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Journal of the ASEAN Federation of Endocrine Societies

Vol. 40 No. 1 May 2025 | eISSN 2308-118x (Online)

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An Editor-in-Chief's Reflections on a 15-Year Journey

As I pause to write this editorial, my second-to-the-last as Editor-in-Chief of the *Journal of the ASEAN Federation of Endocrine Societies (JAFES)*, my heart is full of gratitude for a 15-year journey that has been so rewarding. Fifteen years ago, my team and I accepted the challenge with a sincere hope, a commitment to learning something new, and a clear vision, that is, to provide a platform for Endocrinology in the region and have our voice be heard in the international scene too.

JAFES in 2010 was a modest publication, non-indexed and non-peer-reviewed, with few issues containing abstracts that accompanied our ASEAN Federation of Endocrine Societies (AFES) Congresses. Could we truly transform JAFES into a steady voice for endocrinology in Southeast Asia? Would we find the people, the support, and the perseverance needed to sustain such an endeavor?

Through the collective passion of equally committed members of the international editorial team, the trust of our contributing authors and peer reviewers, and the unwavering support of the AFES countries, our publisher, we continued to build piece by piece, milestone by milestone. To date, our editorial team could count 30 regular and 13 special issues; with 447 articles and 1,554 authors and co-authors, and we keep building on, moving forward, getting more people on board.

Learning from our esteemed colleagues from the Philippines and the Asia-Pacific Association of Medical Editors (APAME), we set forth to institute the most basic requirements of reputable publications. We established a robust peer-review system and launched an online Open Journal Systems-based platform for editorial management, thus streamlining our processes and making submission and publication more efficient and transparent. Slowly but surely, recognition followed. Our journal earned its place in the WHO Western Pacific Region Index Medicus (WPRIM), the Directory of Open Access Journals (DOAJ), Scopus, Clarivate Analytics, PubMed, and PubMed Central. We moved to an online first publishing model in 2018 and started the creation of visual abstracts for JAFES articles in 2019 to more readily amplify our content (for professionals and lay) across digital, multimedia and social platforms. These were signals to the world that Southeast Asia has a steady voice in the field of endocrinology.

Along the way, there were tremendous challenges: evolving editorial standards, coping with the learning curve for authors and peer reviewers, overcoming language barriers, augmenting the limited resources, and, in the last five years, dealing with the disruptions by the global pandemic. In fact, these hurdles served to strengthen our resolve and to reinforce the importance of regional collaboration and scientific communication.

https://doi.org/10.15605/jafes.040.01.01

None of the achievements would have been possible without our authors, reviewers, editorial board members, partner societies, and, last and first, our readers. You believed in JAFES and in what it represents: scientific rigor, regional relevance, and pursuit of better health for all.

Our vision remains focused: to provide and secure that space where the voice of the region can be heard. With the extensive indexing of JAFES, our national and regional data can be recognized. It has become even more apparent that we need to establish our Southeast Asian data that do apply to our populations and can better serve as the basis of national guidelines. We continue to think of regionally relevant research questions to answer through collaboration among Southeast Asian countries, where clearly our commonalities are greater than our differences.

So as I prepare to pass on the torch, so to speak, my heart is also full of pride. JAFES is now well situated in the international publishing landscape. Our platform is strong, our community is growing, our commitment to excellence remains unwavering, and we are getting closer to our vision. Let this journey go on!

Elizabeth Paz-Pacheco
Editor-in-Chief

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ARTICLE PROCESSING CHARGE (APC) WAIVER POLICY

Purpose

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Policy Overview

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Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

A Consensus for Pituitary Adenoma Diagnosis in Indonesia

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Abstract

Pituitary adenomas account for 10 to 15% of all intracranial masses and are the most common type of pituitary disorder. Their clinical manifestations can vary based on the tumor size and whether they secrete excess hormones. Occasionally, they are incidentally diagnosed following an imaging procedure for other indications (pituitary incidentaloma). The Pituitary Working Group of the Indonesian Society of Endocrinology has identified pituitary adenoma as a priority and has called for the development of updated evidence-based practice guidelines. These guidelines aim to provide evidence-based, comprehensive and multidisciplinary recommendations for diagnosing pituitary adenomas in Indonesia and to navigate the limitations of diagnosing pituitary adenomas in Indonesia.

Key words: pituitary adenoma, clinical practice guidelines, Indonesia

INTRODUCTION

The pituitary gland, located at the base of the brain and often referred to as the "master gland," is the most crucial endocrine gland in the body. It regulates the secretion of vital hormones.[1] A pituitary adenoma is a slow-growing benign tumor originating from pituitary gland cells.[2,3] It ranks third among the most common intracranial tumors after meningioma and glioma, comprising about 15% of all central nervous system tumors. Globally, pituitary adenomas are estimated to affect 68 to 115 individuals per 100,000. These tumors can significantly impact patients' quality of life[2-4] as clinical symptoms may vary widely based on mass effect and disrupted hormonal function.[5,6]

In Indonesia, many cases are diagnosed in advanced stages due to a delayed recognition of the symptoms and signs. A study at Cipto Mangunkusumo Hospital, the tertiary referral hospital in Jakarta, Indonesia, revealed that between 2007 and 2012, 97.8% of cases were pituitary macroadenomas, with 44.4% being functional adenomas that could have been diagnosed earlier.[7] Most cases

eISSN 2308-118x (Online)
Printed in the Philippines

Received: April 26, 2024. Accepted: July 17, 2024.
Published online first: April 29, 2025.
https://doi.org/10.15605/jafes.040.01.03

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were diagnosed in tertiary referral hospitals because of limitations in diagnostic modalities and healthcare provider awareness. Between 2017 and January 2024, 959 cases of pituitary adenoma were diagnosed and treated in Cipto Mangunkusumo Hospital, with many coming from various regions across the country. The most common complaints of patients with pituitary adenoma in Indonesia are symptoms related to mass effects, such as headaches (86.7%) and vision disturbances (77.8%).[7] Other common symptoms included hormonal disturbances, such as erectile dysfunction, menstrual irregularities, galactorrhea and facial changes.[7] These findings align with research indicating that patients with pituitary adenomas may first seek consultation with ophthalmologists, neurosurgeons, internists, neurologists, or other relevant specialists.[7]

This consensus on diagnosing pituitary adenomas was formulated as a comprehensive and multidisciplinary guide for diagnosing pituitary adenoma patients in Indonesia. This consensus aims to improve the quality of patient care, enable early diagnosis, and optimize the management of these patients through a multidisciplinary team in Indonesia.

SUMMARY OF THE METHODOLOGY FOR GUIDELINES DEVELOPMENT

The Pituitary Working Group of the Indonesian Society of Endocrinology developed this guideline by summarizing existing literature on pituitary adenoma and incorporating feedback and suggestions from multidisciplinary experts. This collaborative effort resulted in a comprehensive guideline catering to a broad spectrum of medical professionals in Indonesia, making it a versatile tool for daily practice.

SUMMARY OF RECOMMENDATIONS

Clinical manifestations of pituitary adenoma

Pituitary adenomas may present clinically in three ways: (1) with symptoms of hormone hypersecretion or deficiency, (2) with neurologic manifestations from mass effect or (3) as an incidental finding on imaging done for other indications. Pituitary adenomas are categorized based on primary cell origin and the type of hormone secreted for functioning adenomas. On the other hand, larger tumors may cause impingement of pituitary cells, leading to reduced secretion of pituitary hormones, and are termed nonfunctioning. Prolactinomas comprise 40% to 57% of all adenomas, followed by nonfunctioning adenomas (28% to 37%), growth hormone-secreting adenomas (11% to 13%), and adrenocorticotropic hormone (ACTH)-secreting adenomas (1% to 2%). Pituitary adenomas that secrete follicle-stimulating hormone (FSH), luteinizing hormone (LH), or thyroid-stimulating hormone (TSH) are rare. Tumors are also categorized based on size. If the tumor is 10 mm or larger, it is considered a macroadenoma; if it is less than 10 mm, it is considered a microadenoma.

Table 1. Clinical presentation of functioning pituitary adenomas[1,5,6]

Hormone secreted	Clinical syndrome	Presentation
Prolactin	Hyperprolactinemia	*Symptoms* Oligomenorrhea or amenorrhea, galactorrhea, decrease in libido, infertility, gynecomastia, impotence *Signs* Gynecomastia, hypogonadism (testicular atrophy, breast shrinkage, hair loss) *Morbidity* Osteoporosis
Growth hormone (GH)	Acromegaly, gigantism (if it occurs before closure of growth plate)	*Symptoms* Increase in hand and foot size, change in facial features (large and protruded mandible), enlarged tongue, carpal tunnel syndrome, hyperhidrosis, fatigue, proximal muscle weakness, decreased libido, menstrual changes, joint pain, height significantly exceeding normal or peer age (pediatric onset) *Signs* Hypertension, coarse facial features, left ventricular hypertrophy, cardiomyopathy, visceromegaly, hypercalciuria, goiter *Morbidity* Cardiovascular disease, diabetes, sleep apnea, increased risk of colon cancer, osteoporosis
Adrenocorticotropic hormone (ACTH)	Cushing disease	*Symptoms* Labile mood, proximal muscle weakness, skin changes, changes in facial features, weight gain, depression, hirsutism, decreased libido, menstrual changes *Signs* Thin skin, striae, bruising, central obesity, moon facies, plethora, hypertension, acne, glucose intolerance, neutrophilia, lymphocytopenia, eosinopenia *Morbidity* Diabetes mellitus, cardiovascular disease, osteoporosis
Thyroid-stimulating hormone (TSH)	Hyperthyroidism	Hyperthyroid symptoms, such as anxiety, palpitations, weight loss, heat intolerance, tremor
LH/ FSH	No specific syndrome	Symptoms from mass effect, hypopituitarism

Table 2. Clinical manifestations of mass effect and hypopituitarism[1,5,6]

Mass effect	Hypopituitarism
• Headache • Visual field disturbances • Blurred vision • Double vision • Strabismus • Protrusion of the eyeball (proptosis), usually accompanied by redness of the eye (conjunctival chemosis) • Deviation in eye position (esotropia, exotropia, or hypertropia) • Impaired eye movement • Ptosis • Decreased visual field (confrontation test) • Visual acuity examination may reveal decreased visual acuity • Relative afferent pupillary defect • Nystagmus (seesaw nystagmus) • Decreased color sensitivity • Decreased contrast sensitivity	• Growth hormone: growth inhibition (short stature), increased risk of osteoporosis, fatigue, weight gain • LH/ FSH: amenorrhea, decreased libido, infertility, obesity, osteoporosis, and diabetes • TSH: cold intolerance, memory impairment, constipation, excessive sleep, myxedema, coarse hair, weight gain • ACTH: orthostatic hypotension, fatigue, chronic dyspepsia, hyponatremia, hypoglycemia • Antidiuretic hormone (ADH): polyuria, hypernatremia, polydipsia (diabetes insipidus)

Table 3. Diagnostic tests in the evaluation of a suspected adenoma

Indication	Test
Prolactinoma	Serum prolactin
GH-secreting pituitary adenoma (acromegaly)	Serum insulin-like growth factor 1 (IGF-1) and GH suppression test (with oral glucose test)
ACTH-secreting pituitary adenoma*	Cortisol excess test: • 24-hour urinary free cortisol • low-dose dexamethasone suppression test • late-night salivary cortisol ACTH
TSH-secreting pituitary adenoma	TSH and FT4
Hypogonadism	LH, FSH, estradiol. Testosterone
Hypocortisolism	Morning serum cortisol Synacthen test
Hypothyroidism	TSH, FT4
ADH deficiency (diabetes insipidus)	Serum electrolytes, serum osmolarity, urine osmolarity Desmopressin suppression test

*Bilateral inferior petrosal sinus sampling (BIPSS) is indicated when clinical and biochemical evidence suggests Cushing's disease without definitive MRI findings.[8]

The clinical profile of patients with pituitary adenoma may be divided into two groups: 1) those with symptoms related to mass effect and 2) those with symptoms related to hormonal disturbances.[1,5,6] Hormonal disturbances can be further subdivided into functional pituitary adenomas producing too much hormones (Table 1), and nonfunctioning adenomas wherein hormonal hyposecretion is caused by the tumor's mass effect on the healthy pituitary gland (Table 2).

Neurologic symptoms caused by the mass effect are common in nonfunctioning adenomas or lactotroph adenomas in men because the hormonal effects may not be immediately recognizable. Hence, their diagnosis may be delayed until symptoms of mass effect become apparent. Partial or complete hypopituitarism commonly occurs due to direct compression of the pituitary gland. In the case of hyperprolactinemia, hypogonadism can occur because of its inhibitory effect on GnRH secretion and LH pulsatility.

Following thorough history taking and clinical examinations, hormonal laboratory diagnostic tests are warranted if hormone excess or deficiency is suspected (Table 3). In resource-limited healthcare centers where hormonal laboratory testing cannot be performed, general laboratory testing can be done initially to support the clinical findings, such as complete blood count, fasting blood glucose, oral glucose tolerance test and serum electrolytes.

Imaging examination

If a patient presents with neurologic symptoms due to a suspected mass effect, magnetic resonance imaging (MRI) is the best initial imaging study. The study should be done with and without gadolinium enhancement. If an MRI is contraindicated or unavailable, a computed tomography scan (CT scan) with thin sections (1.5 mm or less) and in a coronal plane will improve imaging of the pituitary region. A CT scan is limited in its ability to image the optic chiasm precisely. Adenomas are classified based on imaging using the Hardy and Wilson, and Knosp systems (Figure 1). These classifications aid in determining tumor invasion, management and postoperative prognosis.[9,10]

Classification by Hardy and modified by Wilson:[9,10]

- Microadenoma: classified as grade 0 or grade I based on the appearance of the sella or minimal changes in the sella.
- Macroadenoma: causes diffuse enlargement and can lead to focal and extensive destruction of the sella, categorized as grade II, III, and IV.

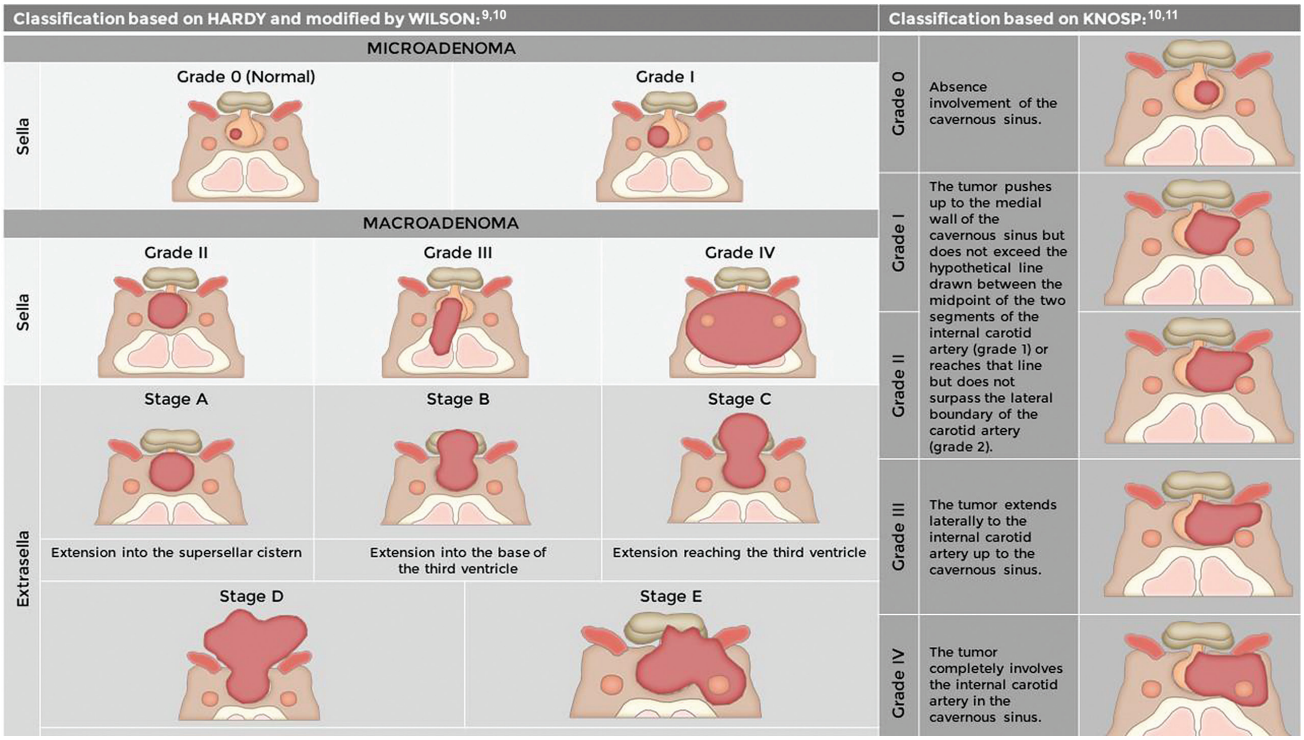

Figure 1. Classifications based on Hardy and modified by Wilson[9,10] and Knosp[10,11] *(redrawn for clarity)*.

- In this system, macroadenomas are also classified based on the degree and direction of extrasellar extension:
  - Extension into the suprasellar cistern alone is classified as stage A.
  - Extension to the base of the third ventricle is classified as stage B.
  - Extension reaching the third ventricle is referred to as stage C.
  - Tumors extending into the lateral intradural or extradural space are classified as stages D and E.

Knosp classification:[10,11]

Used to determine tumor invasion into the cavernous sinus. This classification is beneficial for describing tumor size, management and postoperative prognosis:[9,10]

- Grade 0 indicates no involvement of the cavernous sinus.
- Grade 1 and 2 tumors push up to the medial wall of the cavernous sinus but do not exceed a hypothetical line extending between the midpoints of the two segments of the internal carotid artery (grade 1) or reach that line without crossing the lateral boundary of the internal carotid artery (grade 2).
- In grade 3, the tumor extends laterally to the internal carotid artery into the cavernous sinus.
- In grade 4, the tumor completely involves the internal carotid artery in the cavernous sinus.

Ophthalmologic examination[11-13]

An ophthalmologic examination is performed to determine the extent of the mass effect of the adenoma and includes routine and more specific examinations as indicated (Table 4).

Table 4. Ophthalmologic Examinations

Routine examinations	Examination of specific indications
• Visual acuity test • Color vision and contrast sensitivity test • Perimetry test (confrontation, Goldman or Humphrey visual field test) • Ocular movement test • Funduscopy	• Optical Coherence Tomography (OCT) of the optic disc • Electrophysiological examinations, such as Pattern Visual Evoked Potential (PVEP), Multifocal VEP (mfVEP), or Pattern Electroretinography (PERG)

Anatomical pathology

Histopathological examination is warranted when surgical resection is performed. It is strongly suggested that immunohistochemical staining be done to determine the primary cell origin.[5,14] However, to date, immunohistochemical panel for pituitary adenoma is still not routinely done in Indonesia.

Incidental pituitary mass (incidentaloma)

Increased use and sensitivity of CT and MRI have identified many pituitary lesions incidentally, even when the tests were performed for other reasons.[15]

Differential diagnosis[16]

- Craniopharyngioma
- Meningioma
- Malignant tumors (germ cell tumors, chordomas, primary lymphoma, metastatic disease)
- Rathke's cysts

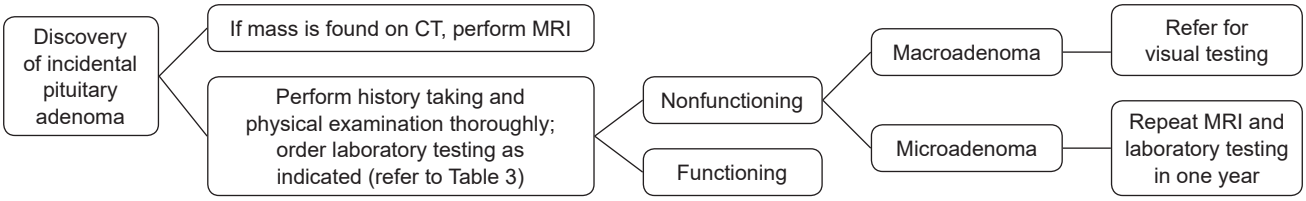

Figure 2. Approach to evaluation of pituitary incidentaloma.

