia post-adrenalectomy (odds ratio 15.6).[2] The normal creatinine level prior to operation did not rule out underlying renal disease as the excess aldosterone induces vasodilation in afferent and efferent arterioles, giving rise to intraglomerular hypertension and glomerular hyperfiltration, resulting in a seemingly normal renal function. In a large Italian PAPY trial by Rossi et al., the adjusted 24-hour urine albumin excretion rate, an early marker of renal injury was significantly higher in the patients with primary aldosteronism than in the essential hypertension group.[13]

Microalbuminuria was present in this patient prior to operation, indicating early renal involvement. The reversal of aldosterone-mediated hyperfiltration by adrenalectomy unmasked the true extent of the underlying renal injury, which was manifested by a decline in GFR seen upon follow-up in this case. Adrenal mass size of more than 1.95 cm on pathology was seen to predict a higher risk of post-operative hyperkalemia (adjusted OR 5.78) and in this case, the size of the resected adrenal nodule was more than 1.95 cm at its widest dimension.[2] Contralateral gland suppression index (CSI) of less than 0.47 was found to have good sensitivity but low specificity (AUC 0.69, sensitivity 100% and specificity 28.9%) to predict post-operative hyperkalemia.[14] CSI in this case was 0.33, reflecting a greater degree of contralateral adrenal gland suppression and therefore would need close monitoring of serum potassium post-operatively. The role of mineralocorticoid receptor antagonist in the development of post-operative hyperkalemia is controversial. Spironolactone was observed to have a direct inhibitory effect on adrenal steroidogenesis and long-term use had been associated with spontaneous remission of primary aldosteronism.[15] However, few large studies concluded that pre-operative use of mineralocorticoid receptor antagonists in fact did not appear to influence the incidence of hypoaldosteronism or hyperkalemia.[1,2] In this case, spironolactone was withheld more than 1 year prior to adrenalectomy and the seemingly short duration of use limited by adverse effect of gynecomastia made it unlikely to be the main cause of persistent hypoaldosteronism by mechanism of impairing aldosterone synthesis in this patient.

The Endocrine Society 2016 recommended withdrawing potassium supplementation and discontinuing spironolactone post-operatively and a generous sodium diet during the first few weeks after surgery.[4] In addition to these preventive measures and instituting a low potassium diet, reversible causes should be addressed in high-risk patients such as hypovolemia, urinary tract obstruction and use of non-steroidal anti-inflammatory drugs and RAAS inhibitors which can contribute to or aggravate hyperkalemia by reducing further an already impaired GFR.[12] In our case, the continuity of ACEI and potassium supplementation albeit at a lower dose could have contributed to the severity of hyperkalemia on top of the potentiating effect of hypoaldosteronism. Monitoring of electrolytes post adrenalectomy has not been standardized. Tahir et al., advocated potassium monitoring at day 2, 14 and 28 post-operation for high-risk groups and monthly monitoring thereafter for mild hyperkalemia (potassium <5.5 mmol/L) till it resolves.[12] Pharmacological therapies for more severe hyperkalemia, i.e., potassium more than 5.5 mmol/L include fludrocortisone, sodium bicarbonate, loop diuretics and potassium binders with treatment choice tailored according to volume status, blood pressure and renal function.[12] Limited by the movement restrictions during the COVID-19 pandemic in 2020, electrolyte monitoring was done at four- to five-month intervals after the initial post-operative clinic review. This may have resulted in delay in the detection of hyperkalemia only at 10 months post adrenalectomy.

Fludrocortisone is the drug-of-choice for the treatment of persistent hypoaldosteronism in this case given the protracted course of disease and absence of contra-indications. Few case studies reported successes after stopping pharmacological therapies at certain point in time with resolution of hyperkalemia or symptomatology related to hypoaldosteronism, while others were unsuccessful due to the recurrences of electrolyte abnormalities such as hyperkalemia, hyponatremia with or without increment in creatinine level.[9,10,12,16-18] Long-term use of fludrocortisone is limited by side effects such as hypertension, peripheral edema and worsening heart failure in those with pre-existing cardiovascular disease.[12] Mineralocorticoid replacement, if indicated, should be administered in physiological doses to avoid hypervolemia and associated suppression of renin and aldosterone secretion.[5] Taniguchi et al., recommended mineralocorticoid replacement to be used as short-term, if possible, to avoid retarding the recovery of the contralateral adrenal to synthesize aldosterone.[19] Further discussions with the patient regarding the optimal timing for fludrocortisone discontinuation to permit recovery of endogenous renin and aldosterone production are required, while carefully weighing the risks and benefits of long-term fludrocortisone therapy.

CONCLUSION

With the increasing number of adrenalectomies done for unilateral primary aldosteronism, clinicians need to be familiar with the potential complications that may arise from the operations, mainly hypoaldosteronism leading to hyperkalemia which may be accompanied by other electrolytes and hemodynamic perturbations. Certain risk factors predispose to post-operative hyperkalemia and identification of such risk factors would warrant close monitoring and implement early preventive measures to prevent catastrophic complications or morbidities. The vast benefits of surgery in unilateral primary aldosteronism should not be offset by the resulting hypoaldosteronism that follows the reversal of aldosterone excess. Optimal duration of mineralocorticoid replacement to date remains unclear. Treatment for hyperkalemia resulting from persistent hypoaldosteronism is not standardized and is largely based on anecdotal reports. More studies would be needed to formulate guidelines on treatment and follow-up on cases of persistent hypoaldosteronism and to identify biomarkers to predict recovery of aldosterone secretion in such challenging cases. This case report highlights the importance of close monitoring of serum potassium, early recognition and timely initiation of appropriate treatment for persistent hypoaldosteronism following unilateral adrenalectomy for primary aldosteronism.

PATIENT PERSPECTIVE

"I'm glad that I no longer need to follow any dietary restrictions since starting on fludrocortisone. Although I experienced leg swelling at the beginning of the treatment, it resolved after furosemide was added. My doctor recently told me that my kidney function has improved, and I haven't needed any hospitalization for high potassium levels over the past year. Overall, I am satisfied with the management."

Acknowledgments
Special acknowledgments to the entire Endocrinology team and Pathology Department from Sultanah Bahiyah Hospital for the support.

Ethical Consideration
Patient consent forms were obtained before manuscript submission.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JET: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **NSYAM:** Validation, Writing – review and editing, Supervision; **SI:** Validation, Writing – review and editing, Supervision; **NRAA:** Validation, Writing – review and editing, Supervision.

Data Availability Statement
No datasets were generated or analyzed for this study.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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CASE REPORT

A Rare Paediatric Adrenocortical Carcinoma with Aggressive Clinical Course

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Abstract

Adrenocortical carcinomas are among the rarest and most aggressive paediatric endocrine neoplasms. We report a case of a functional adrenocortical carcinoma in a 6-year and 7-month-old female who initially presented with hypertensive encephalopathy, later progressing to overt Cushing syndrome with refractory hypertension. Given the presence of distant metastases, the patient was commenced on neoadjuvant chemotherapy and mitotane. Genetic testing for *TP53* to evaluate Li-Fraumeni syndrome was declined. Despite initial response to the treatment, the disease remained refractory, and the patient succumbed after seven months of therapy.

Key words: paediatrics, Cushing Syndrome, adrenocortical carcinoma, antineoplastic agents, hormonal, mitotane, ketoconazole

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy of the adrenal gland, associated with an unfavourable prognosis. In paediatric populations, adrenocortical tumours are exceedingly uncommon, representing only 0.2% of all childhood cancers with an annual incidence estimated at 0.3 cases per million individuals.[1] It commonly occurs within the first five years of life, with a median age of diagnosis between 3 and 4 years, and a smaller secondary peak during adolescence. A female predominance is reported, with a reported female-to-male ratio of 1.6:1.[2]

ACC presents with a broad spectrum of clinical manifestations, most commonly virilization, Cushing syndrome or a combination of both. It is strongly associated with constitutional genetic abnormalities, particularly *TP53* gene mutations, which are implicated in approximately two-thirds of cases.[3,4] The fetal zone of the adrenal cortex is thought to be especially vulnerable to adenoma or carcinoma formation due to the loss of *p53* function. Notably, the endemic *TP53* R337H germ line mutation in Southern Brazil significantly increases the incidence of paediatric adrenocortical tumours there, with rates estimated to be at least 15 times higher than in other regions.[5,6]

Distant metastases and large tumour volume remain the most critical adverse prognostic factors, underscoring the poor outcomes often associated with this malignancy.[7]

We present a case of functional adrenocortical carcinoma in a 6-year and 7-month-old female who initially presented with hypertensive encephalopathy and hypokalaemic hypochloraemic metabolic alkalosis. Ten months later, she then presented with overt Cushing syndrome, refractory hypertension, virilization, extensive fungal skin infection and severe back pain caused by multiple vertebral compression fractures. This case underscores the educational value of recognizing early the evolving clinical manifestations of paediatric ACC, as timely diagnosis is crucial for optimizing management and improving prognosis.