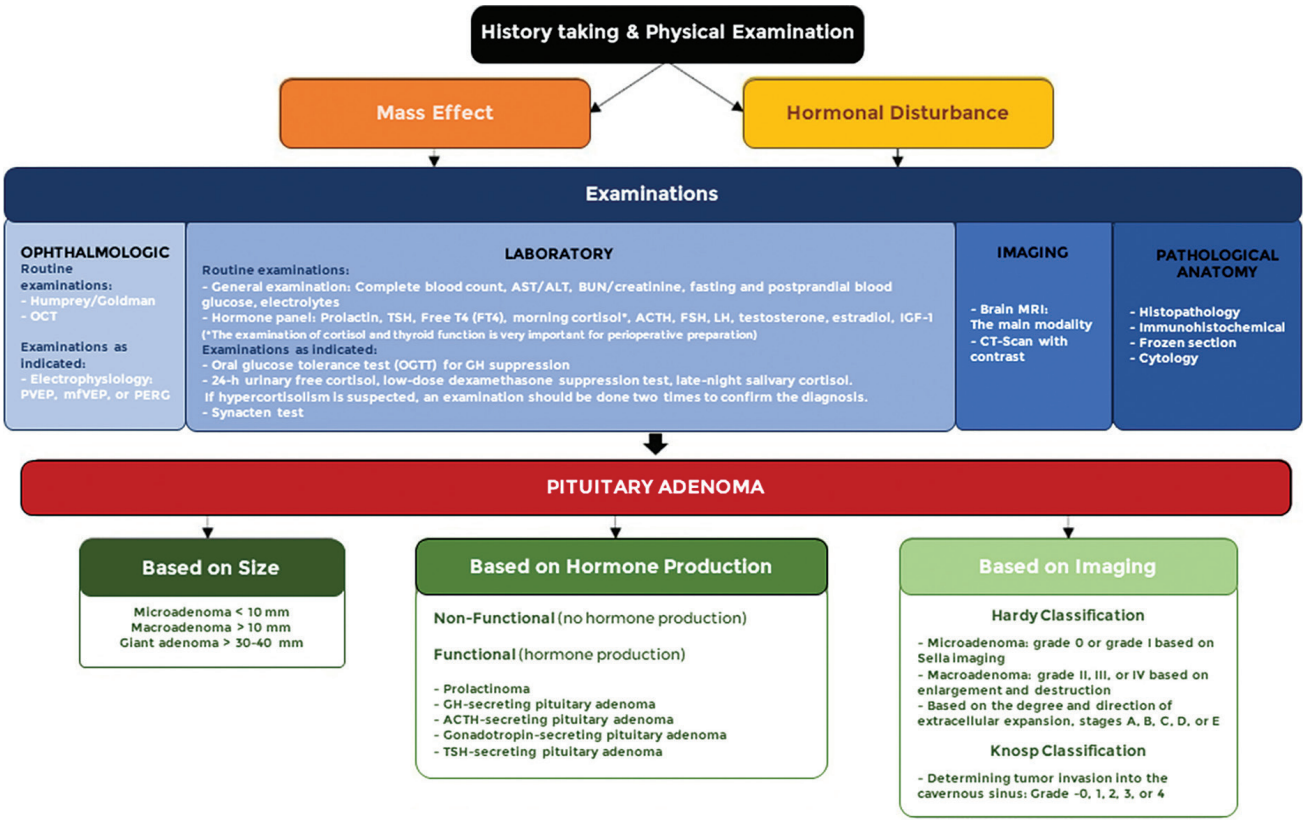

Figure 3. Guideline for the diagnostic approach to pituitary adenoma.

- Abcess
- Arteriovenous fistula of the cavernous sinus
- Hypophysitis
- Drugs that caused elevation of prolactin
- Primary adrenal Cushing syndrome
- Ectopic ACTH-secreting tumors
- Ectopic GH secretion by neuroendocrine tumors (rare)

CONCLUSION

This consensus on diagnosing pituitary adenomas was formulated as a comprehensive and multidisciplinary standard guide in Indonesia. It can be utilized to enhance the quality efficiency of the diagnostic approach to pituitary adenomas. In this regard, we propose an algorithm, that commences with a medical history and physical examination, followed by supportive examinations, including ophthalmological, laboratory, imaging and pathological examinations (Figure 3). This approach ensures a more timely and accurate diagnosis of pituitary adenomas, which will determine subsequent management. In resource-limited settings, prompt referral is strongly recommended if a pituitary adenoma (functioning or nonfunctioning) is suspected.

Acknowledgments
The authors express sincere appreciation to The Indonesian Society of Endocrinology for their invaluable facilitation and support during the development of this guideline. Furthermore, we thank Calysta Nadya Wijaya for the technical assistance in preparing this guideline.

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

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DLT: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration, Funding acquisition; **SO:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Project administration; **MK:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review and editing, Project administration; **DAL:** Conceptualization, Methodology, Validation,

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Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

The Incidence and Severity of Paediatric Diabetic Ketoacidosis Presenting to a Metropolitan Hospital in Western Sydney: A 10-Year Retrospective Review

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Abstract

Objectives. To report the incidence and clinical characteristics of paediatric patients presenting with diabetic ketoacidosis to the Emergency Department (ED) with new and pre-existing type 1 diabetes mellitus (T1DM).

Methodology. A ten-year retrospective data analysis was performed on children under 16 years presenting to the ED with T1DM from January 2010. Demographic and laboratory data were extracted to determine the rates of DKA. Comparative statistics were performed between age groups and pre-existing and newly diagnosed T1DM patients.

Results. A total of 196 children with T1DM were included. The mean age of the cohort was 9.3 ± 4.0 years, with female predominance (54%, $p = 0.38$). Most (60%) were newly diagnosed with T1DM, of which 38% presented in DKA. Amongst the total cohort, 43% presented in DKA.

The older children accounted for 50% of the DKA presentations in the newly diagnosed cohort. Amongst the younger age group, 42% presented with severe DKA. There were higher rates of T1DM in areas of relative socioeconomic advantage.

Conclusion. Children with T1DM presented with unacceptably high rates of DKA and posed a significant medical, psychosocial and financial burden on families and medical services. These findings suggest that a prospective public health campaign to reduce rates of DKA is warranted.

Key words: type 1 diabetes mellitus, diabetic ketoacidosis, child health, pediatrics

INTRODUCTION

One of the most prevalent endocrine diseases in the world is Type 1 Diabetes Mellitus (T1DM).[1] According to the National Diabetes Register, there were 194 new cases per 100,000 population (incidence) of T1DM in Australia in 2021.[2] Despite advances in diabetes management, there remain challenges in all age groups, such as suboptimal glycaemic control and increased frequency of diabetes complications.

The most common complication of T1DM is Diabetic ketoacidosis (DKA). Younger age, delayed diagnosis, lower socioeconomic level (SES), and living in a nation with a low prevalence of type 1 diabetes are risk factors for DKA in newly diagnosed patients.[3] Acute complications of DKA include hypokalaemia, deep vein thrombosis, cerebral oedema and death.[3]

Many community educational campaigns have been launched for T1DM awareness to prevent DKA and related complications, with mixed results.[4,5] A recent retrospective study at a large regional hospital in Queensland, Australia[6] explored the incidence of DKA over 11 years in children and youth under 18 years old at first presentation of T1DM, before and after an educational intervention. Overall, post-intervention DKA incidence had halved (from 55 to 25%). The intervention also managed to lower the incidence of severe and moderate DKA (from 49 to 33% and 27 to 17%, respectively), while mild DKA doubled from 24 to 50%.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: June 17, 2024. Accepted: August 15, 2024.
Published online first: December 12, 2024.
https://doi.org/10.15605/jafes.040.01.02

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Our study aims to report the frequency and severity of presentations of children with T1DM presenting to a metropolitan teaching hospital in Western Sydney. We also aimed to describe the illness severity at presentation of the more vulnerable population of children under five years of age.

METHODOLOGY

A retrospective medical record review was performed at a metropolitan teaching hospital in Western Sydney over a ten-year period from January 2010 to December 2019. The data was extracted from the electronic medical record systems of the hospital for all children under 16 years of age who presented to the Emergency Department (ED) with the diagnosis of T1DM.

The extracted data included age, sex, residential postcode, age of diagnosis, family history, co-morbid conditions (i.e., asthma, coeliac disease, renal disease, psychiatric disorders etc.), presenting symptoms, laboratory investigations and diagnosis (new and pre-existing T1DM), and their subsequent admissions. The study population was divided into two age groups: younger children (less than five years old) and older children (between 5 to 16 years old). Recurrent presentation and recurrent DKA were each defined as more than one presentation without DKA, or more than one DKA presentation within the same year or more than two presentations within three years of the last admission, respectively. All data were complete with no missing values.

The International Society of Paediatric Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2022[7] defined DKA as: hyperglycaemia above 11 mmol/L and pH <7.3, or serum bicarbonate <15 mmol/L in the presence of ketonaemia (blood ß-hydroxybutyrate ≥3 mmol/L) or ketonuria (moderate or large). A venous pH of <7.3 or a serum bicarbonate of <15 mmol/L was considered mild; a pH of <7.2 and a serum bicarbonate of <10 mmol/L was considered moderate; and a pH of <7.1 and a serum bicarbonate of <5 mmol/L was considered severe.

Socioeconomic status (SES) was determined using the Socioeconomic Indexes for Areas (SEIFA).[8] This ranks Australian areas according to relative socioeconomic advantage and disadvantage based on residential postcodes. The SEIFA score is reported in deciles from one to ten, the highest decile representing an area of higher SES.

Ethics

The study was conducted in compliance with The National Health and Medical Research Council's (NHMRC) national statement on ethical conduct in human research. Human ethics approval for the study was obtained from the Nepean Blue Mountains HREC (Approval number: 2020/ETH00898).

Statistical analysis

Statistical analysis was performed using STATA version 15.0 software. Mean, standard deviation, minimum and maximum were used to describe continuous data, while frequency and percentages were used for categorical data. Data comparison by age group was done using the chi-square test or Fisher's exact test for categorical data and t-test for continuous data. Statistical significance was set at p <0.05.

RESULTS

A total of 196 children presented to the ED with T1DM, with 54% being female (n = 105). The characteristics and comorbidities of the study population are presented in Table 1.

Table 1. Patient characteristics and comorbidities of newly diagnosed T1DM

Parameter	Total (n=196)	New Diagnosis of T1DM		*P* value
		Yes (n=118)	No (n=78)	
Age at diagnosis (years)				
Mean	9.3 ± 4.0	8.8 ± 3.8	10.0 ± 4.2	0.38*
Range (Min, Max)	(1.0, 15.0)	(1.0, 15.0)	(1.0, 15.0)	
Age 5 - <16 years (%)		94 (80)		
Under 5 years (%)		24 (20)		
DKA at diagnosis (%)		45 (38)		
Sex, n (%)				
Male	91 (46)	52 (44)	39 (50)	0.42
Female	105 (54)	66 (56)	39 (50)	
Family History DM, n (%)				
Yes	62 (32)	48 (41)	14 (18)	<0.001
No	134 (68)	70 (59)	64 (82)	
Comorbidity Conditions, n (%)				
Atopy (Asthma, Hay Fever)	22 (11)	14 (12)	8 (10)	0.73
Thyroid Disease	8 (4)	3 (3)	5 (6)	0.18
Behavioural / Development Disorder	14 (7)	6 (5)	8 (10)	0.17
Coeliac Disease	8 (4)	5 (4)	3 (4)	0.89

*Chi-square test or Fisher exact test for categorical data and t-test for continuous data
DM: diabetes mellitus

Table 2. Comparisons between DKA, recurrent DKA and recurrent presenters

Parameter	DKA			Recurrent DKA[a]			Recurrent presenter[b]		
	Yes (n=84)	No (n=112)	*p* value	Yes (n=8)	No (n=76)	*p* value	Yes (n=54)	No (n=142)	*p* value
Age, n (%)									
5 - <16 years	68 (81)	92 (82)	0.83	7 (88)	61 (80)	1.00	41 (76)	119 (84)	0.20*
Under 5 years	16 (19)	20 (18)		1 (12)	15 (20)		13 (24)	23 (16)	
Sex, n (%)									
Male	39 (46)	52 (46)	1.00	2 (25)	37 (49)	0.27	23 (43)	68 (48)	0.50
Female	45 (54)	60 (54)		6 (75)	39 (51)		31 (57)	74 (52)	
Family history, n (%)									
Yes	23 (27)	39 (35)	0.26	4 (50)	19 (25)	0.13	20 (37)	42 (30)	0.31
No	61 (73)	73 (65)		4 (50)	57 (75)		34 (63)	100 (70)	

[a] Recurrent DKA: more than one presentation with DKA within the same year or more than two presentations within three years of the last admission
[b] Recurrent presenter: more than one presentation with hyperglycaemia within the same year or more than two presentations within three years of the last admission
* Chi-square test or Fisher exact test for categorical data and t-test for continuous data

Sixty percent of the children (n = 118) were newly diagnosed with T1DM during the study period, of which 38% presented with DKA (n = 45). Children under five years old represented 20% of this cohort (n = 24). The mean age at diagnosis was 8.8 years ± 3.8 years, again with a female predominance (56%) (Table 1). Amongst the total cohort of 196 children, 84 children (43%) presented with DKA. There were 73% of children with DKA who had no family history of diabetes (Table 2).

Overall, the DKA recurrence rate was 10% (n = 8), with two-thirds coming from the newly diagnosed group, with female predominance in all the groups. The older children comprised 50% or more of the overall and new T1DM cohort, while the 5-to-less than10 year old group comprised more than half of the existing T1DM group.

A total of 114 episodes of DKA were recorded: 52% (n = 59) were mild, 24.5% (n = 28) were moderate and 23.5% (n = 27) were severe. The severity comparison between the two age groups is shown in Table 3. Fourteen children (7%) with severe DKA were transferred to a paediatric tertiary care centre, with 78% as newly diagnosed T1DM. No mortality was recorded in our patient cohort.

There were 18 episodes of hypoglycaemia during the study period. Sixteen out of 18 children had mild hypoglycaemia (glucose 3.0-3.9 mmol/l), while two children had severe hypoglycaemia (glucose under 2 mmol/l). The mean age at presentation was 9.3 years ± 4.4 years, mainly on MDI treatment (67%). One-third of the hypoglycaemic events had seizures as their initial presentation, occurring in a younger mean age of 7.5 years ± 4.7 years.

Figure 1 represents the number of presentations during the study period, the majority of which were from the newly diagnosed group.

Table 3. Comparison of DKA severity according to age groups

DKA	Age			*p* value
	Total (n = 114)	Under 5 years (n = 12)	5 - <16 years (n = 102)	
Mild, n (%)	59 (52.0)	5 (42)	54 (53)	0.29*
Moderate, n (%)	28 (24.5)	2 (16)	26 (25)	
Severe, n (%)	27 (23.5)	5 (42)	22 (22)	

*Chi-square test or Fisher exact test

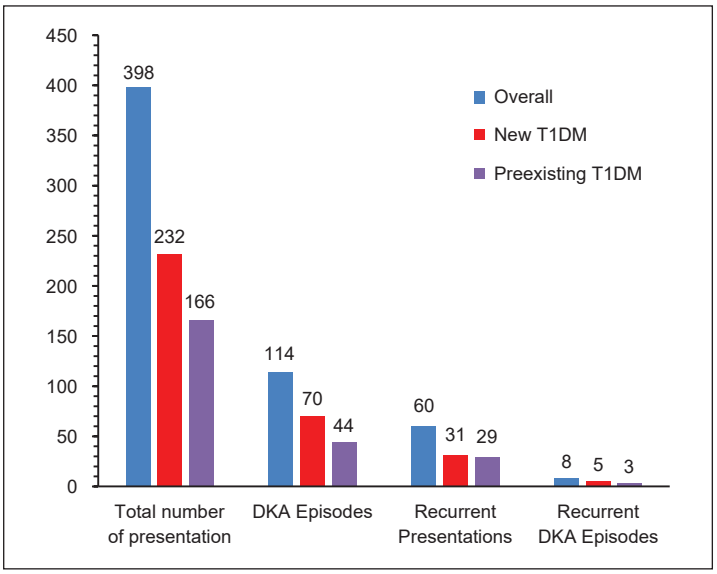

Figure 1. Hospital presentations.

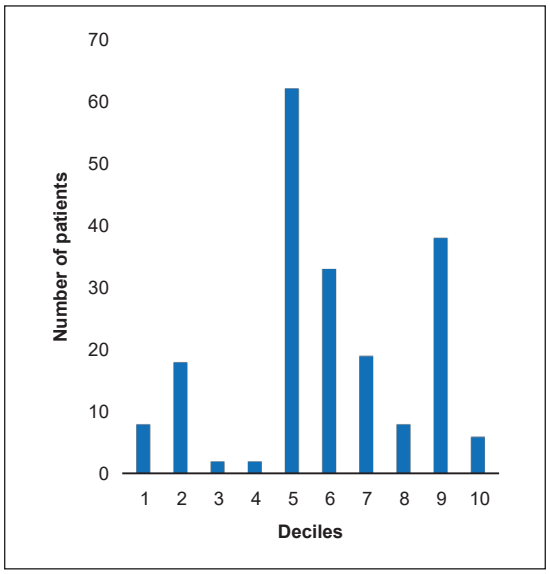

Figure 2. Socioeconomic distribution of patients.

An analysis of the SES of the 196 children in the entire cohort revealed that 32% were in the 5th decile, followed by the 9th decile (19%), while only 4% were in the 1st decile area. Similarly, most recurrent presenters were from the 5th and 9th decile with 37% and 17%, respectively, while 9% were from the 2nd decile and 5% were from the 1st decile.

DISCUSSION

During the ten-year study period, the majority (55%) of the 196 children with T1DM belonged to the older age group, consistent with the national[2] and international data[9,10] indicating that the prevalence and cumulative peak incidence of T1DM is in the 10-to-14 age group. In line with previous reports,[9,10] we noted an overall female predominance (54%) in the cohort and the newly diagnosed group. This has previously been linked to the increased prevalence of autoimmune diseases in females.[11] However, after adjusting for differences in the age structure of the populations, Australian national data reported a 1.4 times increase in T1DM among males than females.[2] Conversely, some studies found no gender difference in the overall incidence of T1DM.[12,13] Contrary to the previously reported increased prevalence of autoimmune diseases like coeliac disease and autoimmune thyroiditis,[11] asthma was the most prevalent comorbid condition, present in 11% of our cohort. This is possibly due to the increased prevalence of allergic conditions in Australia, as previously reported by large multinational studies in children.[14] Despite this increased prevalence of asthma, there was no evidence that it influenced DKA rates in our cohort. In addition, while there appears to be a possible association between atopy/asthma and T1DM, there is no clinical data to suggest that the presence of atopy or asthma alters the risk of DKA in children.

Sixty percent of the children were newly diagnosed with T1DM during the study period. There was an increasing incidence with age, which is in line with findings from a recent similar study from Sydney by Ampt A et al., who gathered data from 2001 to 2013 on the epidemiology and risk factors for DKA in Australian children aged 0 to <15 years.[15]

Over ten years, 75% of the total cohort and 37% of the pre-existing T1DM cohort had one or more episodes of DKA. Previous literature reports the risk of DKA as 1 to 10% per patient per year in children with established diabetes. The likely risk factors include higher HbA1c levels, acute gastroenteritis, peripubertal and pubertal adolescent girls, psychiatric disorders, insulin omission (accidental or intentional), unstable family circumstances and limited access to medical care.[7]

The overall international frequency of DKA at first presentation of T1DM varies from 13 to 80%,[16] depending on the T1DM prevalence, local awareness, young age (<5 years), diagnostic errors, ethnic minority, low SES and lack of access to local health care. A study from New Zealand looking at the 15-year incidence of DKA reported a lower percentage (27%) at the first presentation of T1DM[17] compared to the 48.1% reported by a study from Townsville, Queensland.[6] In contrast, we found that over one-third of the children (38%) had DKA at their first presentation, which is consistent with the previously reported paediatric data from Sydney in 2012 and 2019 and Brisbane in 2013 (i.e., 37.7 per 100 person-years, 33% and 32%, respectively). The national data also indicated relatively stable cumulative incidence rates of T1DM in Australia over the last two decades.[7] Ampt A et al. further quantified the incidence of DKA according to the age groups: 40% in 0 to 4 years, 25% in 5 to 9years, and 33% among 10 to 12-years.[15] These figures align with our findings for 5 to <10-year-old children (24%), but in contrast, we found a lower incidence (24%) of DKA at first presentation in under five-year-old children and highest in the older age group (51%). A possible explanation for this difference may be relatively fewer young families residing in our area during the study period.

National and international studies[18,19] have reported higher DKA rates in young children under five years at T1DM diagnosis. Amongst our total 114 DKA episodes, 52% were mild, while the moderate and severe episodes were 24% each. Alarmingly, among the younger age group with DKA, 42% presented with severe DKA. Like previously mentioned studies, Usher et al.,[18] conducted a systematic review that included 46 studies with more than 24,000 children in 31 countries. They identified risk factors posing the highest risk of DKA at diagnosis, which included younger age, ethnic minority, lack of health insurance, and lower body mass index. This may be due to parents and healthcare personnel having low suspicion of T1DM, atypical presentations and increased difficulty in recognising symptoms as they are young and may have difficulty communicating the symptoms of thirst, with some showing non-verbal cues, which delays diagnosis. Additionally, it has been reported that due to their less developed metabolic compensatory mechanisms, young children may be more prone to decompensation due to dehydration and acidosis, and delayed diagnosis may cause faster β-cell destruction in young children.[20]

DKA recurrence leads to complications that early targeted interventions could avoid through a multidisciplinary team. We report an overall DKA recurrence rate of 10% - 9% in recently diagnosed T1DM and 10% in existing T1DM. In terms of age groups, the older children comprised 50% or more of the overall and new T1DM, while the 5 to <10-year-old children formed more than half of the existing T1DM group. A possible explanation for frequent DKA admissions in older children may be their independence, changes in their daily routine and self-management of BSL, especially when not at home. The very high rates of DKA, approaching 50%, especially in the younger age group <5 years, highlights the need for a campaign towards community diabetes awareness and DKA awareness and prevention, like the 4T campaign first conducted in the UK, then in Newcastle, Australia. However, DKA rates remain

high in both these regions and even nationally, suggesting a lack of translation of this clinical evidence into practice within the existing primary and tertiary care systems.[21]

Studies have highlighted the association of the socio-economically disadvantaged areas with T1DM, DKA and recurrent DKA presentations.[15,22] Contrary to this, we note an increased number of patients from areas of relative socioeconomic advantage consistently with higher prevalence of T1DM, first episode of DKA, recurrent presenters and recurrent DKA presentations. This is consistent with a Western Australian study from 2006.[23] The reasons for this paradoxical observation are unclear, but this increased T1DM association with higher socio-economic areas could be due to unexplained lifestyle differences.[24] Further exploration of this is required.

We also reported the number of children presenting to the emergency department within our cohort with severe hypoglycaemia. Our rates were low, which is consistent with national and international trends for reduced frequency of severe hypoglycaemia. The latter is probably related to the introduction of continuous glucose monitoring systems and improved insulin pump technology preventing hypoglycaemia, as well as better education of families.[25-27]

The main strength of our study was the larger patient cohort, which included follow-up of ten years. The main limitation of the present study was the lack of data on ethnicity, BMI, duration of presenting symptoms and length of hospital stay. This additional data would be helpful in further understanding potential risk factors for T1DM and DKA presentations.