CASE

The female patient first presented to a health clinic at age 5 years and 9 months with a chief complaint of worsening facial acne over a period of eight months. During the consultation, she was incidentally found to be hypertensive, with a blood pressure reading of 185/128 mmHg. She was subsequently referred to a district hospital for further evaluation. Her parents denied any history of rapid weight gain or features suggestive of virilisation. On initial assessment, her weight and height were at the 25th percentile. Clinical examination revealed facial acne and hirsutism, but no clitoromegaly. Within the first 24 hours of hospitalization, she developed multiple episodes of seizures, necessitating intubation for airway protection. An urgent brain CT scan was performed, which revealed no evidence of acute intracranial haemorrhage or meningeal enhancement.

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Lim and Tee.
Received: August 11, 2025. Accepted: September 2, 2025.
Published online first: April 20, 2026.
https://doi.org/10.15605/jafes.041.01.5167

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Blood investigations revealed hypochloraemic metabolic alkalosis with hypokalaemia, with a pH of 7.50, HCO3 of 39 mmol/L and potassium of 2.1 mmol/L. The patient was managed symptomatically with oral captopril (5 mg TDS) and potassium chloride. No abdominal ultrasound was performed at that stage. She was successfully extubated after 24 hours and discharged in stable condition. However, she subsequently failed to attend her scheduled outpatient follow-up appointments.

Ten months later, the patient presented to the same health clinic with complaints of worsening facial acne and, on this occasion, was referred to our tertiary centre for evaluation of suspected Cushing syndrome. Following her earlier discharge from the district hospital, antihypertensive medications had not been continued, and blood pressure monitoring was not performed, likely due to a limited understanding of her illness. During this period, she had gained 12 kg without any documented increase in height. She had no pubic hair development or clitoromegaly. There was no history of exogenous steroid use. Family history was notable only for breast carcinoma in her maternal aunt, with no other relevant hereditary conditions.

On examination, she was found to be hypertensive with a blood pressure of 180/127 mmHg and a heart rate of 124 beats per minute. She exhibited central obesity with disproportionately thin limbs. Her BMI was 30.2 kg/m^2, with a height of 106 cm (<3rd percentile) and a weight of 34 kg (>97th percentile). She appeared plethoric with extensive pustular acne lesions and hirsutism, but there was no evidence of clitoromegaly (Figure 1). Additional findings included multiple purplish striae, generalised fungal skin infections and a vague palpable mass in the left abdomen. She also demonstrated proximal muscle weakness and tenderness of the spine.

Table 1. Investigations at diagnosis

Investigations	Results	Normal Range [Age Specific]
Serum cortisol (diurnal)	1045.0 nmol/L (6 am), 1057.0 nmol/L (12 mn)	250 – 550 nmol/L <50 nmol/L
24Hour urine cortisol	689.55 nmol/24Hr	<50 nmol/24Hr
Serum ACTH	0.3 pmol/L	1.6 – 13.9 pmol/L
Testosterone	33.41 nmol/L	<0.24 – 0.69 nmol/L
Serum DHEA-S	>27 umol/L	<1 umol/L
Renin	>550 mU/L	5.4 – 30 mU/L (Supine)
Aldosterone	983.50 pmol / L	<1108 pmol/L (Supine)
Thyroid function test	TSH 0.075 mIU/L Free T4 16.19 pmol/L	0.47 – 3.41 mIU/L 11.4 – 17.6 pmol/L
HbA1c	5.2%	<5.7 %

Hormonal investigations demonstrated a non-ACTH-dependent hypercortisolism with hyperandrogenism (Table 1). The abdominal ultrasound revealed a large heterogeneous mass in the left suprarenal region, multiple liver lesions and bilateral medullary nephrocalcinosis. Subsequent computed tomography of the thorax, abdomen and pelvis (CT TAP) confirmed the above findings. The large lobulated, heterogeneously enhancing left adrenal mass (8.1 x 9.3 x 8.7 cm) caused significant mass effect, including inferior displacement of the left kidney and resulting in left renal vein thrombosis (Figure 2). Additional findings included multiple lung nodules and liver lesions, consistent with distant metastases. Her lateral spine X-ray demonstrated multiple vertebral compression fractures and generalised osteopenia (Figure 3). A formal echocardiogram revealed left ventricular hypertrophy. However, the patient had no evidence of hypertensive retinopathy and she remained euglycaemic. Her blood pressure was controlled with four antihypertensive medications (captopril, prazosin, amlodipine and spironolactone) at near-maximal dosages.

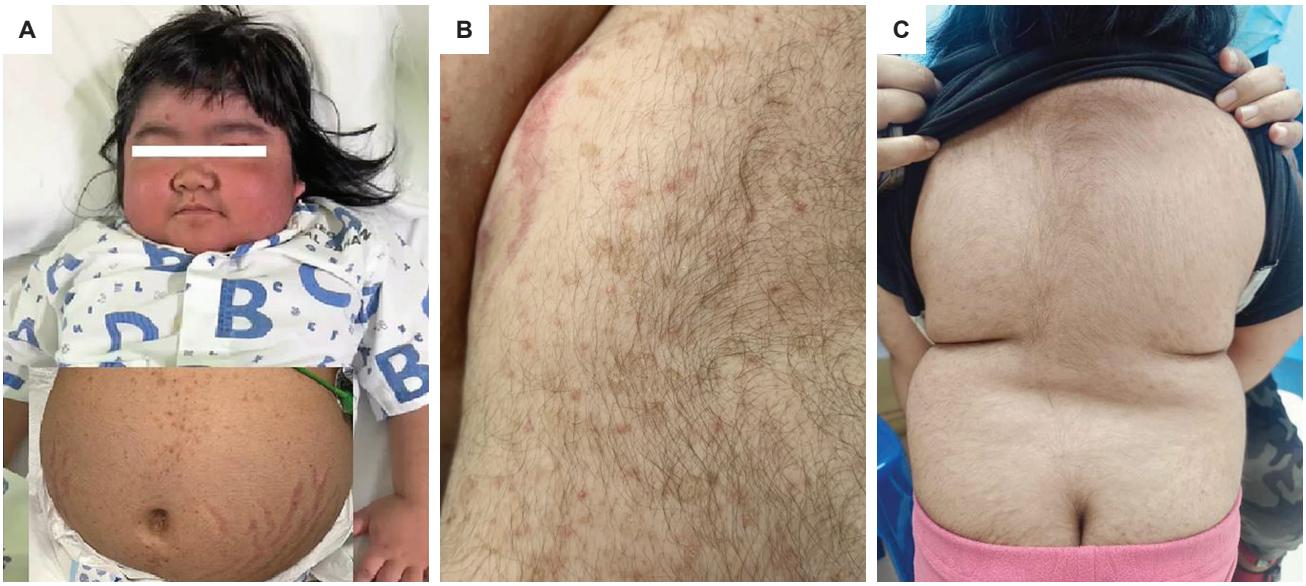


Figure 1. (A) Clinical features of the patient include a plethoric face with extensive pustular acne lesions, hirsutism, **(B)** multiple purplish striae, and **(C)** central obesity.

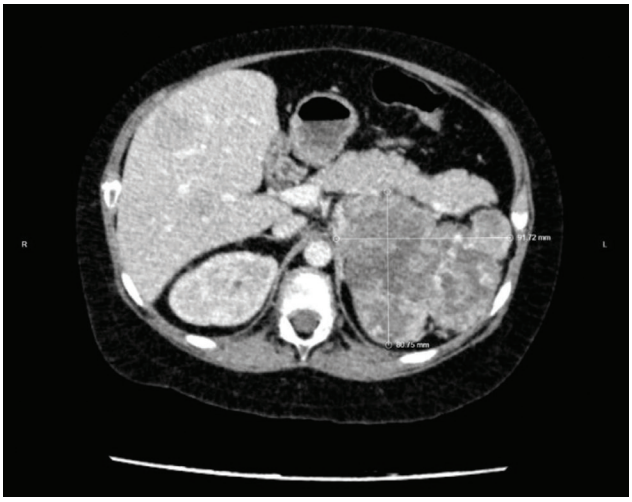


Figure 2. Thoracic, abdominal and pelvic CT revealed a large lobulated, heterogeneously enhancing left adrenal mass (8.1 x 9.3 x 8.7 cm) causing significant mass effect, including inferior displacement of the left kidney.