CONCLUSION

T1DM was more prevalent in older children, particularly females, and in areas of relative socioeconomic advantage. However, the incidence of paediatric T1DM was stable over the 10-year study period. The younger age group of under five years presented more frequently with severe DKA compared to older children. This signifies the importance of increasing community awareness about childhood diabetes and timely recognition of its symptoms to prevent DKA.

Acknowledgements
The authors thank Drs. Amna Jawaid, Naveid Ali, You Sheng Chong, Alia Tun-Ismail and Yadwinder Singh for their assistance in the data collection.

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

CRediT Author Statement
SS: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation; **GL:** Conceptualization, Methodology, Writing – review and editing, Supervision, Project administration; **AL:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – review and editing, Visualization, Supervision, Project administration; **HB:** Conceptualization, Methodology, Writing – review and editing, Supervision, Project administration.

Author Disclosure
The authors declared no conflict of interest.

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

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

The Prevalence of Hypophosphatemia and its Associated Risk Factors in Diabetic Ketoacidosis Patients

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Abstract

Objective. We aimed to study the prevalence of hypophosphatemia and its associated risk factors in Diabetic Ketoacidosis (DKA) patients in the pediatric population.

Methodology. We included 65 subjects aged 7 months to 18 years old who were admitted to Hospital Universiti Sains Malaysia (HUSM) for DKA. Patients' socio-demographic and clinical characteristics, and biochemical examinations from their first admission for DKA were analyzed. The diagnosis of DKA was based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria. Multiple logistic regression models examined associations between different variables and hypophosphatemia.

Result. The prevalence of hypophosphatemia in DKA was highest on day 1, at 70.8%, with a mean age of 11 on presentation. Multiple logistic regression analysis showed plasma bicarbonate at day 3 [adjusted odds ratio (OR) 1.2, with a p-value of 0.027] and baseline hemoglobin [adjusted OR 0.62, with p-value 0.009] were significantly associated with hypophosphatemia during DKA.

Conclusion. The prevalence of hypophosphatemia in DKA pediatric patients admitted to our center was highest on day 1 of admission. There were many factors associated with hypophosphatemia from simple logistic regression analysis. However, our final model revealed that plasma bicarbonate on day 3 and baseline Hb were the only significant risk factors for hypophosphatemia in DKA patients in the pediatric population.

Key words: diabetes mellitus, prevalence, hypophosphatemia, risk factors, diabetic ketoacidosis, children

INTRODUCTION

Diabetes Mellitus (DM) is a primary public health concern worldwide.[1] It leads to significant morbidity and mortality.[2] According to the World Health Organization, the prevalence of DM among pediatrics and adolescents worldwide has increased from 4.7% to 8.5% from 1980 to 2014. Diabetes in Children and Adolescents Registry (DiCARE) found that 71.8% of children under the age of 20 years old had type 1 DM while 18% suffered from type 2 DM.[3]

DKA is a complication of poorly controlled diabetes. However, more than half, or 58% of newly diagnosed DM in Malaysia presented with DKA as the first presentation because of low awareness among the public.[2-4]

Most of the electrolyte management in DKA focused mainly on potassium replacement. Until recently, the latest ISPAD consensus guidelines have emphasized other electrolyte derangements such as phosphate, calcium, and magnesium.[2,5] Hypophosphatemia can lead to complications such as anemia, metabolic encephalopathy, seizures, rhabdomyolysis, myocardial infarction, acute respiratory failure, and renal failure.[5-11]

Several important factors are associated with hypophosphatemia in DKA patients, such as metabolic acidosis, anemia, other electrolyte imbalances, fluid resuscitation, timing to start–insulin, poor glycemic control, fasting time, and length of hospital stay.[5, 12-16] There are not many publications related to hypophosphatemia among DKA patients in our region, and considering its clinical significance and serious acute complications, we conducted a retrospective review of all DKA admissions to study the prevalence of hypophosphatemia and its associated risk factors in DKA involving pediatric patients in Hospital Universiti Sains Malaysia (HUSM), Kelantan.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: July 7, 2024. Accepted: August 16, 2024.
Published online first: April 19, 2025.
https://doi.org/10.15605/jafes.040.01.13

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METHODOLOGY

Study design and setting

This retrospective cohort study included all DKA pediatric cases admitted from January 2010 to December 2023 (13 years duration) at HUSM.

Patient and data collection

This study included 65 patients from one study site (HUSM). No sampling method was conducted as we included all the available records of patients aged 18 years and below diagnosed with DKA and excluded those with underlying primary phosphate synthesis and regulation disorders, records that are missing more than 20% of the required information, and those whose case notes were not available from the record system.

DKA was diagnosed based on ISPAD 2017 criteria (hyperglycemia more than 11 mmol/L, acidosis on blood gas [pH<7.3 or HCO3 <15 mmol/L], significant ketonuria [more or equal 2+] or ketonemia [more or equal 3 mmol/L]) and was categorized into mild, moderate, and severe DKA. Meanwhile, the hypophosphatemia level was based on HUSM laboratory references according to the age and gender of the patient.[17] For patients with recurrent DKA, only the first episode of DKA was analyzed to ensure a homogenous sample type.

Data collection was made using proforma comprising socio-demographic data, past medical history, family history of DM, history of presenting illness, summary of hospital admissions, clinical examination, and biochemical results related to DKA and hypophosphatemia (Tables 1-3). Patients' records were extracted from the HUSM record system from 2010 to 2023. A total of 92 patients were admitted for DKA within the specified time period, and 27 were excluded for the following reasons: case notes not available, admission was not the first event of DKA, and incomplete essential data (i.e., phosphate level and blood gas). This left 65 cases that were included in the final analysis of data. The search term used for tracing the patients' medical records were based on ICD10 of DM, DKA, and Hypophosphatemia.

Sample size estimation

The sample size was calculated by using a single proportion formula based on the sample size calculator web[20] to estimate the prevalence of hypophosphatemia in DKA patients as the primary objective of this study. The power and sample size program were as follows: (a) the prevalence of hypophosphatemia in DKA patients based on the previous study was 78%;[21] (b) the margin of error was set at 5%; and (c) the confidence level was set at 95%. This resulted in a sample size of 264 patients. Anticipating a 10% dropout rate, the sample size was adjusted to 294 patients. However, due to the limited sample size based on the previous record of admissions to our center, we decided to use a finite population correction calculator. Using this formula with previous details of the power and sample size program, margin of error of 6.1% and the population size set at 92 samples, the final sample size required after finite population correction calculations was 65.

Table 1. Demographic and clinical parameters

Variables	n (%)
Gender	
Male	28 (43.1)
Female	37 (56.9)
Race	
Malay	62 (95.4)
Others	3 (4.6)
Parents income status	
Higher income	15 (23)
Lower income	50 (76.9)
Parents education status	
Lower education	36 (55.4)
Higher education	29 (44.6)
****Age***	11.0 ± 4.3
Mother antenatal GDM	
Yes	1 (1.5)
No	64 (98.5)
Family History	
None	43 (66.2)
DM	18 (27.7)
DM + HPT	3 (4.6)
HPT + heart disease	1 (1.5)
Newly diagnosed DM	
No	31 (47.7)
Yes	34 (52.3)
Type of DM	
Type 1	47 (72.3)
Type 2	12 (18.5)
Others	6 (9.2)
Type of Insulin	
Human insulin	24 (37.0)
Analog insulin	5 (7.6)
****Onset of DM (years)***	4.0 ± 5.0
****Duration of DM (years)***	1.8 ± 2.9
****Total insulin/day (unit/kg)***	0.56 ± 0.79
****Total Metformin dose (g/day)***	0.06 ± 0.30
****HbA1c (%)***	11.2 ± 3.35

Parents income: Higher income (M40+T20), Lower income (B40), Malaysian household income update 2023[18]

Parents education: Higher education (Diploma and above), Lower education (Primary and secondary school), Categorical n (%), Mean ± SD*, Median (min, max)#

Statistical analysis

The categorical variables were expressed as frequencies and percentages, while data for numerical variables were either presented as mean (SD) or median (IQR), depending on whether the data was normally distributed. The distribution of numerical (quantitative) variables was determined by multiple tests, including the visual method (histogram) and the normality test (to examine the skewness, kurtosis, Kolmogorov–Smirnov test, and Shapiro-Wilk test). Data with normal distribution was presented as median with SD, whereas non-normally distributed data were presented as median and IQR.

Factors associated with hypophosphatemia were determined by logistic regression. We used simple logistic regression

analysis to identify the factors to be included in the multiple regression analysis. We used the cut-off point of p <0.25 in choosing the variables to be included in the final model. The forward selection technique was used for the variable selection method. The probability of entering the model was set at p <0.05. All the assumptions of the tests were examined. There were no interactions and multicollinearity with a variance inflation factor of less than 10.

Table 2. Clinical parameters

Variables	n (%)
DKA Severity	
Mild	10 (15.4)
Moderate	17 (26.2)
Severe	38 (58.5)
#Duration of hospital stay(days)	8.0 (3.0, 20.0)
****Total fluid bolus (ml/kg)***	21.1 ± 13.5
#Insulin infusion dose(u/kg/hour)	0.1 (0.02, 0.1)
#Duration of insulin infusion(hours)	24.0 (5.0, 168.0)
#Timing of infusion insulin on admission (hours)	2.0 (1.0, 96.0)
#Duration of NBM (hours)	22.0 (0.0, 144.0)
#DKA resolution timing (hours)	24.0 (5.0, 120.0)
****Duration of fluid correction(hours)***	40.8 ± 16.2
Tanner staging	
Prepubertal	45 (69.2)
Pubertal	20 (30.8)
#Weight (kg)	32.0 (6.7, 93.0)
****Weight (z-score)***	-0.72 ± 1.58
#Height(m)	1.4 (0.6, 1.8)
****Height (z-score)***	-0.58 ± 1.13
#BMI (kg/m²)	16.4 (11.1, 46.5)
BMI (z-score)	-0.54 ± 1.67
****SBP (mm Hg)***	116.0 ± 15.94
****DBP (mm Hg)***	70.6 ± 12.92
****HR***	122.6 ± 23.31
#GCS	15 (3,15)

Anthropometry (weight, height, and BMI in z-score) CDC growth chart, 2000[19]

Categorical n (%), Mean ± SD,* Median (min, max)#

Table 3. Biochemical data

Variables	Mean*/Median#
****RBS (mmol/L)***	26.5 ± 9.64
#Serum ketone(mmol/L)	3.9 (0.0, 7.8)
****Urine ketone (+)***	3.1 ± 0.76
#pH on admission	7.0 (6.7, 7.3)
#HCO3 on admission	8.3 (1.0, 20.6)
#BE on admission	-22.8 (-30.8, -1.8)
****pH on day 1***	7.2 ± 0.08
****HCO3 on day 1***	13.4 ± 4.20
#BE on day 1	-15.0 (-27.0, -2.6)
#pH on day 3	7.3 (0.0, 7.4)
****HCO3 on day 3***	16.7 ± 5.74
#BE on day 3	-7.2 (-21.6, 7.8)
****Hb (g/dL)***	16.7 ± 5.74
#Urea (mmol/L)	5.1 (1.0, 18.3)
****Creatinine (micromol/L)***	98.0 ± 41.47
****Sodium (mmol/L)***	132.1 ± 7.00
****Potassium (mmol/L)***	4.4 ± 0.92
#Mg (mmol/L)	0.8 (0.0, 1.3)
****Calcium (mmol/L)***	2.3 ± 0.32
#Phosphate on admission (mmol/L)	0.9 (0.2, 1.9)
#Phosphate day 1	0.7 (0.0, 2.7)
#Phosphate day 3	0.9 (0.0, 2.7)
#AST (U/L)	19.0 (5.0, 4474.0)
#ALT (U/L)	15.0 (6.0, 795.0)
#ALP (U/L)	235.0 (37.0,934.0)
#Albumin (g/L)	43.0 (27.0, 72.0)

Categorical n (%), Mean ± SD*, Median (min, max)#

Ethical approval

The study was approved by the Human Research Ethics Committee USM (USM/JEPeM/KK/23010132).

RESULTS

Majority of the included patients were female (56.9%), and predominantly Malay (95.4%). Most of the patients' parents were from a lower income status (76.9%), and about half (55.4%) had lower educational backgrounds (primary and secondary school). The mean age was 11 ± 4.37 years, with onset of DM at a mean of 4.0 ± 5.0 years old and duration of 1.8 ± 2.9 years. Most subjects did not have a history of maternal GDM (98.5%), and did not have a combined family history of DM, HPT, or heart disease (66.2%). Twenty-seven percent were positive for the family history of DM. DKA occurred in both newly diagnosed DM (52.3%) and those previously diagnosed with DM (47.7%). Thirty-seven percent were on human insulin, while only 5 (7.6%) were on analog insulin. Human insulin brands Insulatard and Actrapid were most often used (37.0%), at a mean dosage of 0.56 ± 0.79 unit per kg per day.

In terms of DKA severity, 58.5% had severe DKA, 26.2% had moderate DKA, and 15.4% had mild DKA. The mean fluid bolus during initial resuscitation was 21.1 ± 13.52 ml/kg, and the duration of fluid correction was 40.8 ± 16.22 hours. The dose of insulin infusion was 0.1 (0.02, 0.1) u/kg/hour with a median duration of 24 (5.0, 168.0) hours, and it was initiated at 2 (1.0, 96.0) hours post-hospital admission.

Other pertinent clinical parameters such as blood pressure, GCS, weight, height and BMI are tabulated in Table 2.

Mean RBS was 26.5 ± 9.64 mmol/L and HbA1c was 11.2 ± 3.3 %. Serum ketone and urine ketone levels were 3.9 (0.0,7.8) mmol/L and 3.1 ± 0.76, respectively. Blood gas on admission showed pH 7.0 (6.7, 7.3), HCO3 8.3 (1.0,20.6) and BE -22.8 (-30.8, -1.8). Blood gas on day 1 of admission improved with pH 7.2 ± 0.08, HCO3 13.4 ± 4.20, and BE -15.0 (-27, -2.6). Subsequently, the blood gas on day 3 admission was pH 7.3 (0.0,7.4), HCO3 16.7 ± 5.74, and BE -7.2(-21.6, 7.8), which were consistent with DKA resolution.

Regarding renal functions and other electrolytes, blood urea nitrogen was 5.1 (1.0, 18.3) mmol/L, serum creatinine 98.0 ± 41.47 micromol/L, sodium 132 ± 7.0 mmol/L, potassium 4.4 ± 0.92 mmol/L, Mg 0.8 (0.0,1.3) mmol/L, and calcium of 2.3 ± 0.32 mmol/L. The liver transaminases were AST 19.0 (5,4474) U/L, ALT 15.0 (6,795) U/L. Whereas, ALP was 235.0 (37,934) U/L and serum albumin 43 (27,72) g/L. The mean Hb of our patients was 16.7 ± 5.74 g/dL.

Table 4. Simple and multiple logistic regression analyses to determine factors associated with Hypophosphatemia in DKA

Variables	Crude OR (95% CI)	*P*-value	Adjusted OR (95%)	*P*-value
Family history				
DM	0.3 (0.1,1.0)	0.069		
DM + HPT	0.6 (0.05,8.3)	0.769		
HPT + heart disease	1.0			
Severity of DKA				
Mild	1.0			
Moderate	2.6 (0.5, 13.7)	0.253		
Severe	10.3 (2.12, 50.2)	0.004		
Heart rate	1.03 (1.002, 1.051)	0.035		
Duration of fluid correction	1.03 (0.9, 1.0)	0.069		
Urine ketone	2.0 (1.0, 4.2)	0.042		
pH on admission	0.003 (0.0, 0.2)	0.007		
HCO3 on admission	0.7 (0.6, 0.9)	0.003		
BE on admission	0.8 (0.7, 0.9)	0.002		
pH day 3	1.3 (1.0, 1.8)	0.049		
HCO3 day 3	1.1 (1.0, 1.2)	0.017	1.2 (1.0, 1.3)	0.027
Hb	0.7 (0.5, 0.9)	0.039	0.62 (0.4, 0.8)	0.009
Calcium	0.2 (0.02, 1.2)	0.080		
Albumin	0.9 (0.8, 1.0)	0.081		

On the day of admission, serum phosphate was noted to be 0.9 (0.2, 1.9) mmol/L, which then dropped to 0.7 (0.0, 1.7) mmol/L on day 1 of admission and improved with a median of 0.9 (0.0,2.7) mmol/L on day 3 of admission. The prevalence of hypophosphatemia among DKA patients on presentation was 66.2% (CI 0.5, 0.70), and it increased to 70.8% (CI 0.5,0.8) while patients were receiving treatment on day 1 and later reduced to 56.9% (CI 0.4,0.6) on the third hospital day.

Based on simple logistic regression analysis, family history of DM (Crude OR 0.3 (0.1,1.0), *p*-value 0.069), severe DKA (Crude OR 10.3 (2.12, 50.2), *p*-value 0.004), heart rate (Crude OR 1.03 (1.002, 1.051), *p*-value 0.035), duration of fluid correction (Crude OR 1.03 (1.002, 1.051), *p*-value 0.069), urine ketone (Crude OR 2.0 (1.0, 4.2), blood gas on admission (pH on admission Crude OR 0.003 (0.0,0.2) *p*-value 0.007), (HCO3 on admission Crude OR 0.7 (0.6,0.9) *p*-value 0.003), (BE on admission Crude OR 0.8 (0.7, 0.9) *p*-value 0.002), pH on day 3 (Crude OR 1.3 (1.0, 1.8), *p*-value 0.049), HCO3 on day 3 (Crude OR 1.1 (1.0,1.2), *p*-value 0.017), baseline Hb (Crude OR 0.7 (0.5, 0.9), *p*-value 0.039), serum calcium (Crude OR 0.2 (0.02, 1.2), *p*-value 0.080) and albumin (Crude OR 0.9 (0.8,1.0), *p*-value 0.081) were significantly associated with hypophosphatemia among DKA patients. However, only HCO3 on day 3 [adjusted OR 1.2 (1.0,1.3), a *p*-value of 0.027], and baseline Hb [adjusted OR 0.62 (0.4, 0.8), a *p*-value of 0.009] proved to be significantly associated with hypophosphatemia using multiple logistic regression analysis (Table 4).

There were no interactions and multicollinearity with a variance inflation factor of less than 10. The Hosmer-Lemeshow test assessed the model's fitness, and 76.9% of cases were predicted correctly. The area under the curve (AUC) was 83% with 95% CI (0.72,0.93). There were no significant outliers, high leverage points or highly influential points as checked by Cook's influential statistics.

DISCUSSION

We managed to review 65 DKA patients, aged 7 months to 18 years old, admitted to our hospital from 2010 to 2023. The prevalence of hypophosphatemia in DKA patients was highest on day 1 (70.8%) and lowest on day 3 admission (56.9%), which was consistent with another local study by Anand et al., that had a prevalence of hypophosphatemia among DKA patients of 78%.[21] A study by Van Der Vaart et al., also showed the prevalence of hypophosphatemia in DKA patients to be similar, at about 74%.[15] However, a study by Sanluis Fenelli G et al., showed a lower prevalence of hypophosphatemia on day 1 admission (after treatment) at only 36.7%.[12] Despite a difference in the prevalence from various studies, we noticed similarities in trend of phosphate levels from a lower level at baseline which further declines to reach the lowest level on day 1 and then slowly improves throughout admission.

Our study showed a female predominance at 56.9% compared to males at 43.1%. The study of Van Der Vaart et al., also showed female predominance at 50.4%.[15] In contrast, a study by El-Naggar A et al., showed male predominance at 64.7%.[16] Most of our patients were Malay since the East Coast of Malaysia is mainly populated by Malay, and they were from lower socio-economic backgrounds. The high prevalence of DKA as the first presentation in new cases of DM and in those previously diagnosed to have DM may be associated with poor public awareness or lack of education.[3]

The mean age of DKA at presentation was 11 years old, the same as a local study by Anand LA et al.[21] According to ISPAD guideline 2017, DKA at diagnosis is commonly seen in younger children aged less than 2 years old, including infants with both transient and permanent neonatal diabetes.[2] However, in the study by Hong et al., the mean age of DKA at presentation was mainly the age of more than 5.[3] It was concluded in most of the studies

that age did not show any significant association with hypophosphatemia.[12-16]

Most of the patients did not have a mother with antenatal GDM (98.5%) and did not have family history of DM, HPT, or heart disease (66.2%). Our patients were mainly type 1 DM, which explained why the family history for DM was negative. This contrasts with a local study by Hong et al., where the proportion was 56.9% for a positive family history of DM in DKA patients.[3] The study recruited patients from mainly Klang Valley with a higher proportion of type 2 DM than our cohort.

Type 1 DM predominates most of our patients (72.3%) compared to type 2 (18.5%) and other types of DM (9.2%). It showed that DKA is more common in type 1 DM since type 1 DM is due to absolute insulin deficiency, leading to increased endogenous glucose production and counter-regulatory hormones.[2] In Malaysia, the rate of DKA occurrence at the onset of T1DM was as high as 57.5% because of poor public awareness since type 1 DM is not common in our region compared to Europe.[4] The overall prevalence of T2DM is on the rise, which is consistent with an increase in the prevalence of obesity.[5] In type 2 DM, DKA occurs as a consequence of relative insulin deficiency. High adiposity in type 2 DM leads to insulin cascade signaling interference, resulting in insulin resistance syndrome. During the time of infection, the rise of counter-regulatory hormones contributes to a high glucose load, and whenever the body is unable to meet the demands, it results in relative insulin deficiency and, ultimately DKA.[22]

Hypophosphatemia correlates with the degree or severity of DKA. In DKA, there is intracellular depletion of phosphate associated with the shift of phosphate from the intracellular to the extracellular compartment associated with metabolic acidosis. Renal tubular phosphate reabsorption is impaired during DKA, resulting in hyperphosphaturia. With fluid and insulin administration during the treatment phase of DKA, phosphate is shifted back into the intracellular compartment, leading to low plasma phosphate levels. Hence, hypophosphatemia is caused by osmotic losses in the urine and secondary to fluid and insulin administration during the treatment phase of DKA.[2] We found that severe acidosis on admission had increased odd 10.3; 95% CI (2.1,50.2) from simple logistic regression analysis.