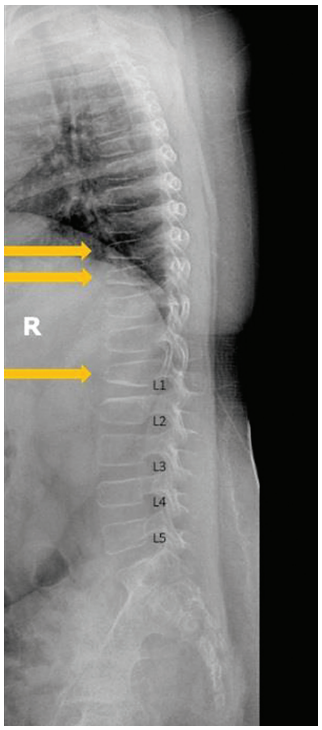


Figure 3. Lateral spine X-ray demonstrated multiple vertebral compression fractures at T9, T10 and L1 *(yellow arrows)* with generalized osteopenia.

The diagnosis of ACC was made based on the non-ACTH-dependent hypercortisolism and hyperandrogenism in the context of a large adrenal mass that demonstrated malignant behaviour. While complete surgical removal of the tumour is the gold standard, it was not feasible due to its substantial size and distant metastases. Neoadjuvant chemotherapy was initiated following the ARAR0332 Stage III/IV protocol,[8] which consisted of IV Cisplatin: 50 mg/m²/day (Days 1–2), IV Etoposide: 100 mg/m²/day (Days 1–3) and IV Doxorubicin: 25 mg/m²/day (Days 4–5). Oral mitotane, an adrenolytic agent, combined with oral ketoconazole, a fast-acting steroidogenesis inhibitor, was started on Day 8 of chemotherapy. Mitotane tablets were crushed and mixed with 10 mL of milk and administered before feeding, starting at 1 g/m²/day. Ketoconazole was initiated at 100 mg daily and increased by 100 mg/day every 3-5 days if liver enzymes remained normal, up to 800 mg/day.

The patient experienced severe complications from her 1st cycle of chemotherapy. She developed nosocomial pneumonia requiring intubation, as well as profuse diarrhoea after initiating mitotane. Additionally, transient transaminitis was observed when the oral ketoconazole dose reached 400 mg/day. Due to severe gastrointestinal symptoms, mitotane was temporarily withheld and later reintroduced at a lower dose with a more gradual titration.

Following two cycles of chemotherapy and while on oral mitotane at 3 g/m²/day, the patient demonstrated a positive response. Her antihypertensive medications were reduced to two medications, and the persistent hypokalaemia was resolved. Given the adrenolytic effects of mitotane, oral fludrocortisone and hydrocortisone supplementation were initiated. Before the third cycle of chemotherapy, cortisol, testosterone and DHEAS levels had normalised.

The patient was scheduled for the 3rd cycle of chemotherapy followed by tumour resection in accordance with the ARAR0332 Stage III/IV protocol. However, her parents were not keen on further chemotherapy and requested discharge. When she was eventually readmitted to the hospital, her condition had significantly deteriorated, with biochemical parameters indicating recurrent hypercortisolism and hyperandrogenism.

She also experienced severe back pain due to the progression of multiple vertebral compression fractures. Disease re-evaluation revealed further progression, including an increased number of lung nodules, along with a mixed response in her original adrenal and liver lesions.

Following repeated discussions with the patient and her family, they opted for symptomatic and palliative care. Her respiratory status further worsened, requiring non-invasive ventilation support. Eventually, she succumbed to her illness.

DISCUSSION

The patient presented with a typical functional adrenocortical tumour phenotype, characterised by virilisation and hypercortisolism, the latter manifesting as endocrine hypertension noted on initial presentation. A retrospective cohort study involving 41 paediatric patients[9] indicates that mixed symptomatology is the most common presentation. In particular, virilisation in a prepubertal female is an alarming feature that warrants extensive investigation to identify the underlying cause,[10] and in this context,

should raise a strong suspicion for an adrenal tumour. Despite the dramatic clinical presentation, delayed diagnosis is not uncommon, which is often attributed to physicians' unfamiliarity with this disease entity.[11]

Hyperandrogenism and ACTH-independent hypercortisolism are pathognomonic of adrenocortical tumours, making it crucial to exclude adrenocortical carcinoma (ACC). In our patient, biochemical evidence of mineralocorticoid excess was observed, as indicated by hypokalaemia and hyperchloraemic metabolic alkalosis. However, there was no evidence of hyperaldosteronism; instead, the aldosterone levels were suppressed, likely due to excessive cortisol exerting a mineralocorticoid effect. Additionally, the elevated renin level detected in our patient was suggestive of left renal vein thrombosis secondary to tumour invasion, a common occurrence in locally advanced ACC.

Definitive diagnosis is based on the gross and histological appearance of surgically obtained tissue, as per the Wieneke criteria. Where feasible, early surgical removal of the tumor is vital for both treatment and diagnostic purposes. Successful tumor removal is associated with better outcomes. Fine needle adrenal biopsy is not recommended due to the friability of the tumor, capsule rupture leading to tumour spillage or needle tract metastases following fine needle biopsy, which are associated with a poorer prognosis.[8] Consequently, the diagnosis of ACC in this patient was initially established based on typical clinical, biochemical and imaging findings.

Given the advanced disease stage, we initiated combination chemotherapy with etoposide, doxorubicin, cisplatin and mitotane as per the ARAR0332 protocol.[8] An important goal is rapid normalisation of cortisol levels, which is crucial for controlling refractory hypertension, managing electrolyte imbalances and reducing infection risk. Mitotane, an irreversible and potent adrenolytic agent, requires approximately 14 weeks to reach therapeutic levels. To bridge this gap, we opted for oral ketoconazole, an imidazole antifungal agent widely used 'off-label' for treating hypercortisolism in Cushing's syndrome due to its rapid anti-cortisol effects. Unlike mitotane, there is no standardised ketoconazole dose for anti-cortisol therapy. However, Castinetti et al., reported a final median dose of 200–1200 mg/day in a cohort of 200 patients aged 8–87 years.[12] Liver dysfunction, typically mild and reversible, was observed in approximately 10% of patients, while serious hepatic injury, though rare, can be fatal.[12] Therefore, close monitoring of liver function is warranted.

Due to mitotane's cytotoxic effects on adrenocortical cells, substitutive doses of hydrocortisone and fludrocortisone should be initiated 1–2 weeks after mitotane initiation. The recommended hydrocortisone dose is 2–3 times higher than that used in primary adrenal insufficiency. The ARAR0320 protocol suggests an equivalent hydrocortisone dose of 40–45 mg/m^2/day, considering its significant alteration of steroid hormone metabolism.

Genetic testing for germline *TP53* mutations is essential, even in the absence of a family history suggestive of Li-Fraumeni syndrome. The lifetime penetrance for individuals with this mutation approaches 90%.[13] If a mutation is detected, genetic screening should be considered for family members. However, in this case, the patient's parents declined genetic testing due to financial constraints and concerns regarding potential implications.

The presence of metastases at the time of ACC diagnosis is an independent factor associated with poor prognosis in paediatric patients. The reported two-year survival rate is 39% in patients with metastases at diagnosis, significantly lower than the 93% survival rate observed in patients without metastases.[9] This creates a particularly challenging situation in balancing parental autonomy with the child's best interest, especially when the prognosis is poor and the chances of treatment success are limited.

Our patient experienced significant distress and severe side effects with each cycle of chemotherapy, including neutropenic fever, refractory thrombocytopenia, extensive mucositis and profound fatigue, often requiring at least 2-3 weeks to recover. Her parents perceived that she was suffering with a markedly reduced quality of life and requested discontinuation of chemotherapy, while continuing oral mitotane. This raised an ethical dilemma, prompting extensive discussion on her best interest – carefully weighing the limited potential benefits of further chemotherapy against its high burden of toxicity, in a context of a reported five-year survival rate of less than 20%.

These findings underscore the importance of early detection and timely diagnosis in improving overall survival outcomes in paediatric ACC. The rapid and aggressive clinical course demonstrates the need for clinicians to be alert to the constellation of presenting features, to undertake comprehensive endocrine assessments and to perform targeted imaging at the first presentation.

CONCLUSION

Paediatric ACC is an extremely rare but aggressive malignancy with high morbidity and mortality if not diagnosed and treated promptly. A high index of suspicion is warranted for any child presenting with prepubertal virilisation and Cushing's syndrome, as early detection and intervention can significantly improve prognosis.

Acknowledgments

We would like to express our sincere gratitude to Dr. Asohan Thevarajah, Dr. Song Hai Lim and Dr. Ay Jiuan Teng for their invaluable clinical expertise and guidance in the management of this patient. Their insights and recommendations were instrumental in providing optimal care. We also extend our appreciation to the medical staff of Sabah Women and Children's Hospital for their assistance in the patient's care. Additionally, we are grateful to the patient and their family for their cooperation and willingness to share their experience.