The majority of our patients were prepubertal with a low BMI of 16.4 kg/m^2 (z-score -0.54), which was typical of type 1 DM with poorly controlled DM, and this finding was similar to Hong et al.[3] They had normal BP with normal GCS on presentation, which showed that even though 58% presented with severe DKA, complications such as decompensated shock and cerebral edema were rare. Their overall HbA1c was high (11.2%), similar to Anand et al., which showed a mean HbA1c of 12.6%.[19] High HbA1c had a significant correlation with low-level serum phosphate, according to Hasan et al.,[13] which was not demonstrated in our current study.

From univariate analysis, positive predictors of hypophosphatemia in DKA were BE on admission [OR 0.8 (0.7,0.9)], HCO3 at day 3 [OR1.1 (1.0,1.2)], urine ketone [OR 2.0 (1.0,4.2)], fluid boluses [OR 1.3 (1.0,1.6)], duration of fluid correction [OR 1.03 (0.9,1.0)], heart rate [OR 1.03 (1.002,1.051)], severe DKA [OR 10.3 (2.12,50.2)], and pH at day 3 [OR 1.3 (1.0,1.8)]. In our study, the BE on admission was high (-22.6), typically seen in severe DKA, which later normalized, as evidenced by normal pH and HCO3 on day 3. This could be explained by the patient's treatment, which includes insulin infusion and fluid therapy. Insulin facilitates glucose and phosphate uptake into the cells, while fluid administration corrects the hyperosmolar state due to hyperglycemia. High levels of blood glucose that exceed the renal threshold for glucose reabsorption result in osmotic diuresis and worsening of hypophosphatemia. When DKA has been reversed, as evidenced by increasing pH and bicarbonate levels, phosphate levels will normalize, too. Protective predictors for hypophosphatemia were positive family history of DM [OR 0.3 (0.1,1.0)], serum albumin [OR 0.9 (0.8, 1.0)], calcium [OR 0.2 (0.02, 1.2)], baseline Hb [OR 0.7 (0.5,0.9)], pH admission [OR 0.003 (0.0, 0.2)] and HCO3 on admission [OR 0.7 (0.6,0.9)]. Those with normal levels of albumin, calcium, hemoglobin, and bicarbonate and a positive family history of DM were less likely to have hypophosphatemia.

There were 2 significant predictors of hypophosphatemia from the multivariate analysis: plasma bicarbonate level on day 3 [OR 1.2 (1.0,1.3)] and hemoglobin level at baseline [OR 0.62 (0.4,0.8)]. The plasma HCO3 level on day 3 admission (while the patient received ongoing treatment) increases the odds of hypophosphatemia by 1.2 times. This is due to increased intracellular glycolysis that consumes phosphate for ATP production, resulting in the reduction of intracellular phosphate, and to compensate for this, the extracellular phosphate will enter cells, leading to low serum phosphate levels. The Hb at baseline was associated with 38% decreased odds of having hypophosphatemia. This important information reflects the volume depletion secondary to osmotic diuresis leading to phosphate loss. These 2 final predictors were also reported by Van der Vaart et al., study in 2021.[15]

Limitations of the study

The study had a few limitations. The cases were limited to our centre alone. They might not truly represent DKA cases with hypophosphatemia in our state since some of the cases were managed at other hospitals. The study design in itself was a limitation as it was a retrospective cohort study which tend to have a lot of missing data. It would be ideal to perform a prospective study with a longer duration to follow the patient up and for more extensive monitoring of important laboratory parameters. In addition, to achieve a good sample size the study might need to be done in multicentre in the future.

CONCLUSION

The prevalence of hypophosphatemia in pediatric patients admitted to our center for DKA was highest on day 1 of admission. Many factors were identified to be associated with hypophosphatemia from simple logistic regression analysis, however, final model revealed that plasma bicarbonate on day 3 and baseline Hb were the only significant risk factors for hypophosphatemia in DKA patients. Nevertheless, with the small sample size of this study, our results need to be verified in larger, well-powered studies of a similar nature.

Acknowledgments
The authors would like to express gratitude to the supervisors, co-supervisors, statisticians, fellow lecturers, colleagues, supporting staff, family, and the team of authors used as references.

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

Author Disclosure
The authors declared no conflict of interest.

CRediT Author Statement
MHR: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **SH**: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **MHK:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **NJA:** 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 generated and analyzed are included in the published article.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Raised Bisphenol A has a Significant Association with Adverse Reproductive Manifestations Rather than Biochemical or Hormonal Aberrations in Women with Polycystic Ovary Syndrome

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Abstract

Background. Bisphenol A (BPA) is a widely used industrial element. Recently it is suspected that BPA may disrupt the endocrine system to influence the manifestations of polycystic ovary syndrome (PCOS).

Objective. This study aimed to assess serum BPA level and its association with manifestations of PCOS in women.

Methodology. This cross-sectional study included 40 young adults with PCOS and 38 age-matched control women [23.0 (20.0, 29.0) vs. 25.0 (21.0, 29.0), years, median (IQR), $p = 0.406$]. After a thorough clinical examination, fasting blood was collected in the follicular phase of the menstrual cycle to measure glucose, lipids, insulin, luteinizing hormone, follicle-stimulating hormone, total testosterone, sex hormone binding globulin, dehydroepiandrosterone sulfate, and BPA. Glucose was measured by glucose oxidase, lipids by glycerol phosphate dehydrogenase-peroxidase, all hormones including SHBG by chemiluminescent immunoassay and BPA by sandwiched enzyme-linked immunosorbent assay. Insulin resistance was measured using homeostasis model assessment of insulin resistance.

Result. Women with PCOS had significantly higher BPA levels (ng/mL) than the control group [27.30 (25.60, 33.40) vs. 24.0 (15.58, 28.70), median (IQR), $p = 0.001$]. Using the 75th percentile value of the control group, 15 (37.5%) women with PCOS had high BPA levels. Those with high BPA levels had a significantly higher frequency of menstrual regulation / abortion among women with PCOS [53.8% vs. 0%, $p = 0.005$]. Women with PCOS with a history of menstrual regulation / abortion [36.7 ± 4.9 vs. 28.5 ± 6.4, mean ± SD, $p = 0.004$] and subfertility [34.3 ± 6.8 vs. 28.5 ± 6.4, mean ± SD, $p = 0.031$] had higher levels of BPA than those without the histories. Serum BPA had no significant association or correlation with any androgenic and metabolic manifestations.

Conclusion. Raised BPA level may be associated with adverse reproductive features in PCOS.

Key words: polycystic ovary syndrome, Bisphenol A, endocrine disruptors, abortion

INTRODUCTION

Polycystic ovary syndrome (PCOS), one of the common female reproductive endocrinopathies, is characterized by irregular menstrual cycles, mild hyperandrogenism as well as poor metabolic features. Despite a wide range of manifestations, the prevalence of PCOS is high throughout the world.[1] However, its pathogenesis is not fully unmasked as yet. Recent studies suggest that environmental factors like Bisphenol A (BPA) may play an important role in increasing the prevalence of this syndrome by interfering with hormone-sensitive systems.[2] BPA is an endocrine-disrupting chemical found in different materials made up of plastics and epoxy resins used for food packaging, the lining of cans, cosmetics, plastic consumer products, etc.[3] It can enter our body by different routes and can produce hyperandrogenemia by various mechanisms. This includes increased ovarian synthesis and reduced catabolism of testosterone, displacing testosterone from sex-hormone binding globulin (SHBG) and up-regulating gonadotropin pulse generator activity.[4] Besides, there is a vicious relationship between BPA and androgens whereby one increases the other and vice versa. Moreover, BPA may act directly as a weak estrogen. Exposure to BPA in utero may produce early puberty, PCOS-like features, metabolic abnormalities and, later, infertility in the animal

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 21, 2024. Accepted: September 22, 2024.
Published online first: April 20, 2025.
https://doi.org/10.15605/jafes.040.01.14

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model.[4-6] Also, BPA may interfere with *in-vitro* fertilization.[7] However, the possible link between human exposure to BPA and manifestations of PCOS is still far from clear. This study aims to determine serum BPA levels and their associations with reproductive, androgenic and metabolic manifestations of PCOS.

METHODOLOGY

This cross-sectional study was done in the Department of Endocrinology of a University hospital for over one year. The protocol was approved by the Institutional Review Board of the same University prior to the conduct of the study. All study participants provide informed written consent. The study was conducted in accordance with the Helsinki Declaration.

The sample size was calculated using the following the formula: $n= (Z\alpha + Z_{\beta})^2 \times (\sigma_1^2 + \sigma_2^2) \div (\mu_1 - \mu_2)$.[2] Using the formula and applying the mean and standard deviation of BPA in PCOS and control from a previous study, the minimum sample size was 36.[8] In this study, we included 40 newly detected young (18-35 years) patients with PCOS and 38 age-matched control using the inclusion and exclusion criteria.

The Revised 2003 Rotterdam Consensus criteria was utilized to diagnose PCOS [presence of any two of the following: oligo/anovulation, clinical and/ or biochemical signs of hyperandrogenism and polycystic ovaries (PCO) by ultrasonography (USG); along with the exclusion of similar diseases [thyroid function abnormality (thyroid stimulating hormone: TSH <0.5 or >5.5 mIU/ml, hyperprolactinemia (>25 ng/ml), non-classic congenital adrenal hyperplasia by appropriate clinical investigations (synacthen-stimulated 17-hydroxyprogesterone >10 ng/ml)].[9] For healthy controls, regular menstrual cycle, insignificant hirsutism (modified Ferriman-Gallwey, mFG score <8) and normal free androgen index (FAI <5%) were considered as inclusion criteria. Those who had significant renal (eGFR <60 ml/ minute/1.73 m^2 body surface area) or liver disease (ALT >2 times upper limit of normal) and a history of taking any oral contraceptives, insulin-sensitizing drugs, anti-androgen, aspirin, statin, warfarin, anti-depressants, non-steroidal anti-inflammatory drugs, corticosteroid and gonadotropin-releasing hormone (GnRH) agonist/antagonist within last six months were excluded from the study.

Relevant personal and family histories (FH) were taken, and thorough physical examinations [height, weight, waist circumference (WC), blood pressure (BP), hirsutism by mFG score and acne] were done by the same investigator to maintain standardization of procedures. Fasting blood (taken 8-12 hours after the last meal) was taken from each participant during the follicular phase of the menstrual cycle (except for those with amenorrhea for whom it was done irrespective of phase) to measure luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S) and BPA. BPA was measured with a commercially available ELISA kit (MyBioSource Ltd., California, United States) using the double-sandwich ELISA technique. All hormones, including SHBG, were analyzed by chemiluminescent microparticle immunoassay, whereas, glucose and lipids were analyzed by glucose oxidase method and glycerol phosphate dehydrogenase-peroxidase method, respectively.

A modified mFG score of at least 8 (eight) was considered significant hirsutism, whereas a BMI of at least 25 kg/m^2 and WC of at least 80 cm were considered general and central obesity, respectively.[10,11] Free androgen index (FAI) was calculated using the following formula: (TT÷SHBG)×100% and a value ≥5 was considered as hyperandrogenemia.[12] An LH/FSH ratio (LFR) >2.0 was considered as an altered LFR.

All the data were checked for any missing or discrepant value by another senior author and corrected accordingly. SPSS Version 22.0 was used to statistically analyze the data collected. The 75th percentile value of serum BPA of the control group was used to categorize the PCOS group into high and not high BPA groups. Qualitative variables were expressed in frequencies (percentages, %). Pearson's chi-square test or Fisher's exact test (if >20% of cells had expected count <5) assessed for the association between two qualitative variables. The choice of test for association between qualitative and quantitative variables was decided considering the distribution of the quantitative variables in each subgroup of the qualitative variable. Quantitative variables were checked according to subgroups (PCOS vs. control and subgroups of different manifestations of PCOS) by the Shapiro-Wilk's test for distribution. If the quantitative variable's distribution was normal in both subgroups, a parametric test (Independent sample's t-test) was chosen (study groups vs. BMI and WC; menstrual cycle, MR/ abortion, subfertility and acanthosis nigricans category vs. BPA). Otherwise, a non-parametric test (Mann-Whitney U test) was carried out. Quantitative variables were expressed in either mean ± standard deviation (SD) or median (inter-quartile range, IQR) depending on the distributions. A Spearman's correlation test was run to assess the correlation between serum BPA (skewed distribution in PCOS) and the different variables among women with PCOS. Statistical significance was set at two-tailed p-values below 0.05.

RESULTS

Among the 40 patients with PCOS, 35 (87.5%) had irregular menstrual cycles, 34 (85.0%) had clinical and/or biochemical hyperandrogenism and 32 (80.0%) had PCO. A total of 48 participants (PCOS: 26, control: 22) were eligible for evaluation of subfertility and menstrual regulation (MR)/ abortion. Women with PCOS had a higher frequency of subfertility, family history of PCOS and obesity than the control group. They also had poor metabolic features (higher BMI, WC, systolic BP, diastolic BP, 2H-OGTT glucose, fasting insulin, HOMA-IR, TC, and LDL-cholesterol; presence of acanthosis nigricans; and lower HDL-cholesterol), greater

features of hyperandrogenism (increased presence of acne; higher levels of TT, FAI and DHEAS; and, lower SHBG) and higher LH/FSH ratio (Table 1).

Figure 1 shows that patients with PCOS had a significantly higher level of serum BPA (ng/mL) than healthy control [mean rank: 48.0 vs. 30.5, U=1101.5, p=0.001]. Using the 75th percentile value of serum BPA (28.7 ng/mL) of the control group, 15 (37.5%) women with PCOS had high BPA.

Among the different features, women with PCOS who have high BPA levels had a significantly higher frequency of only MR/ abortion than those without high BPA levels [53.8% vs. 0%, p=0.005] (Table 2).

Table 1. Characteristics of the study participants (n = 78)

Variables	PCOS, n = 40	Control, n = 38	*p*
Age, years	23.0 (20.0, 29.0)	25.0 (21.0, 29.0)	0.406*
Age of menarche, year	12.0 (11.0, 12.0)	12.0 (11.0, 13.0)	0.530*
Subfertility [n=48]	10 (38.5.0) [26]	0 (0.0) [22]	**0.001†**
Menstrual regulation/abortion [n=48]	7 (26.9) [26]	2 (9.1) [22]	0.151†
Family history of:			
Polycystic ovary syndrome	8 (20)	0 (0.0)	**0.005†**
Obesity	26 (65)	13 (32.50)	**0.004‡**
Diabetes mellitus	27 (67.5)	20 (52.6)	0.180‡
Body mass index, kg/m²	29.0±5.7	22.7±3.2	**<0.001‡**
Waist circumference, cm	92.1±13.1	77.8±9.1	**<0.001‡**
Systolic blood pressure, mm Hg	120.0 (100.0, 120.0)	110.0 (100.0, 110.0)	**0.003***
Diastolic blood pressure, mm Hg	80.0 (70.0, 85.0)	67.50 (60.0, 70.0)	**<0.001***
Acne	23 (57.5)	4 (10.5)	**<0.001‡**
Acanthosis nigricans	28 (70.0)	1 (2.6)	**<0.001‡**
LH/FSH ratio	2.0 (1.1, 2.6)	1.1 (0.7, 1.5)	**0.001***
Total testosterone, ng/dL	46.2 (30.6, 98.2)	20.7 (16.7, 26.1)	**<0.001***
Sex hormone-binding globulin, nmol/L	10.4 (8.1, 20.7)	34.1 (24.3, 64.4)	**<0.001***
Free androgen index, %	13.1 (4.7, 38.5)	1.65 (1.2, 3.2)	**<0.001***
DHEA sulfate, µgm/dL	208.6 (147.4, 301.8)	153.2 (93.8, 189.2)	**0.002***
Fasting plasma glucose, mmol/L	5.0 (4.8, 5.5)	5.20 (4.8, 5.5)	0.531*
02 hours after OGTT glucose, mmol/L	7.50 (6.2, 8.7)	6.9 (5.9, 7.2)	**0.017***
Fasting insulin, µIU/ml	11.4 (10.0, 22.7)	8.3 (6.2, 9.8)	**<0.001***
Homeostasis model assessment of IR	2.6 (2.1, 6.0)	1.8 (1.4, 2.3)	**<0.001***
Total cholesterol, mg/dL	188.5 (172.5, 210.8)	165.5 (147.5, 186.5)	**0.002***
LDL cholesterol, mg/dL	119.5 (102.3, 135.5)	99.0 (88.5, 119.8)	**0.003***
HDL cholesterol, mg/dL	46.0 (40.3, 52.5)	42.5 (37.3, 47.8)	**0.035***
Triglyceride, mg/dL	126.5 (98.0, 163.8)	105.0 (72.3, 143.5)	0.136*

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone (DHEA), oral glucose tolerance test (OGTT), insulin resistance (IR), low-density lipoprotein (LDL), high-density lipoprotein (HDL)

Quantitative variables were expressed in median (IQR) (skewed) or mean±SD (normal distribution) and qualitative variables in frequency (%)

Within parentheses are the percentages over the column total for qualitative variables

*Mann-Whitney U test, ‡independent samples t-test, †Fisher's exact test, and ‡Pearson's chi-square test were done, as appropriate

Table 2. Characteristics of women with PCOS according to Bisphenol A level categories (cut-off of 28.7 ng/mL) (n = 40)

Variables	High BPA, n = 15	Not high BPA, n= 25	*p*
Irregular cycle	13 (86.7)	22 (88.0)	1.000†
Subfertility [26]	7 (53.8) [13]	3 (23.1) [13]	0.107‡
Menstrual regulation/abortion [26]	7 (53.8) [13]	0 (0.0) [13]	**0.005†**
Obesity (body mass index ≥25 kg/m²)	13 (86.7)	17 (68.0)	0.269†
Central obesity (WC ≥80 cm)	14 (93.3)	20 (80.0)	0.381†
Acne	8 (53.3)	15 (60.0)	0.680‡
Acanthosis nigricans	12 (80.0)	16 (64.0)	0.477†
Significant hirsutism (mFGS ≥8)	10 (66.7)	19 (76.0)	0.716†
Hyperandrogenemia (FAI ≥5%)	11 (73.3)	19 (76.0)	1.000†
Altered LH/FSH ratio (≥2.0)	7 (46.7)	12 (48.0)	0.935‡
Insulin resistance (HOMA-IR ≥2.6)	10 (66.7)	10 (40.0)	0.102‡
Metabolic syndrome (3 out of 5 criteria)	4 (26.7)	7 (28.0)	1.000†
Polycystic ovary	11 (73.3)	21 (84.0)	0.444†

Waist circumference (WC), modified Ferriman-Gallwey score (mFGS), free androgen index (FAI), luteinizing hormone (LH), follicle-stimulating hormone (FSH), homeostasis model assessment of insulin resistance (HOMA-IR)

Within parentheses are the percentages over the column total

†Fisher's exact test and ‡Pearson's chi-square test were done as appropriate

Among women with PCOS, having a history of MR/abortion [mean rank: 20.4 vs. 11.0, U=115, p=0.004] and subfertility [mean rank: 17.6 vs. 10.9, U=121.0, p=0.031] had higher levels of BPA than those without unfavorable reproductive histories (Table 3).

Serum BPA had no significant correlation with any of the studied variables among women with PCOS (Table 4) including BMI, 2H-OGTT glucose values and HDL-cholesterol (all $\rho<\pm0.1$, not shown in tables).

DISCUSSION

This study found a significantly higher level of BPA among women with PCOS than in healthy controls. The presence of significant BPA levels also had significant associations with MR/abortion and subfertility in women with PCOS. However, there were no significant associations of BPA with the different androgenic and metabolic manifestations of PCOS.