Ethical Consideration
Patient consent forms were obtained before manuscript submission. This study was registered and approved by the Malaysia Medical Research and Ethics Committee (MREC), with NMRR ID: 24-02177-RUX.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
KYL: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **PPT:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – review and editing, Visualization, Supervision, Project administration.

Data Availability Statement

No datasets were generated or analyzed for this study.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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Letter to the Editor

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Letter to the Editor on the article entitled, *'Perioperative Complications Associated with Routine Preoperative Glucocorticoid Use Among Patients Undergoing Pituitary Surgery with Normal Preoperative HPA Axis: A Retrospective Cohort Study,'* by Magnaye and Paz-Pacheco, published in JAFES Vol. 40. No. 1.

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Key words: hypothalamic-pituitary-adrenal axis, glucocorticoids, perioperative complications

This letter addresses the recent study by Magnaye et al., which investigated the impact of routine preoperative glucocorticoid administration in patients with a normal hypothalamic-pituitary-adrenal (HPA) axis undergoing pituitary surgery. The authors are commended for their valuable contribution to understanding steroid-related perioperative outcomes. However, we highlight the need for further clarification regarding the wide range of steroid regimens reported and the absence of detailed information on timing, indications, and factors influencing steroid administration. Additionally, differentiating between transient and permanent postoperative diabetes insipidus could provide deeper insight into the observed higher incidence among steroid-treated patients. Addressing these aspects, along with establishing standardized steroid protocols, could enhance the specificity and clinical applicability of the study's findings.

I recently came across this study by Magnaye et al.,[1] in which the authors have done a commendable job in addressing a clinically important topic, i.e., whether the routine administration of preoperative glucocorticoids in patients undergoing pituitary surgery with a normal hypothalamic-pituitary-adrenal (HPA) axis is actually beneficial in decreasing the rate of perioperative complications such as diabetes insipidus and postoperative infections. The study has done a great job of comparing the effects of steroid vs. non-steroid administration. The important findings highlighted by the authors provide significant and valuable points that shed light on this topic in a very detailed way.

The authors' work is commendable. However, we would like to bring to the authors' attention to some points. The authors have provided a wide range of regimens (mean hydrocortisone equivalent ≈ 142 mg/day, range 50–583 mg/day). In this case, a proper breakdown about timing and any additional indications or factors influencing the decision of steroid administration could have better explained patients having a higher risk of developing complications.[2] Also, the authors have reported a higher incidence of post-operative diabetes insipidus in patients given preoperative steroids (52.5% vs 28.2%, p = 0.006), but specifying the type of diabetes insipidus (permanent or transient) could maybe clear some doubts regarding the underlying cause. Transient diabetes insipidus is often seen after pituitary surgery and could have other causative factors, so the differentiation could have led to other potential causes being identified.[3]

In summary, this study by Magnaye et al., has raised valid concerns regarding the increased risk of certain post-operative infections in patients given steroids pre-operatively. It is truly commendable and provides a good insight into avoiding complications that could arise as a result of unnecessary steroid administration. However, mentioning the above points could add a touch of more specificity to the study. Discussing standardized steroid protocols that support the steroid sparing strategy and specifying the type of diabetes insipidus would help enhance the understanding of outcomes.

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eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Fatimah et al.
Received: October 25, 2025. Accepted: October 25, 2025.
Published online first: April 29, 2026.
https://doi.org/10.15605/jafes.041.01.6257

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RESPONSE OF THE AUTHORS

The authors appreciate the questions raised in relation to the paper "Perioperative complications associated with routine preoperative glucocorticoid use among patients undergoing pituitary surgery with normal preoperative HPA axis: a retrospective cohort study."

We are pleased to know that readers value the issues related to this important clinical condition. In response to the points raised, indeed, these are critical factors that can provide more clarity to the relationship between preoperative steroid use and perioperative outcomes. As described, this was a retrospective study that relied on available data on patients' medical records.

Ascertainment of detailed information on timing, indications and other factors determining choice for steroid administration was limited. Determination of transient versus permanent diabetes insipidus was not specified. Thus, as stated in the paper, it is recommended that a prospective study be carried out with a randomized controlled trial (RCT) design in a larger group of patients. Thereafter, a consensus can be developed and further discussed.

Franz Michael Magnaye and Elizabeth Paz-Pacheco

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Intraductal Papillary Mucinous Neoplasm of the Pancreas Presenting as Worsening Hyperglycemia in a 72-Year-Old Patient with Type 2 Diabetes

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Key words: intraductal papillary mucinous neoplasm (IPMN), worsening glycemic control, first manifestation

Pancreatic cysts are common findings encountered and increasingly detected through cross-sectional imaging. Intraductal papillary mucinous neoplasm (IPMN) is the most common pancreatic cystic neoplasms and may be macroscopic precursor of pancreatic ductal adenocarcinoma.[1] New-onset diabetes or worsening glycemic control may serve as clinical clues to underlying pancreatic neoplasia.[2] We present an interesting case of worsening glycemic control in a patient with long-standing type 2 diabetes (T2D) as the first manifestation of IPMN with high-grade dysplasia.

A 72-year-old Thai male with well-controlled T2DM for 25 years presented with increase in glycated hemoglobin from 6.9% to 8.5% over 3 months, without other accompanying symptoms. He had regular follow-ups every 3-4 months and his glycemic control had never exceeded 7.5% in the past 10 years. His current medications included metformin 2,000 mg per day and simvastatin 20 mg per day. There was no history of new medications or herbal supplements that could contribute to hyperglycemia. To evaluate for occult malignancies, abdominal ultrasonography was performed, revealing a 1.0-cm cystic lesion in the body of the pancreas with diffuse pancreatic ductal dilatation. IPMN with high-risk features (solid component

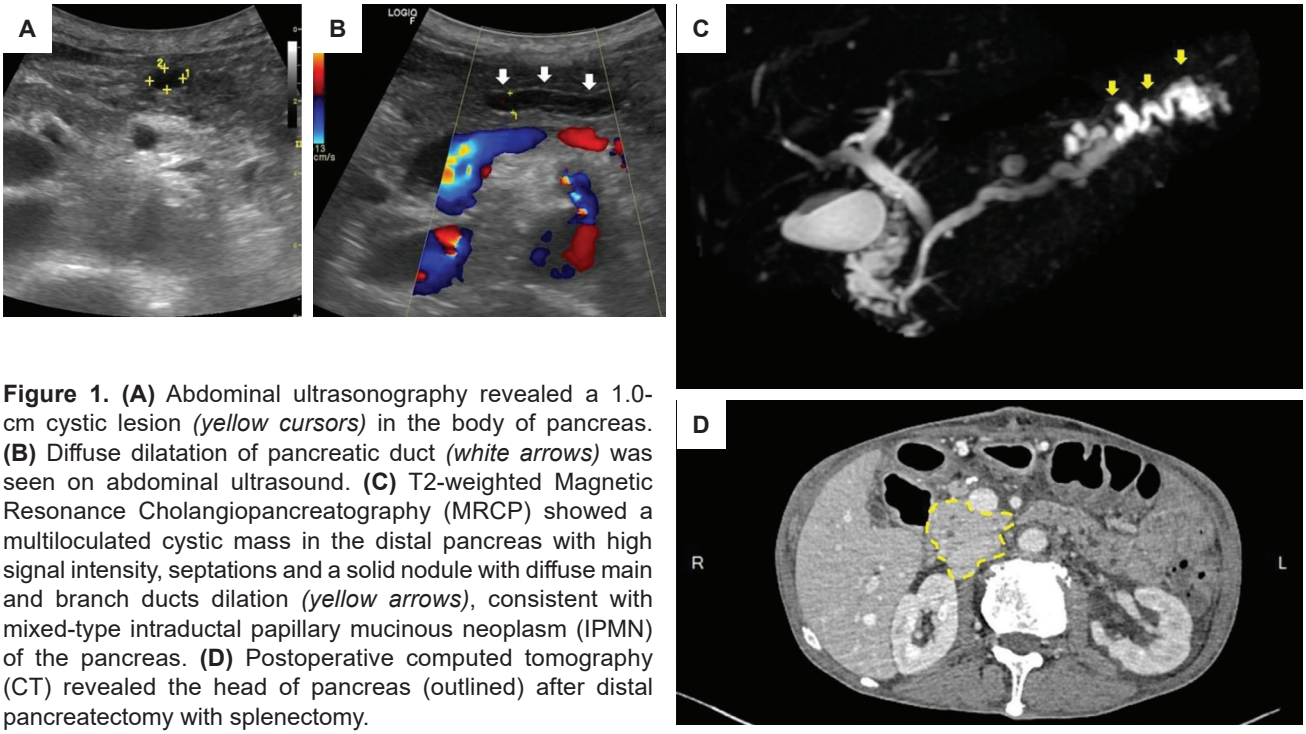


Figure 1. (A) Abdominal ultrasonography revealed a 1.0-cm cystic lesion *(yellow cursors)* in the body of pancreas. **(B)** Diffuse dilatation of pancreatic duct *(white arrows)* was seen on abdominal ultrasound. **(C)** T2-weighted Magnetic Resonance Cholangiopancreatography (MRCP) showed a multiloculated cystic mass in the distal pancreas with high signal intensity, septations and a solid nodule with diffuse main and branch ducts dilation *(yellow arrows)*, consistent with mixed-type intraductal papillary mucinous neoplasm (IPMN) of the pancreas. **(D)** Postoperative computed tomography (CT) revealed the head of pancreas (outlined) after distal pancreatectomy with splenectomy.

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Thewjitcharoen et al.
Received: July 1, 2025. Accepted: August 14, 2025.
Published online first: April 12, 2026.
https://doi.org/10.15605/jafes.041.01.5251

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with internal enhancing septation) was confirmed from T2-weighted Magnetic Resonance Cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS). High amylase and lipase levels in the cystic fluid from presumed side branch cysts suggested continuity with the pancreatic main duct. Subsequently, distal pancreatectomy with splenectomy was performed following shared decision making with the patient. Histologic examination revealed high-grade dysplasia of gastric-type IPMN spreading into the main and branch pancreatic ducts, confirming a diagnosis of mixed-type IPMN with high-grade dysplasia. The patient's post-operative recovery was uneventful, and follow-up imaging was unremarkable. One year later, the patient remains well and is maintained on twice daily insulin treatments.

This case highlights the importance of recognizing worsening glycemic control or new-onset diabetes as potential early indicators of IPMN. Although the pathophysiology of diabetes in IPMN is not fully understood, pancreatic neoplasia has been associated with insulin resistance, possibly through paraneoplastic mechanisms involving altered glycogen synthase and phosphorylase activity.[2] This association is supported by a recent study utilizing MRI-based pancreatic cancer screening in patients with new-onset or worsening diabetes.[3] In conclusion, although rare, IPMN should be considered in the differential diagnosis of unexplained worsening glycemic control. Non-invasive imaging modalities such as abdominal ultrasonography should be employed to detect potential underlying malignancies.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
YT: Conceptualization, Methodology, Writing – original draft preparation; **NT:** Investigation; **VV:** Resources, Visualization; **SN:** Project administration; **TH:** Writing – review and editing, Supervision.

Data Availability Statement
No datasets were generated or analyzed for this research.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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Lingual Thyroid: An Ectopic Presentation at the Base of the Tongue

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Key words: thyroid gland, ectopic, lingual thyroid, scintigraphy

Lingual thyroid is the most common form of thyroid ectopia, resulting from failure of normal caudal migration of the thyroid anlage during embryogenesis.[1] Diagnosis relies on cross-sectional imaging to define anatomy and radionuclide scintigraphy as the gold standard to verify functional thyroid tissue and exclude normally located gland.[2]

The images depict the clinical, radiological, and scintigraphic findings of a 27-year-old woman with ectopic lingual thyroid. Clinical photograph showed a smooth, reddish, round mass at the tongue base (Figure 1). Contrast-enhanced CT in sagittal and axial views demonstrated an enhancing lesion at the posterior tongue with the absence of orthotopic thyroid tissue in the pretracheal area (Figure 2). Tc-99m pertechnetate scintigraphy showed focal tracer uptake in the lingual region (Figure 3), confirming the diagnosis of ectopic thyroid tissue.

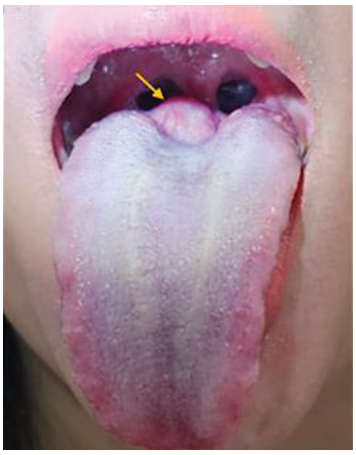


Figure 1. Examination of the tongue revealed a small, smooth, reddish mass located at the base of the tongue.

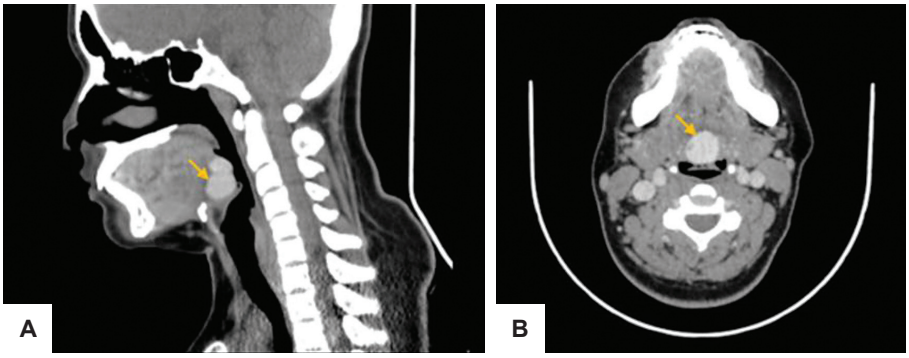


Figure 2. Contrast-enhanced multislice computed tomography (MSCT) of the neck demonstrated an ectopic thyroid gland at the base of the posterior tongue, shown in **(A)** sagittal and **(B)** axial views.

eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2026 by Rifani and Tahapary.
Received: July 16, 2025. Accepted: September 7, 2025.
Published online first: April 26, 2026.
https://doi.org/10.15605/jafes.041.01.6209

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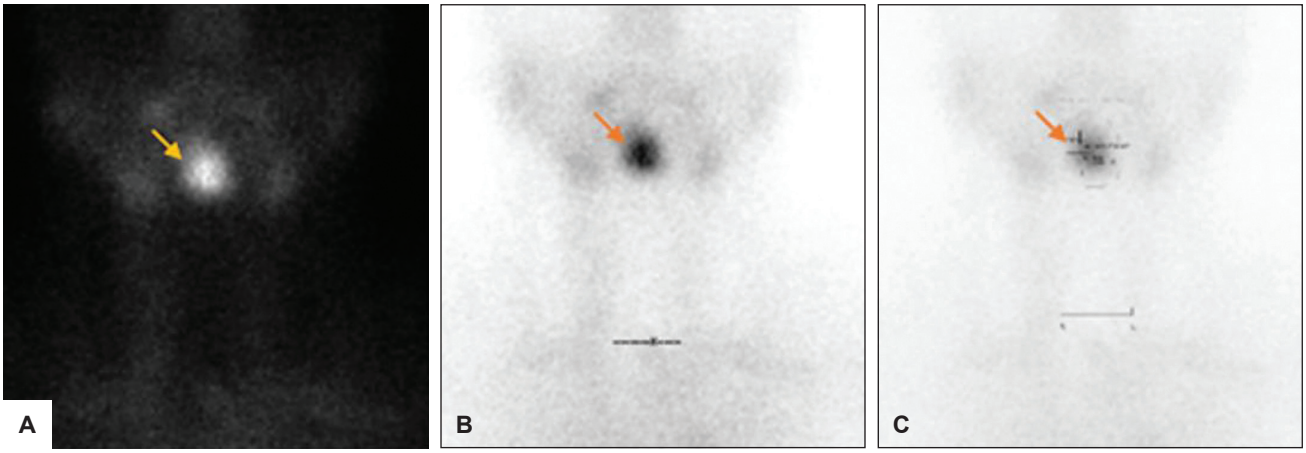


Figure 3. Thyroid scan with technetium-99m showing a round, focal area of radiotracer uptake in the lingual projection. **(A)** Focal area of increased radiotracer uptake in the midline at the base of the tongue *(orange arrow)*. **(B)** Focal radiotracer uptake in the lingual region *(orange arrow)*, suggestive of a lingual thyroid. **(C)** Confirmatory view demonstrating localized uptake at the base of the tongue *(orange arrow)*.

Ethical Consideration
Patient consent forms were obtained before manuscript submission.

Statement of Authorship
Both authors certified fulfillment of ICMJE authorship criteria.

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RR: Conceptualization, Data curation, Visualization, Writing – original draft preparation, Writing – review and editing. **DT:** Conceptualization, Supervision, Writing – review and editing.

Data Availability Statement
No datasets were generated or analyzed for this study.

Author Disclosure
Both authors declared no conflict of interest.

Funding Source
None.

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   2.2. Drafting the work or revising it critically for important intellectual content; AND
   2.3. Final approval of the version to be published; AND
   2.4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
3. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate.
4. Name and location of no more than one (1) institutional affiliation per author may be included.
5. If the paper has been presented in a scientific forum or convention, a note should be provided indicating the name, location and date of its presentation.