Table 3. Serum bisphenol A levels with different manifestations among women with PCOS (n = 40)

Variables	Subgroups	No. (%)	Serum BPA levels	*p*
Menstrual cycle	Irregular	35 (87.5)	29.4 ± 6.7	0.975‡
	Regular	5 (12.5)	29.5 ± 5.5	
Menstrual regulation/ abortion [26]	Present	7 (26.9)	36.7 ± 4.9	**0.004**‡
	Absent	19 (73.1)	28.5 ± 6.4	
Subfertility [26]	Present	10 (38.5)	34.3 ± 6.8	**0.031**‡
	Absent	16 (61.5)	28.5 ± 6.4	
Hirsutism (modified F-G score ≥8)	Significant	29 (72.5)	26.9 (25.3 – 33.5)	0.437*
	Insignificant	11 (27.5)	27.8 (25.9 – 33.7)	
Acanthosis nigricans	Present	28 (70.0)	29.8 ± 6.8	0.617*
	Absent	12 (30.0)	28.6 ± 5.9	
Acne	Present	23 (57.5)	27.4 (24.6 – 32.4)	0.386*
	Absent	17 (42.5)	27.0 (26.1 – 36.6)	
Body mass index (≥25 kg/m²)	Obesity	30 (75.0)	27.2 (25.9 – 35.1)	0.259*
	Non-obesity	10 (25.0)	27.5 (22.6 – 29.5)	
Androgen levels (free androgen index ≥5%)	Hyperandrogenemia	30 (75.0)	27.3 (25.0 (33.9)	0.612*
	Normoandrogenemia	10 (25.0)	27.3 (26.3 – 34.9)	
LH/FSH ratio (≥2.0)	Altered	19 (47.5)	26.9 (24.6 – 34.5)	0.708*
	Normal	21 (52.5)	27.7 (25.9 – 33.1)	
HOMA-IR (≥2.6)	Insulin resistance	20 (50.0)	28.7 (26.5 – 33.4)	0.547*
	Insulin sensitive	20 (50.0)	27.1 (25.0 – 33.1)	
Metabolic syndrome (3 out of 5 criteria)	Present	11 (27.5)	26.9 (26.4 – 31.5)	0.976*
	Absent	29 (72.5)	27.4 (25.3 – 34.1)	
Polycystic ovary	Present	32 (80.0)	27.0 (25.0 – 33.4)	0.396*
	Absent	8 (20.0)	29.5 (26.2 – 35.6)	

Ferriman-Gallwey (F-G), luteinizing hormone (LH), follicle-stimulating hormone (FSH), homeostasis model assessment of insulin resistance (HOMA-IR)
Quantitative data with normal and skewed distribution were expressed in mean±SD and median (IQR) respectively
*Mann-Whitney U test and ‡independent samples t-test were done, as appropriate

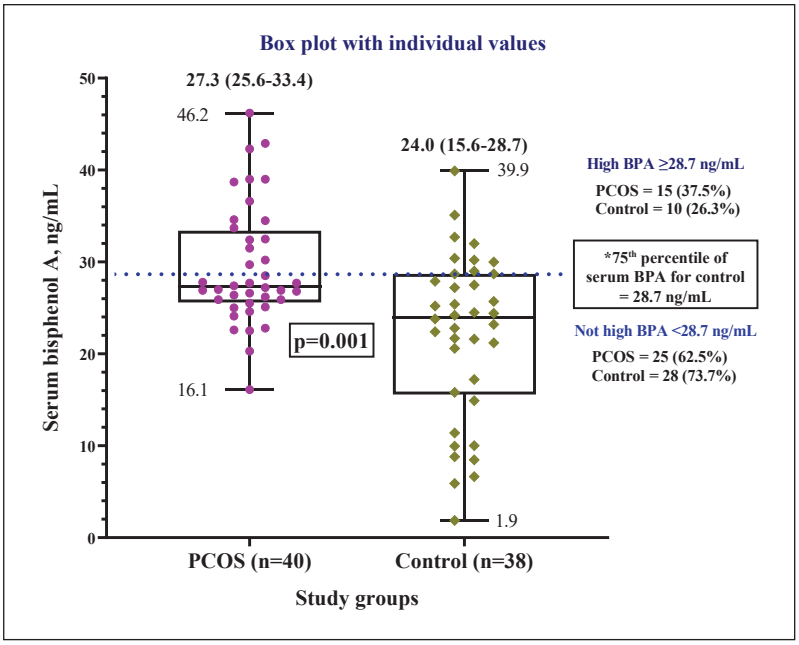

Figure 1. Serum bisphenol A levels [median (IQR)] of the PCOS group compared to the healthy control group. (n= 78)

*Based on the 75th percentile of BPA levels in the control group, study participants were divided into high (≥28.7 ng/mL) and not high (<28.7 ng/mL) BPA subgroups.

Table 4. Correlations between serum bisphenol A and different manifestations among women with PCOS (n= 40)

Variables	ρ (rho)	*p*
Age, years	0.3	0.364
Age of menarche, year	0.5	0.135
Waist circumference, cm	0.3	0.405
Systolic blood pressure, mm-Hg	-0.1	0.713
Diastolic blood pressure, mm-Hg	0.1	0.749
Modified Ferriman-Gallwey score	0.1	0.749
Total testosterone, ng/dL	0.4	0.214
Sex hormone-binding globulin, nmol/L	0.1	0.777
Free androgen index, %	0.4	0.328
DHEA sulfate, µgm/dL	-0.4	0.200
LH/FSH ratio	0.4	0.244
Fasting plasma glucose, mmol/L	-0.2	0.637
Total cholesterol, mg/dL	0.2	0.651
Low-density lipoprotein cholesterol, mg/dL	0.1	0.828
Triglyceride, mg/dL	-0.6	0.082
Fasting insulin	0.2	0.189
HOMA-IR	0.3	0.116

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone (DHEA), homeostasis model assessment of insulin resistance (HOMA-IR)

Spearman's correlation test was done.

We found a detectable level of BPA in all study participants. It indicates chronic exposure to BPA in the general population. It is hypothesized that the increase in the prevalence of PCOS in our setting may be attributable to industrialization and urbanization in the population and its possible interaction with unhealthy lifestyle habits. These enhance the chance of exposure to different endocrine disruptors, including BPA, which may play a role in the development of PCOS. We have seen an increased level of BPA in women of reproductive age, most of whom were from the areas around the hospital, which is located in an urban area. Moreover, control subjects also inhabit the same area as with their PCOS counterparts. The concept that incremental increases in BPA levels is associated with the presence of PCOS is unfounded. It is worth mentioning that BPA is also detectable in the control group. We can only surmise that some of them may also develop PCOS as time lapses. This is beyond the scope of this study. In the future, such studies may be done to periodically and longitudinally follow similar women to determine the link between BPA and PCOS.

Several studies also found significantly higher serum or urinary BPA in the PCOS group than in the control.[8,13-15] In this study, we observed a numerically higher BPA level in the PCOS group than in the previous studies.[8,15] A meta-analysis has shown a potential association between BPA and PCOS, as well as higher BPA in Asians than in other populations.[16] On the other hand, other authors did not find a significant difference in serum or urinary BPA levels in PCOS compared to the control group.[17,18]

Tarantino et al. (2013) found that PCOS patients with a higher level of BPA (cut-off of 0.45 ng/mL, the 95th percentile of BPA in control) had significantly higher HOMA index, FAI, and inflammatory markers than those with lower (<0.45 ng/mL) BPA.[19] We did not find a significant association of higher BPA (≥28.7 ng/mL) with any androgenic or metabolic manifestations of PCOS. However, we only found a significant association of higher BPA with MR/ abortion in PCOS patients. Furthermore, these women with a history of MR/abortion and subfertility had a higher level of serum BPA than those without. These indicate that BPA may create an adverse environment in the early development of the embryo. Studies have also shown significantly higher BPA levels in ovarian follicles and fetal amniotic fluid that may affect preimplantation development of embryos via estrogen receptors.[20,21]

We did not find significant association of BPA with any previously studied androgenic manifestations in PCOS. Our findings are consistent with Jerwickz et al. (2021).[22] While some studies found significant positive associations of BPA with androgenic features, others found a negative association.[8,13,1] Similarly, we did not find significant associations of BPA with any metabolic features of PCOS. Konieczna et al. (2018) and Akgül et al. (2019) also did not find significant associations of BPA with any metabolic manifestations in PCOS.[15,23] However, some authors have found significant associations of BPA with different metabolic manifestations in PCOS.[8,24,25] So, the exact associations of BPA with different manifestations of PCOS are not yet fully elucidated.

Although the sample size was adequate for the assessment of the association between BPA and PCOS, it was not sufficient enough to run a regression analysis to see the independent association between BPA and PCOS or its manifestations. The cross-sectional nature of the study design cannot provide a causal relationship between BPA and PCOS. Due to limitations, we could not measure serum estradiol, androstenedione and free testosterone in our study participants. Moreover, we were unable to assess the exposure level of the study participants to BPA.

CONCLUSION

In conclusion, BPA is detectable in all the study participants with a significantly higher level in the PCOS group in whom it may be associated with MR/abortion and subfertility. BPA is not associated with other reproductive, hormonal and metabolic manifestations in women with PCOS. It is hoped that the study findings will help clinicians as well as policymakers to understand the possible adverse roles of BPA in human reproduction. A larger sample size with a longitudinal study design may provide further clarification about the role of BPA in the pathogenesis of PCOS.

Acknowledgment
The authors acknowledge the contribution of the Department of Microbiology and Immunology and Biochemistry and Molecular Biology, BSMMU for biochemical analyses.

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

CRediT Author Statement

EURC: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Original draft preparation, Funding acquisition; **HB**: Conceptualization, Methodology, Validation, Writing – review and editing, Supervision; **MSM:** Conceptualization, Methodology, Formal Analysis, Data Curation, Writing – original draft preparation, Visualization; **IAJ**: Conceptualization, Methodology, Investigation, Writing – original draft preparation, Visualization; **SK**: Conceptualization, Methodology, Investigation, Data Curation, Writing – Original draft preparation; **MAH**: Conceptualization, Methodology, Validation, Resources, 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.

Authors Disclosure

The authors declared no conflict of interest.

Funding Source

The authors obtained a partial grant from the University Research and Development, BSMMU for the measurement of serum bisphenol A.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Perceptions, Attitudes, Behaviours and Barriers in Obesity Care: Findings from the ACTION-Vietnam Study

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Abstract

Objective. The ACTION Asia Pacific (ACTION-APAC) study was designed to identify the perceptions, attitudes, behaviours and potential barriers to effective obesity management in people with obesity (PwO) and healthcare professionals (HCPs) in nine countries of Southeast Asia. This study represents the findings in Vietnam.

Methodology. This cross-sectional, non-interventional study gathered information from Vietnamese PwO (n = 1000) and HCPs (n = 200) via an anonymous online survey between April and May 2022.

Results. The majority of PwO (67%) and HCPs (80%) believed that obesity is a chronic disease that profoundly impacts a person's overall health (76% PwO, 81% HCPs). About 58% of PwO agreed that managing weight loss was solely their responsibility. Meanwhile, 76% of HCPs believed they should actively contribute to their patients' weight loss efforts. Most of the PwO (82.7%) had attempted weight loss with an average of four times. PwO and HCPs cited lack of exercise (63% vs. 86%) and lack of motivation (60% vs. 80%) as the principal barriers to weight loss. HCPs cited PwOs' lack of interest (52%) and motivation to lose weight (45%) as top reasons for not discussing weight.

Conclusion. The study emphasised raising awareness for obesity management among PwO and HCPs and suggested early weight management conversations with HCPs.

Key words: barriers to weight loss, healthcare professionals, patients with obesity, Vietnam, weight management

INTRODUCTION

Obesity is a globally prevalent, chronic, progressive disease,[1,2] with an alarming rise in prevalence in the Asia-Pacific (APAC) region. The prevalence is estimated to have doubled between 2010 and 2030 in South and Southeast Asia.[3] Consistently, obesity prevalence in Vietnam has also increased from 10% in 2009 to 16.4% in 2015 amongst women and from 10.3% to 15% amongst men.[4] The prevalence of obesity and overweight among children and adolescents in Vietnam has increased from 8.5% to 19% from 2010 to 2020. Interestingly, the prevalence is greater in urban areas (26.8%) than in rural areas (18.3%).[5,6] This may partly be attributed to significant economic transition and urbanisation in the last two decades in Vietnam, leading to an increasingly obesogenic environment due to high-calorie food consumption and an inactive lifestyle.[7,8] The rise in obesity impelled the Vietnamese government to understand its considerable association with chronic non-communicable diseases (NCD), reduced quality of life and premature mortality.[4] The Vietnam government has launched the "National Strategy for the Prevention and Control of NCD 2015–2025" program to keep overweight and obesity prevalence under 15% in adults.[4,9] Despite the endorsement of the national strategy, the steady rise in obesity prevalence in Vietnam indicates a lack of implementation or assurance of consistent obesity care.

A consensus guideline on the care and management of obesity in South and Southeast Asian countries suggested prioritising effective management approaches, setting realistic and clinically meaningful weight loss targets to lower health risks or improve quality of life (QoL) and maintaining it long-term. A 5% to 15% weight loss over 6

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 21, 2024. Accepted: October 25, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.17

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months was considered safe and realistic.[3] Modest lifestyle modifications (reduced food intake with a healthy diet and physical activity) and behavioural therapies are important first-line interventions to target obesity.[3,10,11] Pharmacologic treatment is an adjunct therapy when lifestyle alterations fail to reduce weight in people with obesity (PwO). Furthermore, bariatric surgery is suggested in addition to lifestyle modifications for those PwO having BMI ≥35 kg/m^2 and are unresponsive to medications.[3,10,11]

The ideal obesity management requires awareness and interaction among PwO and healthcare professionals (HCPs) regarding obesity- its relapsing nature, associated comorbidities and complexities.[12] The Awareness, Care, and Treatment in Obesity Management International Observation (ACTION-IO) study reported that a lack of awareness about clinical obesity management among PwO and HCPs led to delays in initiating conversations on weight management.[13] Similar to the ACTION-IO study, the Asia-Pacific study also identified perceptions, attitudes and behaviours toward obesity, its management and barriers to effective care among PwO and HCPs in the APAC region.[14] This remains to be unexplored in Vietnam. The current study is a sub-analysis of the ACTION-APAC study and aims to present the results on perceptions, attitudes, behaviours and barriers of obesity among PwO and HCPs of Vietnam.

METHODOLOGY

Study design

The ACTION-APAC study was a non-interventional, cross-sectional descriptive study, which gathered information from PwO and HCPs across nine Asia-Pacific countries: Vietnam, Malaysia, Philippines, Indonesia, Singapore, Pakistan, India, Bangladesh and Thailand via an anonymous online survey between April 14, 2022 and May 23, 2022. The countries included are a part of the APAC region as categorised by the World Obesity Federation.[15] A third-party vendor (KJT Group, Inc., Rochester, NY, USA) surveyed existing online databases/panels using English and Vietnamese. They assisted in developing detailed inclusion and exclusion criteria for participant selection and worked with local panel partners to access samples from opted-in respondents. A thorough data review was conducted and strict quality control procedures were implemented to maintain data integrity throughout the study. The ACTION-APAC study methodology was recently published.[14] The current study is a subgroup analysis of the Vietnam cohorts of the ACTION APAC study. It was exempted from the Western Copernicus Group (WCG) Institutional Review Board due to sufficient protections taken to maintain the data confidentiality and privacy of the study participants.

Study cohorts

Separate surveys were conducted for PwO and HCPs. Before the survey initiation, all participants provided electronic informed consent. Eligible Vietnamese PwO (n=1000) were ≥18 years old with a current BMI of ≥25 kg/m^2 (obese)[16] determined based on self-reported height and weight. The main exclusion criteria included pregnancy, previous participation in the study, enrolment in intense fitness programs, or significant unintended weight loss 6 months before completing the survey.

Eligible HCPs (n = 200) were adult medical practitioners of Vietnam (≥18 years old) with ≥2 years of practice experience, who spent ≥50% of their time in direct patient care and had seen ≥100 patients (including ≥10 PwO) during the past month. HCPs were excluded if they previously participated in the study or had language barriers that hindered understanding of or cooperation in the study. Sample sizes for both HCPs and PwO were determined to balance statistical power, recruitment feasibility and cost. The sample sizes of PwO were calculated to obtain an error margin of 2-3% around a proportion estimate of 50%, with the error margin calculated using standard normal (Z-) distribution with Z = 1.96, or around a 95% level of confidence.[14]

Study outcomes

Survey questions were developed based on the earlier ACTION worldwide study.[13] However, questions were modified based on inputs from scientific experts from Vietnam and were formulated to ensure comprehensive data collection. In the PwO questionnaire, participants provided insights on (a) readiness for change and prior weight loss success; (b) their perceptions and attitudes towards obesity; (c) available support structures; (d) interactions with HCPs regarding obesity; and (e) strategies for weight management. In the HCP questionnaire, participants shared their views on (a) patient readiness for change and past weight loss outcomes; (b) their awareness and attitudes towards obesity; (c) perceived helpful support structures for patients; and (d) patient interactions. HCPs were also asked demographic questions regarding clinical specialty, years of practice, practice setting, frequency of obesity diagnosis among patients, comfort discussing weight, and adherence to obesity management guidelines. The responses on diverse obesity-related issues were quantified using single-item and multiple-item selection (reported as percentages or frequencies). To measure certain attitudes or opinions, a 5-point Likert scale was used where 1 meant "strongly disagree" and 5 meant "strongly agree." However, the results would focus only on the responses of the participants who responded with 4 (Agree) or 5 (Strongly Agree).

Data collection

Data of eligible respondents (PwO and HCPs) collected through an online survey programmed with Decipher Survey Software (Focus Vision Worldwide Inc., Stamford, CT, USA) were reviewed by the WCG Institutional Review Board and approved according to local regulations. The study and data collection process complied with all country, federal, or state laws. All participants provided informed consent. The data was collected online via a

27-minute survey for PwO and a 31-minute survey for HCPs compliant with the requirements of each country. A secure link was sent to all the participants so they could complete the consent form, screener and online survey. The survey was designed to ensure every question was answered so there were no missing data. This study was sponsored by Novo Nordisk and was conducted in accordance with the Declaration of Helsinki and the European General Data Protection Regulation (GDPR).

Data analysis

De-identified data were analysed using different statistical software programmes, such as SPSS (version 23.0, IBM, Armonk, NY, USA), Stata (version IC 14.2, StataCorp LLC, College Station, TX, USA), and Excel (version 365, Microsoft, Redmond, WA, USA). Descriptive statistics were calculated using Q Research Software for Windows 23 (A Division of Displayr, Inc., New South Wales, Australia). Categorical variables were presented as counts and percentages.

RESULTS

Demographics

In the current study, 200 HCPs and 1000 PwO from Vietnam completed the survey. The participating PwO had an average age of 39.2 years, with 51% classified as Class 1 obesity (BMI: 25–29.9 kg/m^2) and 33% as Class 2 obesity (BMI 30–34.9 kg/m^2). The obesity classification was based on the WHO Asia-Pacific region cutoff.[16]

Among the participating HCPs, 56% were male, had an average practice experience of 11.3 years and spent about 78% of their professional time on patient care. In the HCP cohort 25% were obesity specialists (i.e., ≥50% of patients seen primarily for obesity) 57% considered themselves obesity experts, and 59% had advanced training in obesity management (Table 1).

Perceptions of obesity

The majority of PwO (67%) and HCPs (80%) agreed that obesity is a chronic disease (Figure 1). A weight loss of 5-10% body weight was regarded to be highly beneficial to health by both PwO (78%) and HCPs (92%) (Figure 1). Both cohorts believed that obesity profoundly affects a person's overall health (76% of PwO and 81% of HCPs).

Attitude toward weight loss and their motivators

More than half of PwO (58%) assumed full responsibility for their weight loss, and even 55% of HCPs believed that PwO was solely responsible for their weight loss. Half (50%) of the PwO expected active involvement of their HCPs towards their weight loss, while a substantial proportion (76%) of HCPs considered they were responsible for actively contributing to their patients' weight loss. Over half of PwO (55%) were motivated to achieve weight loss, while HCPs thought 69% of PwO were motivated to do so (Figure 1). Approximately 32% of PwO had weight loss intentions within the next month or were committed to/enrolled in a weight loss program. The top three motivators for weight loss as per PwO were to become more fit/have better shape (32%), feel better physically and more energetic (31%), and improve confidence/self-esteem (29%) (Supplementary Figure 1). However, HCPs considered general health concerns (60%) as the chief weight loss motivator apart from being in better shape or fitter (48%) or improving self-esteem/confidence (49%) (Supplementary Figure 1).

Weight loss barriers

PwO considered lack of exercise (63%), lack of motivation (60%), unhealthy eating habits (59%) and the possibility of regaining weight (60%) to be the principal weight loss barriers. Consistently, most HCPs believed lack of exercise

Table 1. Key demographics and characteristics of the study population

	PwO (n = 1,000)	HCPs (n = 200)
Age, years, mean	39.2	39
Male, n (%)	500 (50)	112 (56)
Obesity class, n (%)		
Class 1 (BMI 25-29.9 kg/m^2)	510 (51)	
Class 2 (BMI 30-34.9 kg/m^2)	330 (33)	Not applicable
Class 3 (BMI 35-39.9 kg/m^2)	120 (12)	
Class 4 (BMI ≥40 kg/m^2)	50 (5)	
Setting, n (%)		
Urban area	720 (72)	182 (91)
Suburban area	210 (21)	16 (8)
Rural area	70 (7)	2 (1)
Comorbidities, n (%)[a]		
High blood pressure	230 (23)	
High cholesterol	260 (26)	
Eating disorder	190 (19)	
Depression / anxiety	140 (14)	Not applicable
Type 2 diabetes	150 (15)	
Cardiovascular disease	200 (20)	
Others	10 (1)	
None listed	300 (30)	
HCP practice category, n (%)		
Family practice		12 (6)
General practice		42 (21)
Internal medicine		48 (24)
Endocrinology / Diabetology		28 (14)
Cardiology		30 (15)
Gastroenterology		NA
Nutrition specialist		NA
Obstetrics / Gynaecology	Not applicable	14 (7)
Bariatrics / Obesity Medicine		Not applicable
Aesthetics medicine		16 (8)
Orthopaedist		16 (8)
Years in practice, mean		11.3
Considered self an obesity expert, n (%)		114 (57)
Obesity specialist, n (%)[b]		50 (25)
Received advance training in obesity		118 (59)

BMI, body mass index; HCPs, healthcare professional; PwO, people with obesity

[a]Percentages do not add to 100 because respondents could select more than one condition.
[b]An obesity specialist is defined as a physician who reported seeing 50% or more patients specifically for obesity/weight management.

(86%), unhealthy eating (86%), limited mobility (82%) and lack of motivation (80%) as the top barriers to weight loss for PwO. Additionally, PwO also blamed the nature of their jobs (58%) and the tendencies to regain weight (60%) as other weight loss barriers (Figure 2).

Interactions between PwO and HCPs about weight management and outcomes

About 50% of PwOs had discussed obesity with their HCPs (obesity specialist or dietitian) in the past 5 years; 62% of HCPs acknowledged discussing weight issues with their PwO, and in 53% of cases, HCPs initiated the conversation. Of these, 56% of PwOs whose HCP raised the topic of weight appreciated their HCP for raising the topic. Meanwhile, 40% of HCPs stated that they felt uncomfortable discussing weight loss with their patients unless it was patient-initiated, as they assumed that their patients lacked interest in weight loss. The primary reasons mentioned by PwO for not initiating weight discussion with HCPs was the belief that weight loss was their responsibility (24%) and also lack of financial means to support weight loss efforts (24%) (Figure 3). In contrast, HCPs cited a lack of patients' interest (52%) and motivation (45%), as well as the absence of weight-related comorbidities (38%) and lack of confidence among PwO (39%) as the main reasons for not initiating weight loss discussions (Figure 3). About 75% of PwO were diagnosed with obesity by their HCPs. Nearly 75% of PwO said they felt positive following weight loss discussions with their HCPs. Three in four PwO (76%) who discussed weight with their HCP scheduled a follow-up appointment. Although 70% of HCPs mentioned recording obesity diagnoses in patient records most or all the time and had notified approximately 71% of patients about obesity diagnoses, 52% of their patients scheduled follow-up appointments with them.