Abstract

For original articles, the abstract should contain no more than 500 words with a structured format consisting of the objective/s, methodology, results and conclusion. For feature articles, case reports, interhospital grand rounds, and brief communications, the abstract should be no more than 200 words and need not be structured.

Keywords

At least 3 keywords but no more than 6, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

Text

1. Generally, the text should be organized consecutively as follows: Introduction, Methodology, Results and Discussion, and Conclusion (IMRAD format).
2. All references, tables, figures and illustrations should be cited in the text, in numerical order.
3. All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the long names.
4. All measurements and weights should preferably be in System International (SI) units.
5. If appropriate, information should be provided on institutional review board/ethics committee approval.
6. Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

References

1. References in the text should be identified by Arabic Numerals in superscript on the same line as the preceding sentence.
2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
3. All references should provide inclusive page numbers.
4. Journal abbreviations should conform to those used in PubMed. Include PMID, PMCID and DOI of the references.
5. A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
6. The style/punctuation approved by JAFES conforms to that recommended by the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org. Follow the format of the examples shown below:

Journal Article

Padua FR, Paspe MG. Antinuclear antibody in the rheumatic and non-rheumatic diseases among Filipinos. Acta Med Philipp. 1990; 26(2):81-5.

One to Six Authors (Commentary, Online)

Krause RM. The origin of plagues: Old and new. Science. 1992;257:1073-8. PMID: 1509258 DOI: 10.1126/science.257.5073.1073.

Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. J Translational Med. January 20, 2004; 2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the US. JAMA. 2001;286(10):1195-200. PMID: 11559264 DOI: 10.1001/jama.286.10.1195.

More than Six Authors

McGlynn EA, M.Asch S, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med. 2003;348(26):2635-45. PMID: 12826639 DOI: 10.1056/NEJMsa022615.

Jasul Jr. GV, Paz-Pacheco E, Jimeno CA, et al. AFES A.S.-O.N.E.: ASEAN Survey Of Needs in Endocrinology in the time of the COVID-19 pandemic. J AFES Fed Endocr Soc.2020;35(1):5-13. PMID: 33790494 PMCID: PMC7992306 DOI: 10/15605/jafes.035.01.10.

Authors Representing a Group

Moher D, Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-91. PMID: 11308435 DOI: 10.1001/jama.285.15.1987.

Book

Byrne, DW. Publishing your medical research paper: What they don't teach in medical school. Baltimore: Williams & Wilkins, 1998.

World Wide Web

The key and critical objectives of JAMA. http://jama.ama-assn.org/misc/aboutjama.dtl. Accessed April 4, 2007.

Tables

1. Cite all tables consecutively in the text and number them accordingly.
2. Create tables, preferably using Microsoft Excel, with one table per worksheet.
3. Tables should not be saved as image files.
4. The content of tables should include a table number (Arabic) and title in capital letters above the table, and explanatory notes and legends as well as definitions of abbreviations used below.
5. Font should be Arial Narrow size 8.
6. Each table must be self-explanatory, being a supplement rather than a duplicate of information in the text.
5. Up to a maximum of five (5) tables are allowed.

Figures and Graphs

1. Figures or graphs should be identified by Arabic Numeral/s with titles and explanations underneath.
2. The numbers should correspond to the order in which the figures/graphs appear in the text. It is recommended that figures/graphs also be submitted as image files (preferably as .tif, .jpeg, or .png files) of high resolution (at least 300 dpi).
3. Editable figures or graphs can also be created using Microsoft Word.
4. Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
5. All identifying data of the subject/s or patient/s under study such as name or case numbers should be removed.
6. Up to a maximum of five (5) figures and graphs are allowed.

Illustrations and Photographs

1. Where appropriate, all illustrations/photographic images should be at least 600 dpi and submitted as image files (preferably as .tif, .jpeg, or .png files). All images should be checked for resolution. Right click on the image and click properties to see the resolution.
    1.1 There should be minimal processing of digital images submitted with a manuscript for review to the JAFES. A certain degree of image processing (lighting, color, contrast, size, orientation, cropping, placement of identifying markers and labels) is deemed acceptable only if the final image correctly and accurately represents the original information or data. Thus, JAFES requires all unprocessed, unaltered, and raw image files to be submitted with the manuscript to facilitate evaluation and review. These shall serve also as JAFES' records for issues that may arise after publication of the manuscript.
    1.2 Adjustments in brightness, color balance, or contrast should be applied equally to the whole image and should not result in the exclusion, hiding, obscuring, or deletion of any information that is present in the original image, enhancement of any particular portion of the image. Manipulations such as grouping of images for comparison should be indicated with image margins or clear demarcations, and must be described in the caption. Other types of manipulation such as copying and pasting of images and passing them off as multiple figures is not acceptable. Appropriate re-orientation of the whole image, as well as superimposition of arrows, markers, or other figures and labels is acceptable.
2. For photomicrographs, the stain used and the resolution at which the image was acquired (e.g., H&E, 100X) should be included in the description.
    2.1 All image adjustment and processing tools/software used should be disclosed in the methodology section of original articles or described in the caption or description if in article types without a separate section on methods.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn and digitized (preferably as .tif, .jpeg, or.png files) at least 600 dpi. All letterings for illustrations should be done professionally and be of adequate size to remain readable ever after size reduction during layout.
4. All letterings for illustration should be done professionally and should be of adequate size to retain even after size reduction.
5. Figure legends should be numbered sequentially, typed double-spaced on a separate sheet of paper. Give the meaning of all symbols and abbreviations used in the figure.
6. Up to a maximum of five (5) illustrations/photographs are allowed.

N.B.: For tables, figures, graphs, illustrations, and photographs that have been previously published in another journal or book, a note must be placed on the specific item stating that such has been adapted or lifted from the original publication and referenced in the **References** portion. Appropriate copyrights and permissions should be secured from the original author/publisher.

SCREENING

Upon receipt of the manuscript, the Editorial Coordinator shall review the submission, check if it has met all submission requirements. The Editorial Coordinator shall communicate with the author/s should there be any clarifications or incomplete requirements.

INITIAL EDITORIAL ASSESSMENT
Once submission requirements are satisfactorily met, the Editor-in-Chief to decide whether it shall be considered for publication and proceed to peer review.

Authors shall be notified through e-mail that their manuscript either (a) shall be sent to referees for peer-review or (b) has been declined without review.

PAYMENT OF SUBMISSION FEES
All manuscripts that shall be to peer review shall be required to settle the Submission Fee in order to proceed.

PEER REVIEW
The JAFES implements a strict double blind peer review policy. Each manuscript is referred to two (2) peer reviewers who are deemed as subject experts. A third reviewer may be needed in case there is discordance in the peer reviewer recommendation.

The manuscript is routinely referred to a statistician/ method expert to check appropriateness and validity of data analysis and conclusions. In addition, the manuscript is also referred to the radiologists or pathologists for review if there are diagnostic imaging studies or microscopic images, respectively.

For manuscripts that are reviewed, authors can expect an initial decision within forty five (45) days after submission. There may be instances when decisions can take longer than 45 days, in such cases, the Editorial Coordinator shall inform the authors.

FINAL EDITORIAL DECISION
The Editor-in-Chief shall make the final decision for publication.

Editorial decisions shall be one of the following:
- **Acceptance without further revision**
- **Acceptance with minor revisions**
- **Major manuscript revision and resubmission**
- **Not accepted for publication**

COPYEDITING AND PRODUCTION
Accepted manuscripts are subject to copyediting and editorial modifications to bring them in conformity with the style of the journal.

EDITORIAL OFFICE CONTACT INFORMATION:
Journal of the ASEAN Federation of Endocrine Societies
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San Miguel Avenue, Ortigas Center,
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Website: https://www.asean-endocrinejournal.org

ARTICLE TYPES

Editorials
Articles that represent the scientific opinion and views of an author. Every issue of JAFES includes an Editorial by the Editor-in-Chief and may include one or two additional editorials from experts from the scientific community commenting on a particular field or issue on endocrinology.

No abstract or keywords necessary.

Letters to the Editor and Author Responses
JAFES welcomes Letters to the Editor that provide scholarly commentary on published articles, including constructive critique, clarification or alternative interpretation of findings.

When a Letter to the Editor raises substantive scientific, methodological, or interpretive concerns, the corresponding author of the original article will be invited to submit a formal response. While submission of a response is strongly encouraged to promote balanced academic discourse, publication of the Letter is not contingent upon receipt of an author reply.

Author responses must:
- Address the issues raised in a clear, professional, and evidence-based manner
- Adhere to the journal's word limits and formatting requirements
- Refrain from introducing new data unless explicitly permitted by the editor

All Letters to the Editor and corresponding author responses are subject to editorial review and may be edited for clarity, length, and tone. The Editor-in-Chief retains final authority over publication decisions.