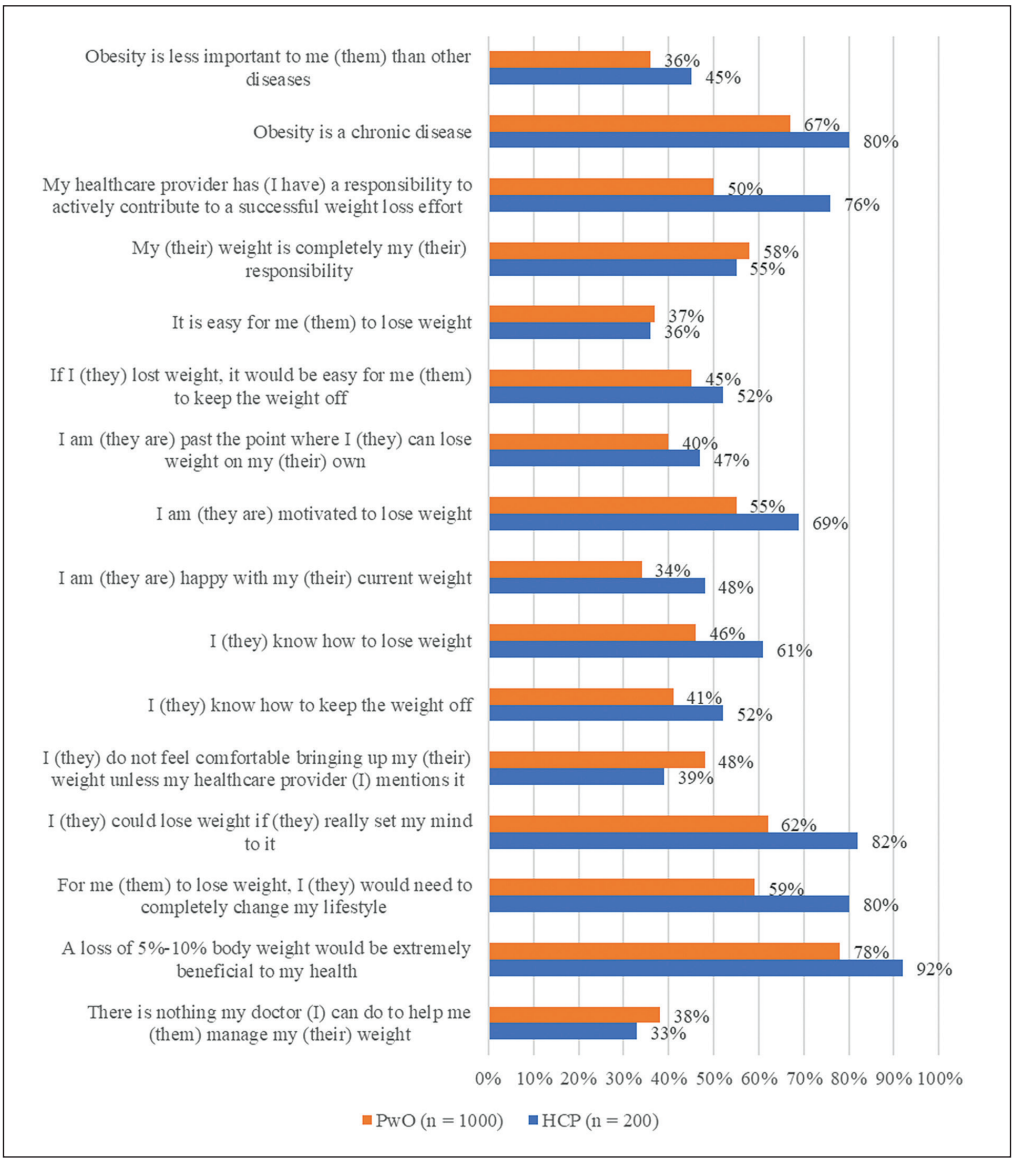

Figure 1. PwO and HCPs' attitudes towards obesity and weight management.

PwO and HCPs indicated their level of agreement (4 or 5) on a 5-point scale (1: Do not agree; 5: Completely agree)

HCPs, healthcare professionals; PwO, people with obesity

Perceptions about current weight, weight loss efforts by PwO and outcome

Although all participating PwO were obese (based on their self-reported weights and heights), only 30% of PwO considered themselves overweight and 56% as obese (Supplementary Figure 2). Most PwO began struggling with their weight at a median age of 30 years and first discussed weight loss with HCP at a median age of 35 years (Supplementary Figure 3). However, 34% of PwO were happy with their current weight despite struggling with weight loss. Although 51% of the PwO mentioned about 1 to 4 weight loss attempts, 45% regained weight after successfully maintaining a low weight for at least 6 months. Only 4% of PwO had ≥10% weight loss (not due to illness or injury) and had maintained weight loss for ≥1 year (Supplementary Figure 4A). HCPs, on the other hand, believed less than half of the PwO had made a serious weight loss effort, and nearly 40% were successful. The three most common reasons for regaining weight cited by PwO were not following an eating plan (34%), difficulty in staying motivated (32%), and discontinuing exercise (28%) (Supplementary Figure 4B).

Perceptions of weight stigma among overweight patients

According to both PwO and HCPs, the societal stigma towards obesity negatively impacted PwO to develop a romantic relationship (30% and 59%, respectively), obtain a job (17% and 57%, respectively) and be successful in the workplace (16% and 41%, respectively) (Supplementary Figure 5). Moreover, weight stigma influences how

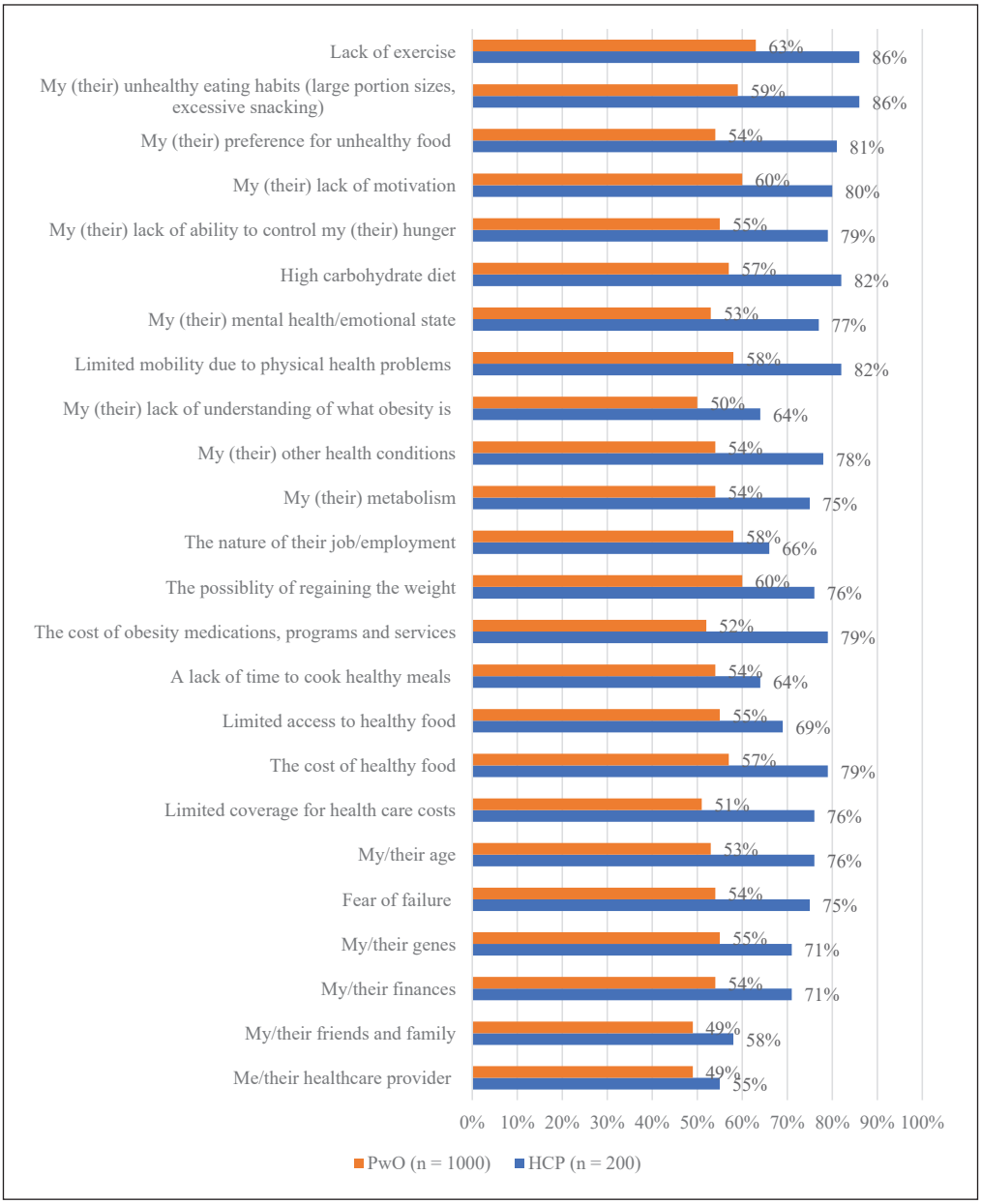

Figure 2. Barriers to weight loss reported by PwO and HCPs.

PwO and HCPs indicated their level of agreement (4 or 5) on a 5-point scale (1: Do not agree; 5: Completely agree)

HCPs, healthcare professionals; PwO, people with obesity

people are perceived in terms of athleticism, health and intelligence. Only half of the PwO are viewed as athletic (PwO: 50%; HCP: 49%) or healthy (PwO: 54%; HCP: 60%), and an even lesser percentage is considered as smart (PwO: 43%; HCP:26%).

Weight management strategies and goals

The majority of PwO relied on the internet (42%), or smartphone apps (36%) as a source of information for weight management, and about 32% of PwO sought relevant information from their HCPs and 34% from their dietitian (Supplementary Figure 6). The most common weight management goals among PwO after weight loss discussion with their HCP were to improve mental and physical well-being (32%), lifestyle (31%) and appearance (30%) (Supplementary Figure 7). Additionally, 60% of PwO who had weight-related conversations with their HCPs agreed that their HCPs listened to them and they trusted their HCP's advice on weight management.

The top three weight management strategies considered by PwO were improvement in eating habits or decreasing calories (33%), elimination diets (32%) and specific diet or diet programme (24%) (Figure 4). On the other hand, 53% of HCPs considered exercise and increased physical activity for effective weight management. Most PwO (64%) preferred losing weight by themselves rather than using anti-obesity medications. Most PwO (69%) and HCPs (67%) were worried about the side effects and long-term safety

Figure 3. Reasons for not having weight discussion between PwO and HCPs.

HCPs, healthcare professionals; PwO, people with obesity.

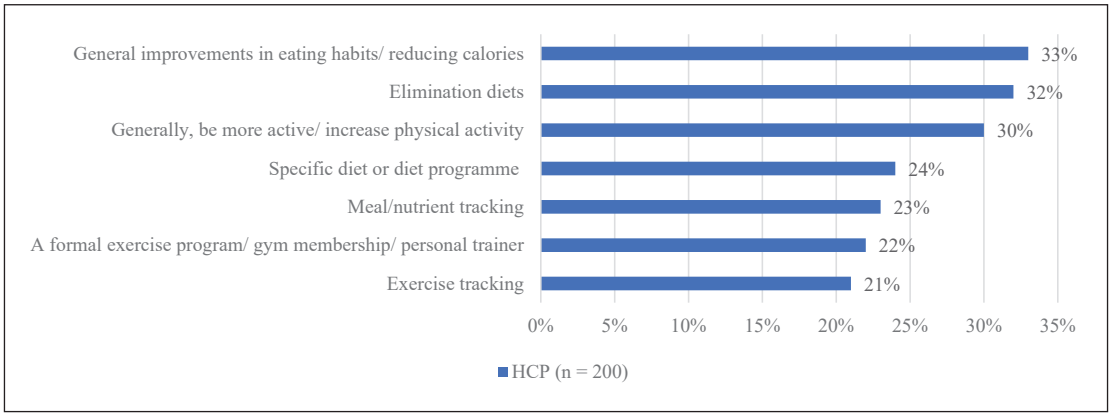

Figure 4. Methods recommended by HCPs for weight management, as reported by HCPs.
HCPs, healthcare professionals.

of anti-obesity medications (Supplementary Figure 8). Most PwO (72%) and HCPs (84%) preferred weight loss through diet and exercise rather than undergoing bariatric surgery.

DISCUSSION

Results from the ACTION-Vietnam subgroup analysis revealed differences in perceptions, attitudes and knowledge about obesity management between PwO and HCPs, as well as a lack of awareness about obesity in both groups. Even though a large majority of PwOs (76%) and HCPs (81%) believed that obesity considerably impacts overall health, fewer PwOs (67%) than HCPs (80%) recognised obesity as a chronic disease. This was in line with the global population (ACTION-IO) and ACTION-APAC studies.[13,14] The study showed that although both PwO and HCPs were aware of obesity and its impact on overall health, it is still undermined in the country. Despite all participating PwO being obese, only 56% of PwO considered themselves obese. This misperception of weight status among PwO is alarming as it could deter them from seeking help or attempting to manage their weight.

Most PwOs (58%) assumed complete accountability for their weight management, and 50% believed HCPs should support their weight loss efforts. This is in accordance with the ACTION-APAC study, where 63% of PwO reportedly held themselves responsible for weight loss.[14] The Korean and Japanese ACTION-IO studies echoed similar opinions.[10,11] Over half of the HCPs (55%) believed that PwO are solely responsible for their weight loss, compared with the findings from the ACTION-APAC study, where 41% of HCPs considered weight loss a responsibility of PwO entirely.[14] This could be due to cultural and economic differences between different countries in the APAC region.

In Vietnam, 47% of the PwO who had weight-related conversations with HCPs reported that they initiated the conversation. Similar results were reported from the APAC region.[14] In contrast to the ACTION-IO studies from Japan and Korea, where the PwO did not prefer their HCPs to initiate the weight loss conversations,[10,11] most PwO in Vietnam preferred their HCPs to initiate the conversation. This finding aligns with the ACTION-IO study from Israel.[17] Moreover, in this ACTION-Vietnam study, PwO thought that weight loss was their responsibility (24%), and only half sought consultation with an obesity specialist or dietitian. From these findings, it is evident that there is a lack of adequate communication between PwO and HCPs about obesity management and weight loss discussions, leading to the increasing obesity rates in the country.

The current study identified poor dietary habits and lack of exercise as the leading weight loss barriers, consistent with ACTION-IO and ACTION-APAC studies.[13,14] However, only 59% of PwO in the current study considered these two as the main barriers, suggesting a lack of awareness about obesity in the general population. More than 50% of PwO stated that they were motivated to lose weight, and most of them had already made a minimum of one serious weight loss attempt in the past. Conversely, less than 50% of HCPs appreciate the weight loss efforts in their patients. This lack of acknowledgment and motivation from HCPs may discourage and dishearten PwO from discussing their efforts openly with HCPs, resulting in either failed weight loss attempts or revert to unhealthy lifestyles. A significant proportion (48%) of PwO felt embarrassed or ashamed if their HCPs initiated a weight loss discussion. This self-blame mindset of PwO often creates barriers for the HCPs to initiate weight loss conversations. This could be why PwO seeks weight loss-related information from other sources, such as the internet and social media, rather than HCPs. Inaccurate and short-term solutions for faster weight loss from the internet or non-HCPs might lead PwO to follow extreme lifestyle changes without proper healthcare guidance, causing more harm than benefit. Therefore, HCPs should develop a supportive, empathetic and compassionate approach toward their patients.[18]

Obesity management is a team effort with the active involvement of HCPs and PwO. However, only half of the PwO in this study considered HCP involvement vital in weight loss. This aligns with the findings from ACTION-APAC study, which revealed that PwO hesitated to initiate

discussions about their weight with HCPs, and only 43% sought advice on weight loss strategies.[14] Moreover, the Vietnamese HCPs cited the patient's lack of interest in losing weight as the main reason for not initiating weight discussion. This indicated the importance of developing effective obesity management guidelines and health policies in Vietnam, aligned with the current Southeast Asian consensus to include regular patient counseling, regular health check-ups and encouraging obesity-related open discussions between HCPs and PwO.[3]

The study demonstrated that HCPs and PwO agreed on obesity diagnosis (74%), follow-up appointments (76%), specialist referrals and weight loss strategies. Both cohorts preferred lifestyle modifications over pharmacotherapy and bariatric surgery for weight loss. This may be attributed to a knowledge gap among HCPs and the unavailability of other effective treatment methods in the country, similar to the global study, Japanese and Korean ACTION studies.[10,11,13] The limited availability of pharmacotherapy and bariatric surgery options, as well as a scarcity of effective and individualised treatment and referral options in Vietnam, affect HCPs' understanding of weight loss treatment options. It is, therefore, essential to educate the HCPs on different approaches to obesity management with a clear specialist referral pathway. Moreover, regular follow-up visits with HCPs should be encouraged for adequate monitoring and timely implementation of appropriate treatment strategies.

Lastly, this study included aspects of weight bias and stigma. Both PwO and HCPs deemed that it is difficult to find a job and form a romantic relationship due to the stigma of obesity. Different societal and environmental stigmas,such as stereotyping, prejudice and discrimination, faced by PwO have a profound negative impact on their overall perception and attitude toward obesity.[19] Weight prejudice ensuing stigma is reported to be widespread globally, both in public and personal domains.[20,21] This weight stigma among HCPs might impact the relationship between PwO and HCPs, making PwO reluctant to participate in weight management in clinical settings.[14] The stigma associated with obesity can be mitigated through proper awareness among the general population and HCPs. The HCPs should be adequately trained and educated to use patient-first language and should be aware of the obesity-related stigma and bias typically experienced by patients. This will help strengthen the patient-HCP interaction and even the wider population, regarding obesity care.[20,22,23] Moreover, it is crucial to educate society about the obesity stigma to debunk the myths around obesity and encourage empathy towards PwO. A collaborative approach involving HCPs, PwO, their family members, dietitians, psychologists and key decision-makers in society will be essential to reduce the societal stigma associated with obesity.[23]

Strengths and limitations of the study

This study is the first to focus on views and attitudes about obesity and its management in Asia. This study included a relatively large cohort of PwO and HCPs, including both primary care providers and specialists from Vietnam. The survey also covered stigma and bias related to weight, which were not covered in earlier studies.

Although this study included a sizable percentage of respondents from urban regions, this may not accurately represent the opinions of all PwO and HCPs in Vietnam. Self-reported heights and weights may also underestimate BMI among included PwO. Moreover, using only BMI may undervalue excess adiposity and fail to represent the entire PwO cohort in this region correctly. Furthermore, participants of online surveys could differ from those who do not belong to survey research panels. Participants were blinded about the theme and the study goal to reduce bias before meeting the study's eligibility criteria. To mitigate selection bias, the data from PwO were adjusted based on age, gender, level of education, household income and region to align with each country's representative demographic targets.

CONCLUSION

The current study highlighted the need to address knowledge gaps in obesity complications and treatments among PwO and HCPs in Vietnam. It emphasises the importance of national-level education on weight management for PwO and the general public, as well as specialised training for HCPs in obesity care. The findings suggested that improved education and training could reduce stigma, enhance patient-provider relationships and increase the effective use of interventions. Collaboration between governmental and non-governmental organisations is recommended to develop and implement comprehensive strategies for weight loss and obesity management on a large scale. Subsequent research is warranted to formulate and assess approaches to close these perception gaps and convert enhanced comprehension into more efficient obesity treatment strategies.

Acknowledgments
The authors thank the participants of the study. The authors thank Ms. Somdatta Mukherjee, Ms. Anju Dhiman, and Ms. Khushboo Lakhani from Turacoz Healthcare Solutions (www.turacoz.com) for providing writing support for this manuscript.

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

Authors Disclosure
Drs. Tran and Bich received honoraria as Advisory Board and speaker of Abbott, AstraZeneca, Bayer, Boehringer Inghelheim, Novo Nordisk, Roche and Sanofi. Dr. Nhuyet received honoraria as Advisory Board and speaker of Novo Nordisk and Abbott. Dr. Ahn received honoraria as Advisory Board and speaker of Medtronic, Braun and Novo Nordisk. Drs. Huu, Ba and Ha are employees of Novo Nordisk.

CRediT Author Statement
NQT: Conceptualization, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision,

Project administration, Funding acquisition; **DNTB:** Validation, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **TNN:** Validation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **TNA:** Validation, Resources, Writing – review and editing, Visualization, Project administration; **NLL:** Conceptualization, methodology Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **TDB:** Conceptualization, methodology Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **YSH:** 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 generated and analysed are included in the published article.

Funding Source

This study was funded by Novo Nordisk, which also provided financial support for medical editorial assistance.