No abstract or keywords necessary.

A Letter to the Editor must not exceed 2 typewritten pages or 500 words.

Feature Articles
JAFES may feature articles, either as part of an issue theme, such as Summary Clinical Practice Guidelines on endocrinology from each AFES country society, or a special topic on endocrinology by an international expert or authority.

A manuscript for feature articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Review Articles
Review articles provide information on the "state of the art." JAFES encourages that reviews not only summarize current understanding of a particular topic but also describe significant gaps in the research, and current debates.

A manuscript for reviews should not exceed 15 typewritten pages (including tables, figures, illustrations and references) or 4000 words.

Original Articles
The abstract should contain no more than 500 words with a structured format consisting of the objective/s, methodology, results and conclusion.

A manuscript for original articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Case Reports
A manuscript for case reports should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words.

Case Series
A case series, defined as a report describing more than one patient with similar clinical features, presentations, interventions, or outcomes, may be submitted as a distinct article type.

Manuscripts should not exceed 4,500 words or 15 typewritten pages, inclusive of tables, figures, illustrations, and references.

Authors are encouraged to present individual case details concisely, preferably using tables or summary formats where appropriate, and to avoid repetitive narration of similar clinical information. Greater emphasis should be placed on the comparative analysis, identification of patterns, and the clinical or scientific insights derived from the series.

The number of cases included should be sufficient to support meaningful observations, typically ranging from three to ten patients, although flexibility may be exercised depending on the rarity or significance of the condition.

Submissions that primarily describe a single patient should be submitted as a Case Report and must adhere to the corresponding limits.

Interhospital Grand Rounds
JAFES encourages submission of special articles that summarize and document the proceedings of endocrinology grand rounds, which includes presentation of medical problems of a particular patient, evaluation and work-up, treatment and clinical course, discussion of key diagnostic and management points, and commentaries by specialty experts. JAFES recognizes the importance of this type of article as an educational tool for physicians and health practitioners.

A manuscript for grand rounds should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Brief Communications
Brief Communications are short reports intended to either extend or expound on previously published research OR present new and significant findings which may have a major impact in current practice. If the former, authors must acknowledge and cite the research which they are building upon.

A manuscript for brief communications should not exceed 5 typewritten pages (including tables, figures, illustrations and references) or 1500 words.

Images in Endocrinology
Images may include photographs of clinical cases encountered and documented during practice. They may also include diagnostic images (e.g., photomicrographs of histopathologic diagnosis, radiographs) or special studies performed (e.g., spectral karyotype imaging, fluorescent microscope images, immunostains) that aided in diagnosis.

A 250-word text should accompany the images. Submissions to this category should comply with the journal's image integrity guidelines.

Special Announcements
Special announcements may include upcoming conventions, seminars or conferences relevant to endocrinology and metabolism. The Editors shall deliberate and decide on acceptance and publication of special announcements. Please coordinate with the Editorial Coordinator for any request for special announcements.

Checklist Guide for Submission of Manuscripts to JAFES	
Instructions to Authors	☐ Review manuscript submission guidelines
Cover Letter	☐ Include cover letter as an attachment ☐ Indicate in the letter the title of the work ☐ Indicate all the authors (complete names, affiliations, ORCID iD, specific role/s in writing the manuscript and e-mail address) ☐ Indicate in the letter the Corresponding author: and provide complete contact information (post address, telephone, fax number, e-mail address)
EQUATOR Network Guidelines	☐ Review manuscript if compliant with appropriate EQUATOR Network Guidelines and submit checklist (e.g., CONSORT for clinical trials, CARE for case reports)
Author Form	☐ Ensure all authors have read and agreed to the following: (1) the Authorship Certification, (2) the Author Declarations, (3) the Author Contribution Disclosure, and (4) the Author Publishing Agreement, and (5) the Conversion to Visual Abstract (*optional for original articles) ☐ Submit a scanned copy of the fully accomplished form
ICMJE Form for Disclosure of Potential Conflicts of Interest	☐ Ensure all authors have read and agreed to disclose potential Conflicts of Interest ☐ Submit the PDF copy of the fully accomplished form *The form is also downloadable at: http://www.icmje.org/conflicts-of-interest/
Ethics Review Approval	☐ For Original articles, submit a scanned copy of the Ethics Review Approval of research ☐ For manuscripts reporting data from studies involving animals, submit a scanned copy of the Institutional Animal Care and Use Committee approval
Patient Consent Form (if applicable)	☐ For Case Reports, Images in Endocrinology and Clinical Case Seminars, submit a scanned copy of the fully accomplished form; otherwise, obtain appropriate ethical clearance from the institutional review board.
Title Page	☐ Full names of the authors directly affiliated with the work (First name and Last name), highest educational attainment ☐ Name and location of 1 institutional affiliation per author
Abstract	☐ Provide an abstract conforming with the format ☐ Structured for Original Articles: Objective/s, Methodology, Results, Conclusion ☐ Unstructured for Case Reports and Feature Articles
Keywords	☐ Provide 3-5 keywords (listed in MeSH)
Content	☐ Provide text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion) ☐ Make sure all abbreviations are spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses; the same abbreviation may then be used subsequently ☐ Make sure all measurements and weights are in SI units ☐ If appropriate, provide information on institutional review board/ethics review committee approval ☐ Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references; grants and subsidies from government or private institutions should also be acknowledged
References	☐ All references should be cited in the text, in numerical order. Use Arabic numerals ☐ Ensure all references follow the prescribed format
Tables, Figures, Illustrations and Photographs	☐ All tables, figures, illustrations and photographs should be cited in the text, in numerical order per type ☐ Provide separate files for tables, figures and illustrations ☐ Provide a title and legend (if appropriate) for each table ☐ Provide a title, legend (if appropriate), and caption for each figure and illustration (caption should be no longer than 15-20 words) ☐ If table, figure, or illustration is adapted, state so and include the reference.

Journal of the
ASEAN Federation of
Endocrine Societies

Editorial Policies

FOCUS AND SCOPE

The *Journal of the ASEAN Federation of Endocrine Societies (JAFES)* is a peer-reviewed, open-access journal dedicated to advancing knowledge and practice in endocrinology, diabetes, and metabolism within the ASEAN region and beyond. The journal publishes high-quality original research, reviews, clinical practice guidelines, case reports, and policy-relevant studies that address the unique epidemiologic, clinical, and health systems challenges of endocrine disorders in Southeast Asia.

It aims to serve as a platform for regional collaboration, promote locally generated evidence, and contribute to global scientific discourse by highlighting perspectives and innovations from ASEAN countries.

PUBLICATION FREQUENCY

Starting 2026, JAFES shall be published three (3) times a year. Articles are batched at the end of April, August, and December of each year and released as an issue on the JAFES website.

While awaiting assignment to an issue, articles are published as "Early Access" on the JAFES website as soon as the review and editing process is complete.

EDITORIAL INDEPENDENCE

The Journal of the ASEAN Federation of Endocrine Societies (JAFES) is committed to maintaining the highest standards of editorial integrity, transparency, and academic freedom. **This policy outlines the principles and safeguards that ensure editorial independence in all aspects of the journal's operations.**

JAFES upholds editorial independence as essential to the integrity and credibility of the journal. The Editor-in-Chief and the Editorial Board have full authority over the editorial content of the journal, including decisions on which manuscripts to accept, revise, or reject.

Editorial decisions are based on the quality, originality, scientific rigor, relevance, and clarity of the submitted manuscripts, and are not influenced by:

- The policies or positions of the ASEAN Federation of Endocrine Societies (AFES) or its member societies;
- The identity, affiliation, or position of authors, reviewers, or institutions;
- Commercial, political, or personal interests;
- Pressure from sponsors, advertisers, or organizational stakeholders.

ROLE OF THE PUBLISHER AND AFES

While JAFES is the official publication of the AFES and supported by its member societies, the publisher or AFES leadership shall not interfere in the evaluation, selection, or editing of individual articles. Their role is limited to ensuring the journal's operational and financial sustainability, without infringing on editorial decisions.

CONFLICT OF INTEREST AND TRANSPARENCY

All editors, reviewers, and authors must declare any actual or potential conflicts of interest that could affect the objectivity of editorial decisions. Editors must recuse themselves from handling manuscripts in which they have a conflict of interest and delegate such submissions to another qualified editor.

PROTECTION OF EDITORS AND REVIEWERS

Editors and reviewers are protected from undue influence or intimidation from any internal or external party. JAFES will not tolerate attempts to influence editorial decisions and will take appropriate action against any breaches of ethical conduct.

APPEALS AND COMPLAINTS

Authors have the right to appeal editorial decisions. Appeals will be considered in accordance with the journal's appeals policy and handled by an independent editorial member or advisory board, ensuring impartiality and fairness.