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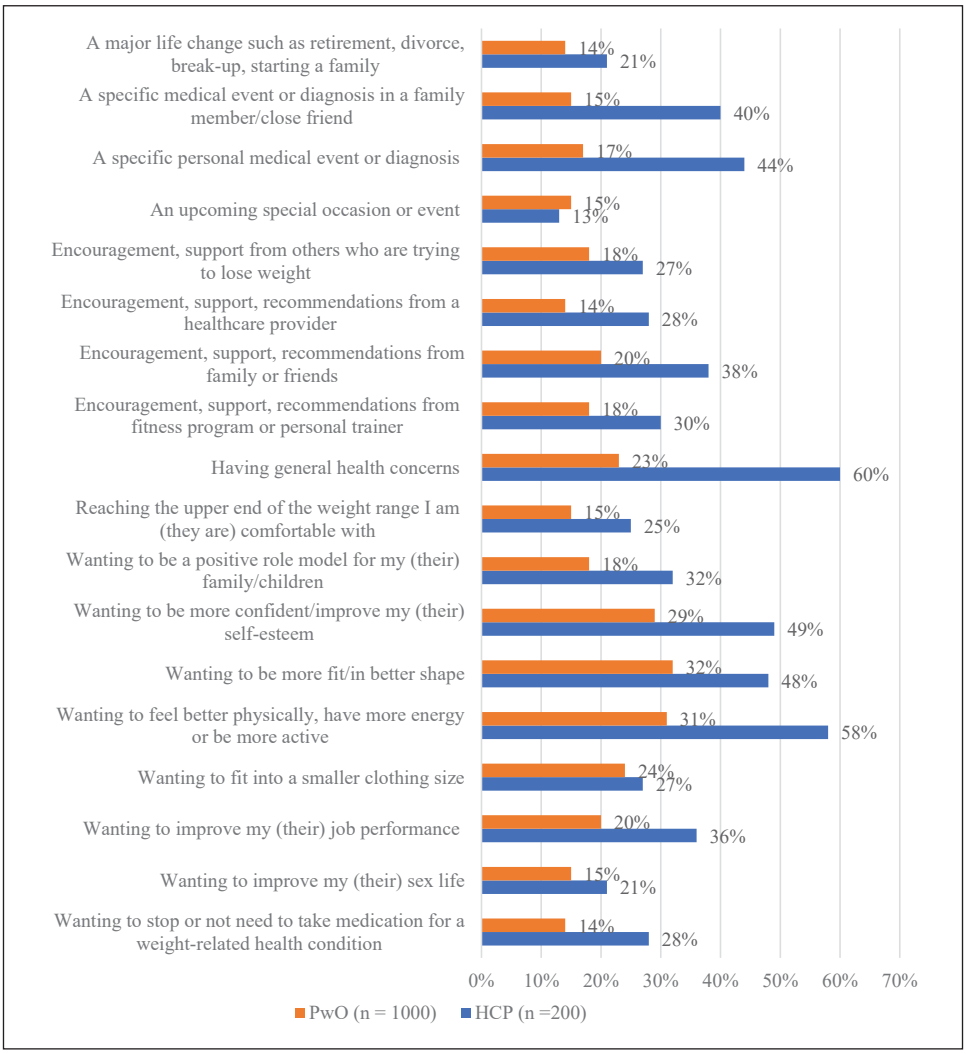
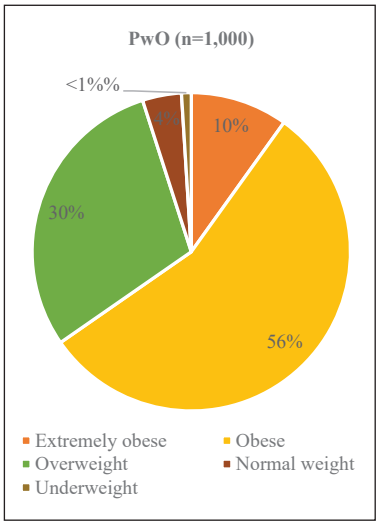
SUPPLEMENTARY FIGURES



Supplementary Figure 1. Motivators of weight loss reported by PwO and HCPs.

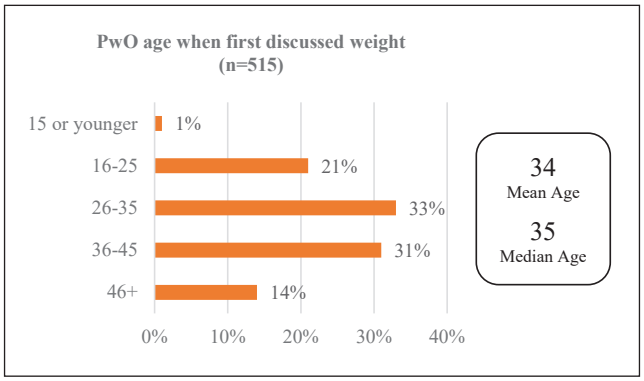
PwO and HCPs indicated their level of agreement (4 or 5) on a 5-point scale (1: Do not agree; 5: Completely agree)

HCPs, healthcare professionals; PwO, people with obesity



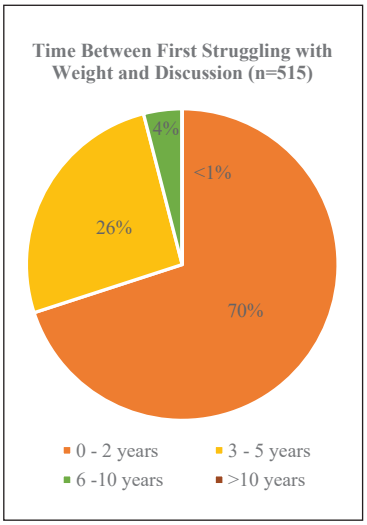
Supplementary Figure 2. PwO's perceptions of their weight.

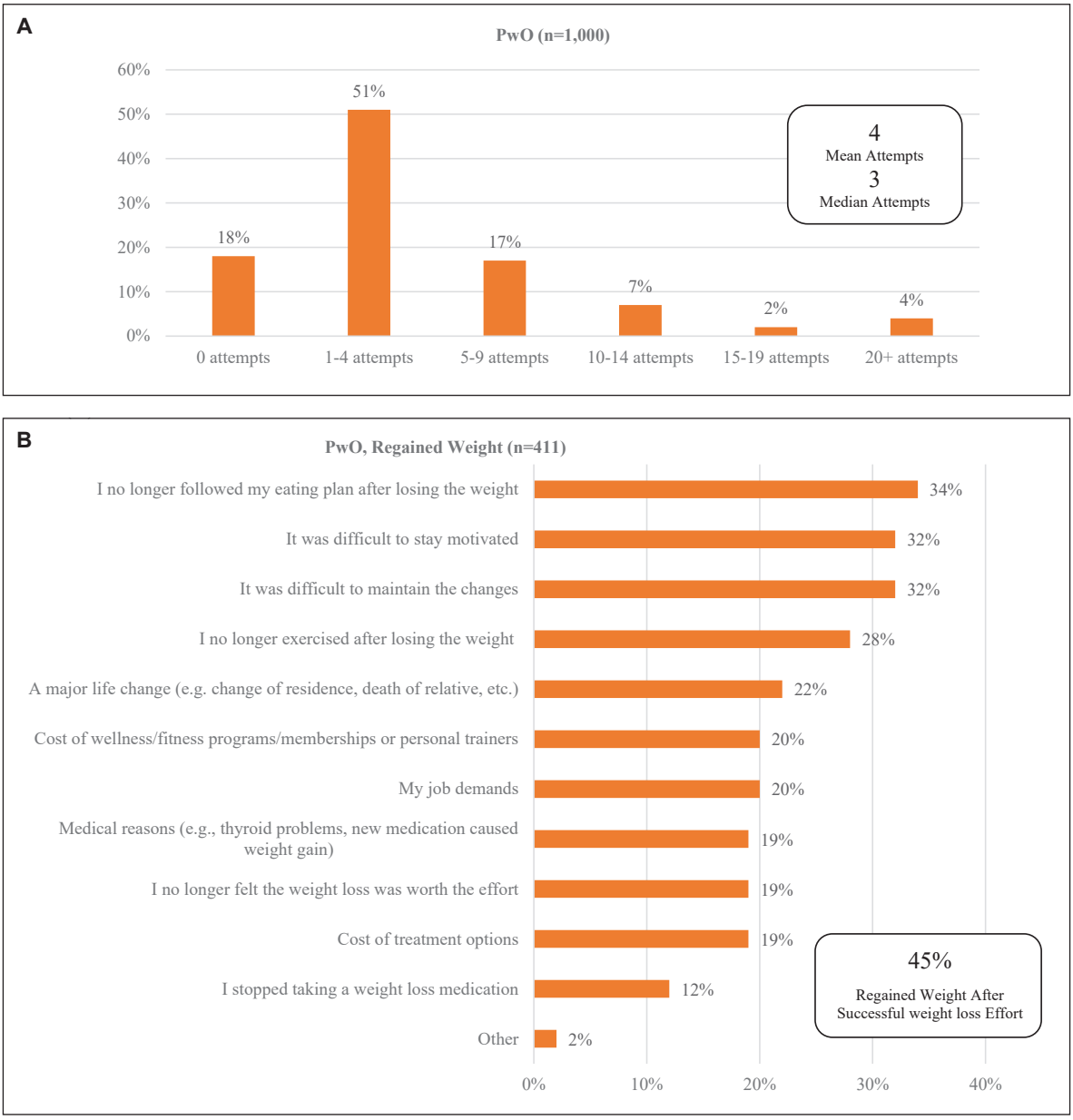
PwO, people with obesity



Supplementary Figure 3. Age at which PwO first struggled with weight and discussed their weight with their HCPs.

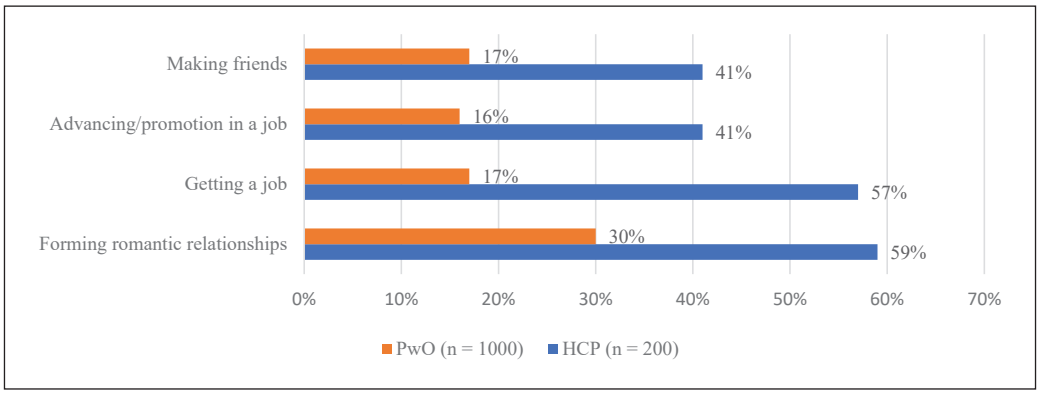
HCPs, healthcare professionals; PwO, people with obesity.





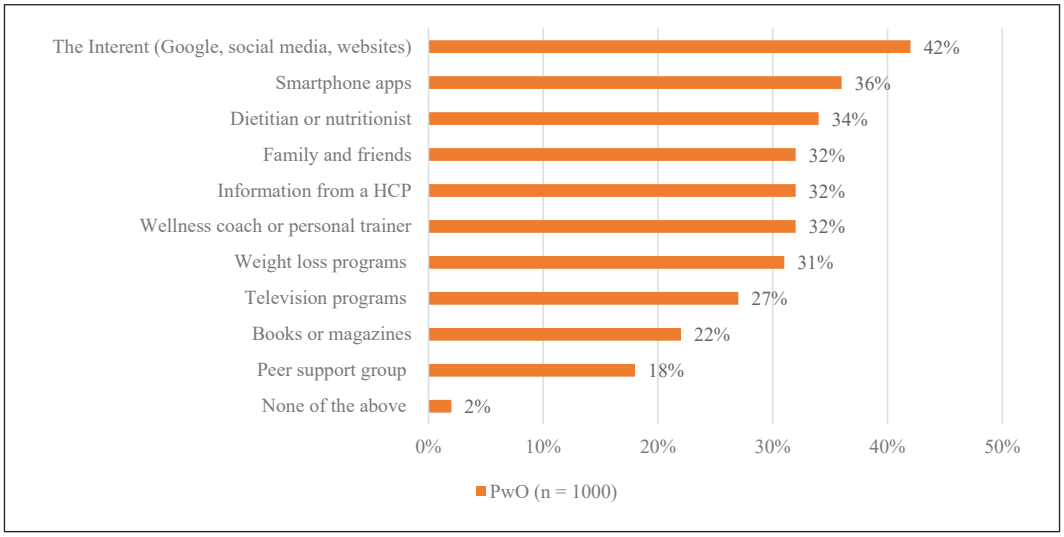
Supplementary Figure 4. Weight loss attempts and success rate. **(A)** PwO-reported weight loss attempts. **(B)** Reasons for weight regain, as reported by PwO.

PwO, people with obesity



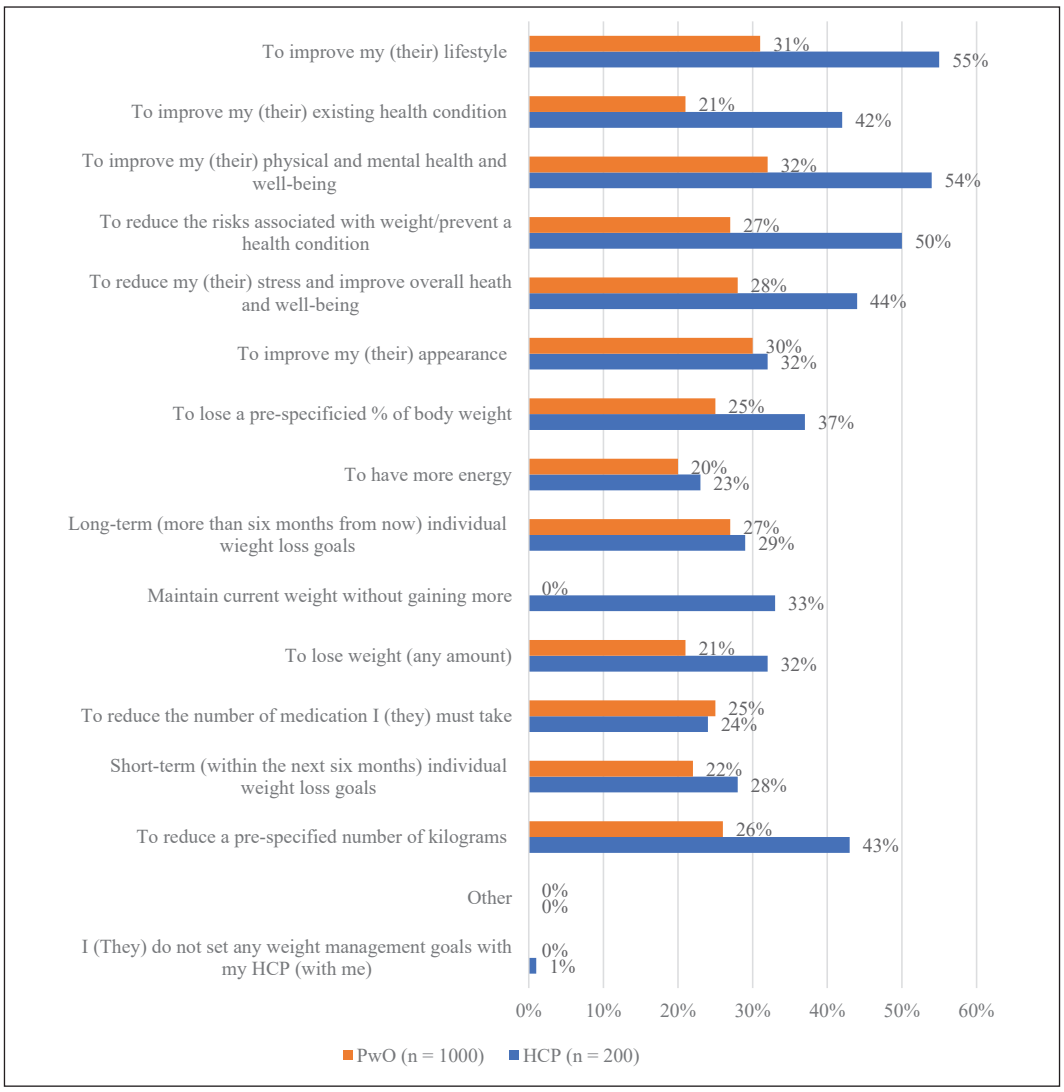
Supplementary Figure 5. PwO and HCP's perceptions of weight stigma and its effect in forming relationship and obtaining job.

HCP, healthcare professionals; PwO, people with obesity



Supplementary Figure 6. Sources of information used for managing weight.

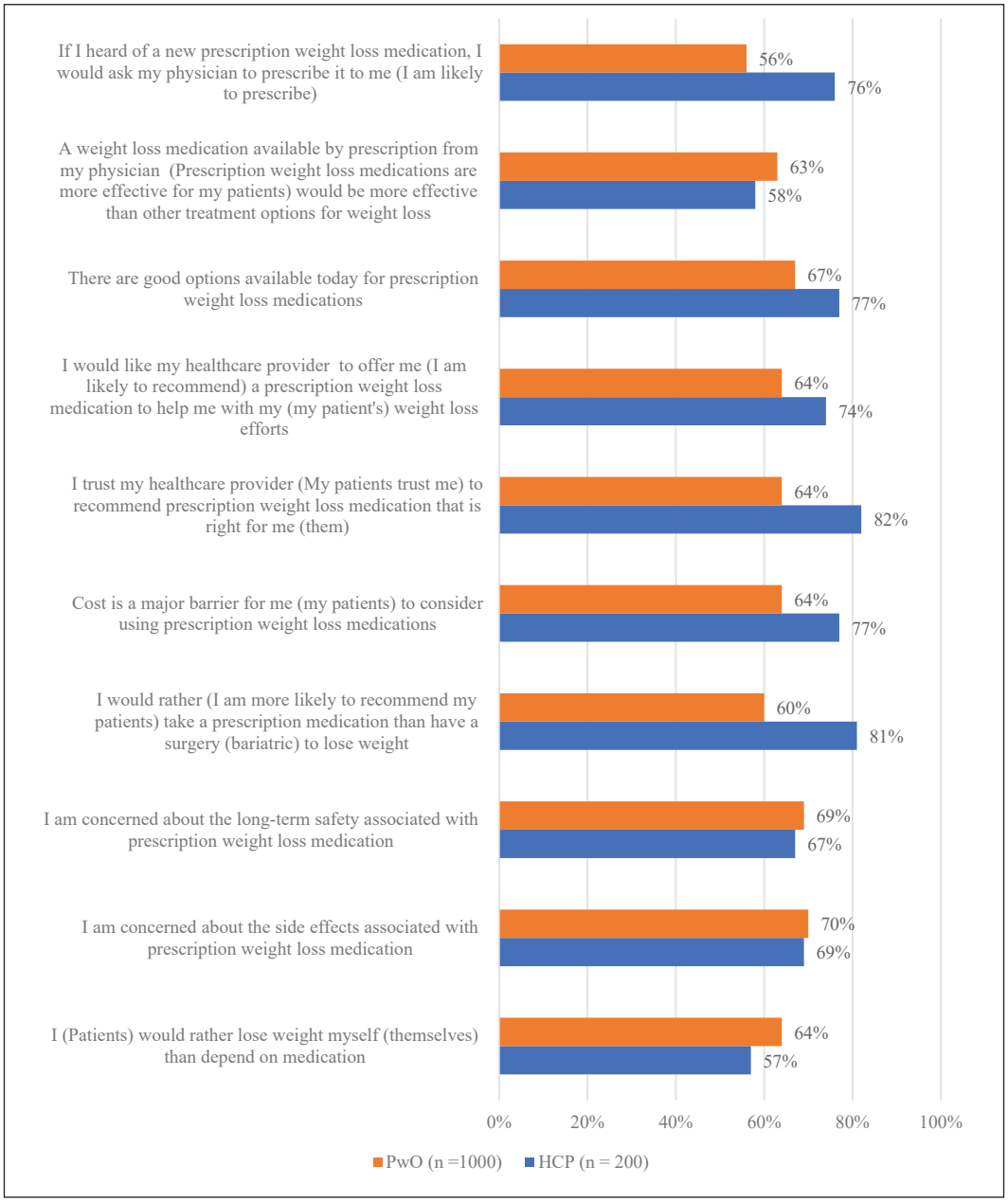
HCP, healthcare professionals; PwO, people with obesity



Supplementary Figure 7. Weight management goals reported by PwO and HCP.

PwO and HCPs indicated their level of agreement (4 or 5) on a 5-point scale (1: Do not agree; 5: Completely agree)

HCP, healthcare professionals; PwO, people with obesity



Supplementary Figure 8. Attitudes towards prescription weight loss medications.

HCP, healthcare professionals; PwO, people with obesity

ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Tailoring Educational Content for T2DM Patients: A Qualitative Study on Preferences for Interactive Multimedia Applications

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Abstract

Background. The development of interactive multimedia-based applications has become increasingly important in providing effective health education to Type 2 Diabetes Mellitus (T2DM) patients. Understanding the educational content required for such applications from local patients' perspectives is crucial for designing a user-friendly and impactful tool for T2DM management.

Objective. This study aims to investigate patients' views and preferences on the educational content and features of an interactive multimedia-based application for T2DM patients.

Methodology. Semi-structured qualitative interviews were carried out with a sample of T2DM outpatients (n = 16) at a tertiary referral university hospital in Kuala Lumpur between October 2022 and January 2023. The interviews were recorded, transcribed and subjected to thematic analysis.

Result. The majority of participants had been diagnosed with T2DM for less than ten years. The thematic analysis identified several key aspects related to the educational content required for development of a multimedia-based application. These include preference for educational materials, essential contents and interactive features. The participants also proposed a discussion area within such applications that would allow them to communicate and receive immediate advice from healthcare professionals, thus eliminating the need for frequent hospital visits.

Conclusion.The findings of this study highlight the significance of interactive multimedia-based applications in providing health education for T2DM patients. The identified essential content areas from the patients' perspectives can inform the development of effective tailored educational materials for patient's benefit.