ALIGNMENT WITH INTERNATIONAL GUIDELINES

This policy is informed by international editorial standards, including those set by the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), and the Committee on Publication Ethics (COPE).

PUBLISHING AGREEMENT, COPYRIGHT NOTICE AND COPYRIGHT CLEARANCE FEES

Author Retention of Copyright

- The author(s) shall retain the copyright and all other intellectual property rights for the article, but transfers only commercial rights to the JAFES.

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This agreement shall also give JAFES exclusive rights to license others to do the same as above through the user license, and to enforce these rights against third parties.

Reversion of Rights upon Withdrawal, Rejection, or Retraction

The author(s) understand and agree that all rights granted under this agreement shall revert to the author(s) should the submitted manuscript be withdrawn or rejected, or the published manuscript be retracted.

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A **written agreement** will be emailed to the requester once permission has been granted.

JAFES is given authority by our Authors to impose fees for commercial uses (outside the license). The below fee schedule shall apply only to commercial use requests. Our objective is not to earn profit but to standardize the approach to such requests.

1st step is the base fee

Journal Item	Base Price (USD)		
	Print	Electronic	Multi-Format (25% discount)
Per Chart/Graph/ Table/Figure	20	20	30
Per Image/ Photograph	20	20	30
Per Excerpt	20	20	30
Per Full Article	150	150	180

2nd is to determine the type of requesting party and we will impose a surcharge

Requesting Party	Surcharge
Publisher, for profit	10%
Academic institution, for profit	5%
Non-academic, for profit	10%

3rd step is to determine the number of copies

Circulation	Surcharge
Up to 499	2%
Up to 999	4%
Up to 4,999	6%
Up to 9,999	8%
More than 9,999	10%

Examples of request and computed fee:

Request for 1 article, in electronic and print format (180 USD), to be used for profit by a non-academic institution (10% surcharge), with a projected circulation of 1000 copies (6% surcharge). The computed fee is **208.8 USD.**

Request for 1 figure, in print format (20 USD), to be used for profit by an academic publisher (5% surcharge), with a projected circulation of 10,000 (10%). The computed fee is **24 USD.**

Data Sharing and Availability

For purposes of transparency and scientific integrity, JAFES requires that authors provide a statement on the availability of data described in the manuscript submission. Depending on the circumstances, one of the following data availability and sharing statements may be selected:

- Datasets generated and analyzed are included in the published article.
- No datasets were generated or analyzed for this study.
- Datasets for the study are publicly available in the data repositories* listed in References.**
- Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.
- Datasets analyzed in the study are under license and not publicly available for sharing.

If the above statements are not appropriate, the authors are asked to contact the JAFES Editorial Coordinator at jafes.editor@gmail.com.

Repositories for deposit of datasets may include institutional repositories or third-party repositories such as but not limited to:

- Figshare [https://figshare.com/]
- Dryad [https://datadryad.org/]
- Zenodo [https://zenodo.org/]
- Open Science Framework [https://osf.io/]
- Dataverse [https://dataverse.harvard.edu/]

Note: Deposited datasets should bear a persistent identifier (e.g., Digital Object Identifier or DOI; or accession number) and be publicly available through a license (at least CC-BY 4.0).

Artificial Intelligence (AI)-Generated Content
Authors are required to disclose their use of generative artificial intelligence (AI) and AI-assisted technologies for all submissions to JAFES. This shall be described in the cover letter AND the submitted work in the appropriate section as to how it was used.

Authors are expected to exercise due diligence in reviewing, editing, and finalizing the output arising from use of such technologies, to include ensuring that there is appropriate attribution of all quoted material, including full citations.

Use of AI for data collection, analysis, or figure generation
The use of AI/AI-assisted technologies for data collection, analysis, or figure generation shall be described in sufficient detail as part of the Methodology.

Use of AI for manuscript preparation
A statement reflecting the use of AI/AI-assisted technologies shall be included as part of the Acknowledgments.

Example statement:

Acknowledgments
The author(s) used [NAME OF TOOL/SERVICE] to [OBJECTIVE OF USING AI/AI-ASSISTED TECHNOLOGY] and have duly overseen, reviewed, edited, and finalized the content.

Submission Fees
To support the long-term sustainability of the Journal of the ASEAN Federation of Endocrine Societies (JAFES), **a standard, fixed fee for all manuscripts** following the below fee schedule shall be required.

Fee Schedule	Submission Fee*
Members of the following AFES societies: • Indonesian Society of Endocrinology (PERKENI) • Malaysian Endocrine and Metabolic Society (MEMS) • Philippine College of Endocrinology, Diabetes, and Metabolism (PCEDM) Endocrine and Metabolic Society of Singapore (EMSS) • Endocrine Society of Thailand	100 USD
Members of Vietnam Association of Diabetes and Endocrinology (VADE)	Partially waived – 50 USD
Members of the Myanmar Society of Endocrinology and Metabolism (MSEM)	Fully waived
Non-AFES Members	300 USD
All submission fees are net of Bank Transfers. Applicable online bank transfer fees shall be to the account of the author/s.	

By adopting a fixed Submission Fee, JAFES aims to ensure fairness, transparency and financial stability. Every submission contributes to the journal's operations, enabling us to uphold our commitment to rigorous peer review, ethical standards and open access dissemination of Southeast Asian endocrine research. This shift helps secure JAFES' future as a trusted, regionally grounded and globally accessible scientific journal.

The Submission Fee shall be paid once a manuscript is decided by the Editor-in-Chief to proceed to peer review. The fee covers the full cycle of editorial and production work: from initial screening, similarity checks, administrative processing, peer review management, technical editing, copyediting, layout and design, proofreading, publication and online hosting, up to long-term archiving.

These processes require sustained investment in skilled editorial staff, digital infrastructure and high-quality publishing systems, regardless of the final editorial decision.

FOR ADDITIONAL INFORMATION ON SUBMISSION FEE WAIVERS, CLICK HERE.

https://asean-endocrinejournal.org/index.php/JAFES/SubmissionFeeWaiver

ARTICLE WITHDRAWAL, RETRACTIONS AND CORRECTIONS

Article Withdrawal
Manuscripts may be withdrawn by the author until the point when the article has not yet been included in the galley of the full issue and only upon the formal written request of the author stating the reason for the withdrawal. Should there be a need to correct the article of record as part of a published issue, the article shall be retracted and the corrected version shall be uploaded.

Confirmation of Withdrawal
All withdrawal requests shall be formally acknowledged in writing by the JAFES Editorial Office. Until such confirmation is received, the manuscript shall remain under active consideration by the Journal and must not be submitted to another publication venue.

Article Retraction
There may be instances when an article published by the JAFES must be retracted or corrected.

Retraction is indicated when there are violations of responsible and ethical scholarly publication guidelines, such as multiple submissions, plagiarism, false or fraudulent data, OR when there is a need to correct serious or major errors in the original published article. "Serious or major errors" refer to those which invalidate the article's results and conclusions.*

For all retractions:

- A retraction notice signed by all authors shall be published as the cover page of the PDF version.
- The article shall remain in the database and published issue but a notation shall be placed in the table of contents indicating that the article has been retracted, following the convention: "RETRACTION: [Title]."
- The HTML version shall be removed and the link button to the HTML version disabled.
- A watermark indicating that the work is retracted shall be placed on each page of the original article published and shall be uploaded to replace the PDF version.

*Authors may resubmit after addressing serious or major errors but the manuscript shall be considered an entirely new submission.

Article Correction

Errors that do *not* change or invalidate the article's results and conclusions shall undergo correction. For all corrections:

- A correction notice/erratum signed by all authors shall be published as the cover page of the corrected PDF version.
- The corrected article version shall include details of the changes from the original version and the dates on which the changes were made.
- All prior versions of the article shall be archived by the JAFES and made available upon request approved by the Editor-in-Chief.
- Previous versions archived by the JAFES shall indicate that there is a corrected version.
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Cover Letter

(Date)

To: **The Editor-in-Chief**
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Subject: **SUBMISSION OF MANUSCRIPT FOR PUBLICATION**

We intend to publish the manuscript/, entitled "_____," under the Section *[Original Article, Review Article, Feature Article, Case Report, Case Series, Interhospital Grand Rounds, Brief Communications, Letter-to-the-Editor, Special Announcements]* in the Journal of the ASEAN Federation of Endocrine Societies.

LIST OF AUTHORS

Complete Name	Position/ Designation	Institutional Affiliation	Role in writing the manuscript	Email address	ORCID iD

On behalf of all the authors, I shall act as the corresponding author with the journal from this point onward.

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For case reports/series, patient consent forms have been secured for the publication of information.

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Furthermore, we respectfully suggest the following **reviewer**(s) for our manuscript.

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