Key words: educational material, diabetes mellitus, multimedia applications, health education, patient communication

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by an increase in blood glucose level and other metabolic dysfunctions due to insufficient insulin or insulin resistance.[1] This chronic disease has affected more than 450 million people worldwide and is anticipated to reach approximately 650 million by the year 2040.[1] Malaysia has been listed as one with the highest prevalence rates of diabetes mellitus (DM) in the Western Pacific region and among the highest in the globe, with an estimated annual expenditure of USD 600 million.[2] With a 68.3% increase, the prevalence of DM rose from 11.2% in 2011 to 18.3% in 2019.[3] This national survey also revealed that in 2019, approximately 3.6 million adults (18 years and older) in Malaysia had DM, of which 49% (3.7 million) were undiagnosed. With a prevalence of 31.3%, DM is anticipated to affect 7 million Malaysian adults aged 18 and older by 2025, posing a significant public health risk.[3] T2DM can result in a variety of microvascular and macrovascular complications, such as diabetic retinopathy, neuropathy, heart disease and stroke.

Patient health education for self-management is essential, particularly for those with chronic illness. An essential component of diabetes education should focus on the improvement of self-management and disease knowledge.[4-6] T2DM self-management includes the following: main-

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 5, 2024. Accepted: September 25, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.18

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taining a healthy weight, engaging in regular physical activity, monitoring blood sugar levels regularly, adhering to prescribed medication regimens, caring for diabetic feet, possessing effective problem-solving abilities, health coping strategies and engaging in risk-reduction behaviors.[7] Inadequate patient health education is consistently associated with unfavorable results, including increased hospitalization, greater use of emergency care, decreased adherence to medication regimen and a diminished capacity to interpret labels and health resources.[8] Furthermore, according to a report by the International Diabetes Federation, 80% of complication associated with diabetes are preventable through education in self-management behaviors, such as physical activity and dietary control.[9]

Traditional patient health education methods for T2DM, such as printed pamphlets and face-to-face counselling, often fail to meet the diverse needs of patients. Many patients face barriers such as low health literacy, limited access to healthcare resources and challenges in understanding medical terminology. These factors contribute to poor disease management and suboptimal health outcomes. Furthermore, static and text-heavy educational materials are often disengaging, particularly for patients with limited literacy or those who are not accustomed to reading complex health information.[10,11]

Multimedia is an information transmission method that integrates multiple forms of communication, such as text, graphics, audio, video and animation.[12] Research has demonstrated that the utilization of multimedia in patient education, such as incorporating audio or video, can enhance the exchange of information, sustain audience engagement and facilitate effective communication regarding a patient with chronic illness.[13] Previous research has found that individuals with T2DM who were receiving patient health education through multimedia platforms experiences a moderate improvement in their understanding of diabetes and the efficacy of self-management.[14,15] Interactive multimedia presents numerous significant advantages in health education. For instance, interactive video media has been shown to improve motivation and retention of health information, especially in older adults.[16] In the context of diabetes education, digital self-management education programs have shown efficacy in reducing HbA1c levels, indicating improved diabetes management.[17] Additionally, apps such as myDiabetes have demonstrated significant user engagement, as patients have accessed educational videos, suggesting a strong preference for digital learning tools.[18]

Multimedia solutions can also be tailored to meet the cultural and linguistic requirements of diverse populations, thereby improving their effectiveness in patient health education.[10] The effectiveness of interactive multimedia in other chronic conditions, including obesity interventions in Malaysia, highlights the potential for similar approaches to be effective in T2DM education.[19] Although these multimedia solutions demonstrate significant potential, it is essential to investigate the specific preferences and requirements of T2DM patients in Malaysia, ensuring that educational content is culturally relevant, specifically tailored to the local population's needs and effective in enhancing health outcomes. Despite several previous published studies which reported the views and perceptions of Malaysian patients regarding the potential use of multimedia-based applications in managing various health conditions,[20,21] qualitative studies involving T2DM patients in Asian settings, particularly in Malaysia, are scarce.[22,23]

This study aims to identify the preferences of T2DM patients regarding the educational content and features of an interactive multimedia-based application. By identifying specific local patients' preferences and requirements, this research hoped to provide valuable insights for healthcare providers and developers in adopting or developing more effective, user-friendly multimedia tools that cater to the unique needs of T2DM patients in Malaysia.

METHODOLOGY

Study design

This study employed a qualitative research design using semi-structured interviews to gather in-depth insights from participants. This study adhered to the Standard of Reporting Qualitative Research (SRQR) to ensure methodological rigour, transparency and comprehensive reporting throughout the research process. The SRQR framework was applied to provide consistency in reporting of the research process and outcomes.

Researcher characteristics and reflexivity

All interviews were conducted by the primary researcher (NS) to maintain consistency. Researcher reflexivity was maintained throughout the study to reduce biases arising from preconceptions or assumptions. The researcher's background in pharmacy and experience with diabetes management were acknowledged as factors influencing the researcher's approach and interpretation of data.

Context and setting

The study was conducted at Hospital Canselor Tuanku Muhriz (HCTM), a tertiary hospital in Kuala Lumpur, Malaysia, between October 2022 and January 2023. Participants were recruited from the pharmacy outpatient department, where they were receiving routine care and medications for T2DM.

Sampling strategy

A purposive sampling strategy was employed, targeting participants who met the study's inclusion criteria and able to provide rich and relevant data, such as vocal participants and both technologically and non-technologically savvy participants. The inclusion criteria were: 1) adult aged

18 years and above; 2) diagnosed with T2DM; and 3) able to speak and understand either Malaysia or English language. Exclusion criteria were: 1) pregnant woman; 2) individuals with neurodegenerative diseases that impair communication; and 3) those who were unable to give informed consent.

A total of 16 participants were included in the study, representing a diverse range of socio-demographic characteristics including age, ethnicity and educational backgrounds. Data saturation was achieved, with no new themes or insights emerged from the data following discussion and consensus within the research team.

Data collection

Data was collected through semi-structured interviews conducted by NS in the outpatient pharmacy's counselling room during follow-up visits. Each interview lasted approximately 30 minutes. No follow-up interview occurred. The interview guide (Table 1) was developed based on research questions and pre-tested with two patients, leading to slight modifications for clarity. The interview covered participants' views on and preference of educational materials and multimedia-based applications for managing their condition. Interviews were recorded, transcribed and stored securely in password-encrypted files.

Data analysis

The 6-step thematic analysis was conducted to identify patterns and themes within the data, as recommended by Braun and Clarke.[24] The steps involved were (1) familiarizing with data; (2) generating initial codes; (3) searching for themes; (4) reviewing themes; (5) defining and naming themes; and lastly (6) producing the report. An inductive coding was performed to develop codes and themes without trying to fit into an existing framework. Inter-rater reliability was achieved through discussion within the research team and coding discrepancies were resolved through series of discussion and iterative review until disagreements were resolved and consensus was achieved.

A number of themes were derived and classified under three domains namely: (1) patient preferences for educational materials; (2) views on important educational content; and (3) preferred features of a multimedia-based application.

Ethical consideration

Ethical approval for the study was obtained from the University Kebangsaan Malaysia Ethics Committee (UKM PPI/111/8/JEP-2022-508). All participants provided informed consent before participation and were assured of their right to withdraw from the study at any time without penalty. Participant confidentiality was maintained by anonymising the interview transcripts and all data were securely stored following ethical guidelines.

Table 1. Interview guide

Key questions
1. What kind of educational materials do you like the most? (Probe: Conventional type of materials e.g. pamphlets or multimedia-based materials?)
2. Would you rather learn from materials on paper or on your computer? (Probe: Why do you think so?)
3. What would you like to see in educational materials about diabetes that will help you take care of it? (Probe: Content of conventional type of materials or multimedia-based materials?)
4. Do you have any ideas for what should be in multimedia-based educational materials? (Probe: What would be the important features to be included in a mobile application?)
5. Before this, when people used multimedia to learn, did they run into any problems? (Probe: What kind of problem(s)? Why do you think so?)

Table 2. Participants' socio-demographic and clinical characteristics (n = 16)

Variable	Category	Frequency, N
Age	Years, Mean (± SD)	58.06 (± 11.11)
Gender	Male	7
	Female	9
Ethnicity	Malay	11
	Chinese	1
	Indian	4
Highest education qualification	Secondary school	5
	Diploma	4
	Degree	7
Duration of T2DM since diagnosis	1 - 10 years	13
	11 - 20 years	1
	21 - 30 years	1
	31 - 40 years	1
Type of anti-diabetic medication(s)	Oral hypoglycemic agent (OHA)	10
	Insulin therapy	2
	Mixed OHA + Insulin	4

RESULTS

Patients demographic

A total of 16 T2DM patients, consisting of 9 females (n = 9, 56%) and 7 males (n = 7, 44%), participated in this study. The participants' age range was between 44 and 83 years old. The majority of the participants were Malay (n = 11, 69%) and the rest were Indian (n = 4, 25%) and Chinese (n = 1, 6%). Ten participants (n = 10, 63%) were taking oral antihyperglycemic medication, including metformin, gliclazide MR, and a metformin/sitagliptin combination tablet. The majority of the participants (n = 13, 81%) had been diagnosed with T2DM within the past 1 to 10 years. The study participants' socio-demographic and clinical characteristics is summarised in Table 2.

Themes identified

Domain 1. Patients' preference for educational materials

Theme 1. Convenience and accessibility of digital media

It is essential for patients to receive health education to increase their knowledge and awareness of illness manage-

ment and consequently enhance their health outcomes and quality of life. In the present study, participants rated an interactive multimedia-based application as a more effective health education resource than a paper-based educational resource. This is due to its accessibility and availability at all times. It was believed that delivering instructional content through multimedia-based applications would enable participants to read and refer to the information at their leisure, at any time and place. Moreover, with multimedia-based applications, participants can easily and quickly obtain information in audio and video format.

> "*I would choose digital because it's easy to store. With pamphlets, they are easily lost or thrown away because they are large and do take up space" (Participant 6, male, 48 years old).*

> *"I can access the mobile apps at any time, and easier to understand because there are pictures, video and not a long text" (Participant 15, male, 63 years old).*

Theme 2. Technological accessibility challenges for older adults

There were several participants who prefer hardcopy forms of educational materials over multimedia technology due to their lack of exposure to digital technology and compromised visual function. This is particularly relevant for older adult patients. A participant also addressed few technical issues with the use of a multimedia-based application as interactive health educational content. These include application consuming phone storage, reliance on a strong internet connection and absence of data backup if the app or mobile device crashes.

> *"I prefer pamphlets because apps are so troublesome for me. It is easier to see on paper than on a phone because the view of this phone is tiny for my eyes" (Participant 10, female, 83 years old).*

> *"It is challenging for us to read from the phone. The writing fonts in the apps are too small to be read" (Participant 3, male, 74 years old).*

> *"It might consume the phone data, and if there is no internet at that time, apps cannot be opened and used as usual" (Participant 8, male, 54 years old).*

Domain 2. Views on important educational content

Theme 1. Personalized health monitoring

The results indicate that participants appear enthusiastic to learn about the normal range of monitoring parameters for T2DM prevention such as fasting blood sugar, blood pressure and BMI. Consequently, it will enable patients to modify their treatment, behaviour and lifestyle in order to achieve effective glucose control and avoid negative side effects. In addition, the patient would avoid hypoglycemic episodes and diabetes complications by understanding the normal monitoring parameter range.

> *"What is the best reading for sugar level and BMI based on my age? Moreover, what should I do if, let's say, my sugar level is too high or too low?" (Participant 16, female, 59 years old).*

> *"I always have hypo problems when fasting, sometimes, I skip the insulin because I'm afraid of fainting, but when I check my sugar the next day, my sugar is still high. So I want to know the normal sugar level range based on my age" (Participant 14, male, 68 years old).*

Theme 2. Cultural and practical considerations in dietary choices

Additionally, the patient was aware of dietary portions and food selection to control the disease but lacked adequate knowledge regarding food selection. Participants were concerned about the dietary requirements of patients with diabetes. They suggested an explanation of dietary information in educational materials, particularly regarding appropriate food selection, portion control and calorie counting. They prefer that the information regarding food selection be tailored to their dietary preferences, such as local cuisine. Additionally, they would like to know the total daily calorie requirement and calorie counting based on their daily food intake, without discouraging them from attaining a normal blood glucose level range.

> *"I'm from Kedah, and rice is our breakfast routine. I cannot eat a sandwich, and it does not suit my stomach. I would like to know more about the diet suitable for Malaysians"(Participant 8, male, 54 years old).*

> *"What food can be eaten, the suitable portion of food, food that needs to be avoided, the timing of eating, the best time to finish the meal" (Participant 9, female, 58 years old).*

> *"What are the appropriate types of food? How do you count your calories? How do you know if the food we eat exceeds the calorie requirement for the day" (Participant 15, male, 63 years old).*

Theme 3. Understanding and managing diabetes medications

In the interactive patient education materials, participants would also like to learn about medication management, including medication storage, particularly insulin and adverse effects such as hypoglycemia. A participant needs to understand how to adjust insulin dosage to prevent hypoglycemic episodes. They were curious about how the medication functions in the body, especially insulin. As mentioned by a patient in this study, overcoming the anticipation of insulin treatment requires this step. With knowledge of medication management, the patient would have a high level of self-efficacy to deal with disease-related tasks.

> *"I want to know why we have to take this diabetes medicine every day, how it affects our body and how*

it works to reduce blood sugar. Furthermore, what happens if I skip the medication for one or two days and just control my diet" (Participant 16, female, 59 years old).

"Insulin-related facts, benefits and how to use. Because many people are frightened by insulin injections because of the perception that insulin injection is for severe cases of diabetes only. While with insulin injections, the sugar level is easy to control" (Participant 7, female, 52 years old).

"Video on how to store insulin because I cannot read it. If in the form of a video, it is easy to see and understand" (Participant 5, female, 49 years old).

Participants in this study also desire greater knowledge of T2DM and its management. Understanding the disease is crucial for preventing complications and enhancing quality of life. When asked about diabetes in general, the majority of participants were unable to provide adequate responses. Some were unaware of the complications of diabetes and the treatment objectives for T2DM. If the patient does not comprehend the disease, they may not be motivated to take the medication, making it difficult to achieve the therapeutic goal.

"What is diabetes, what happens in the body and why does the patient need to start the medication" (Participant 2, female, 47 years old).

"What is diabetes, and what are the complications if we do not control the sugar level? For me, this is important to create awareness of what happened and why the patient needs to start any medication." (Participant 11, female, 44 years old).

Domain 3. Preference features of multimedia-based application

Theme 1. User engagement and support in digital health applications

Participants agreed that patient education materials using multimedia-based applications should be user-friendly for people of all ages, with fewer buttons to select, clear instructions and engaging video and audio for each app topic. To increase therapy adherence, they favor applications that provide continuous motivation, support and medication reminder. Participants also suggested incorporating a communication function with the healthcare provider into the applications so that they could receive immediate feedback on urgent disease-related matters, such as insulin dose adjustments.

"Attractive video education, a reminder on taking the medication, not too many buttons to click with simple to understand instructions and maybe some motivational quote" (Participant 9, female, 58 years old).

"Room for a message with the pharmacy because sometimes I might have hypoglycaemia, but I am unsure whether to continue taking medicine the next time" (Participant 3, male, 74 years old).

Participants expressed a strong preference for features such as reminders for medication, motivational content and communication functions to interact with healthcare providers for immediate advice**.**

"Reminder push notifications, health records section inside apps, search features, video guide for counselling especially method of handling insulin pen" (Participant 13, female, 48 years old).

"Maybe a chat area for me to have immediate advice without having to go to the hospital too often" (Participant 11, female, 44 years old).

DISCUSSION

This study explored T2DM patients' preferences for educational content and features of a multimedia-based application for T2DM management. The findings in the present study indicate that multimedia applications are generally favoured in our local setting. However, individual preferences and needs vary depending on patients' factors such as age and digital literacy. This is consistent with another local recent study for diabetes[25] and other various health conditions.[20,21] Previous studies have shown a strong correlation between multimedia application usage with improved diabetes management and adherence, diabetes awareness and self-management behaviors, such as blood glucose monitoring, insulin administration and a lower HbA1c level.[26-29] Another study done in Iran also demonstrated that multimedia applications had a positive impact on improving health beliefs and increased physical activity leading to improved health outcomes.[9] Therefore, it was suggested that T2DM patients use a multimedia-based application as an educational tool to improve clinical outcomes as well as health belief and behaviors.

In the present study, we have highlighted that older adult participants preferred using traditional hardcopy or paper-based educational material as compared to the digital educational material. Nonetheless, a technology survey indicates that the older adults must catch up with the general population in terms of technology adoption[30] despite the basic human abilities such as perception, cognition, motor control and functional anthropometry being altered by the aging process.[31] Older adults may utilize some technologies less frequently because they do not meet their requirements for a particular purpose. Individuals' strengths, limitations and life experiences will have an impact on how they will interact with technology adoption. According to the National Diabetes Registry Report in 2020, 29.73% of Malaysians with T2DM were over 60 years old, making up the largest proportion of the population.[32] Therefore, the employed technology should

enhance the lives of the older adults and contribute to an increase in the quality of life. It is necessary to conduct extensive research to ensure that technologies can be effectively utilized and are beneficial to older adults. The interactive mobile application must meet the requirements of older adults by accommodating their cognitive level, capitalizing on their intact talents, assisting them with performing daily tasks and safeguarding their privacy, independence and safety. In addition, the patients' views on important educational content of an interactive multimedia-based application for T2DM demonstrate that the patients expect personalized health monitoring. It may include FBS, BP, BMI and disease knowledge. This indicates that the patient is aware of the importance of self-management and prevention of disease complication. A previous study concluded that in order for educational materials to have an effect on patient behavior on self-management, they must include information on medication adherence, blood glucose monitoring, problem-solving, living with the disease, complication risk, dietary modification and physical activity.[14] Most multimedia applications in the market are limited to dietary modification, physical activity and glucose monitoring.[14] Additionally, the patient's educational materials should aid in the development of self-efficacy which is an individual's belief in their capacity to think, experience and act over time.[33,34] Individuals with a high level of self-efficacy are therefore confident in their ability to execute, whether it be administering medications correctly, modifying their diet, preventing hypoglycemia episodes, or adhering to therapy.

Patients also viewed the importance of dietary modification for T2DM patients. According to a study, the necessary non-pharmacological approach for T2DM is weight loss-promoting lifestyle changes.[35] Another study also indicates that the use of multimedia educational material in nutrition therapy has an impact in achieving metabolic control in T2DM patients.[6] In particular, nutritional therapy enhances weight loss and metabolic outcomes, thereby decreasing insulin resistance associated with diabetes-related metabolic diseases.[36] The patient educational material should include the patient's daily nutritional needs tailored to local dietary practices. The Malaysian Ministry of Health outlines that effective diabetes management requires culturally relevant dietary education. This includes understanding local food selections, types and preparation methods, which differ from Western dietary practices.[37] Therefore, patients should have a sufficient nutritional intake based on Asian local dietary preferences. Using multimedia-based applications, the daily dietary needs should be able to recommend meal quantities, calories monitoring and appropriate food selections based on the local dietary intake.

In addition to effective and educational content, a multimedia-based application should also incorporate interactive features. The benefits of implementing interactive features in such applications include the ability to analyze personal health data and provide targeted education and personalized feedback, which is the most effective strategy to improve patient understanding and self-management of diabetes.[38] T2DM patients must acquire new coping skills and adopt a healthier lifestyle, which requires ongoing information, care, therapy and a high level of commitment.[7] In addition, a multimedia-based application should include a messaging feature with the healthcare professionals (HCPs) so that patients can receive personalized feedback or prompt advice on urgent matters requiring HCPs' attention, such as adjusting the insulin dose during hypoglycemic episodes. Previous research suggests that digital interventions that incorporate both educational content and communication with HCPs tend to have higher patient satisfaction and better health outcomes, based on the Health Promotion Model.[9] Implementing such features in future multimedia applications could bridge gaps in care and reduce unnecessary hospital visits, ultimately improving patient adherence to treatment.

Nonetheless, implementing multimedia-based applications in healthcare settings faces several significant challenges and barriers. One of the primary concerns is the cost associated with developing, deploying and maintaining these technologies. Initial investments in software development, hardware procurement and ongoing updates can be substantial, posing a financial burden on healthcare institutions.[39,40] Additionally, accessibility remains a critical issue, as not all patients have equal access to the necessary technology, such as smartphones or high-speed internet. This digital divide can limit the reach and effectiveness of multimedia applications, particularly in rural or underserved areas.[41,42] Furthermore, patient literacy is a significant barrier. Those who have low health literacy may struggle to understand and use these applications effectively, reducing their potential benefits. They may also find it challenging to navigate these tools, leading to lower adoption rates.[41,43,44] Addressing these challenges require various approaches, including investment in infrastructure, training for healthcare providers and efforts to improve patient literacy. Additionally, robust data, security measures and clear regulatory guidelines are essential to foster trust and compliance.

The findings from this study offer valuable insights for healthcare providers and developers of multimedia applications aimed at T2DM patients. Future mobile applications should focus on providing comprehensive, culturally relevant and easily accessible educational content tailored to individual patient needs. Moreover, features that enhance patient-provider communication should be prioritized to support real-time care and guidance.

Further research is needed to explore the long-term impact of multimedia applications on patient outcomes, including glycemic control, medication adherence and quality of life. Additionally, future studies should examine the cost-effectiveness and feasibility of implementing such tools in routine clinical practice, especially in resource-limited settings.

Limitations

This study has several limitations. The relatively small sample size, though sufficient for data saturation in qualitative research, limits the generalizability of the findings to the wider T2DM population. Furthermore, this study relied solely on qualitative data and future studies may benefit from triangulating qualitative findings with quantitative data to provide a more comprehensive understanding of patient needs and preferences. Therefore, future research should employ a mixed-method approach involving larger and diverse populations to confirm the study's findings and explore variations across different subgroups.

CONCLUSION

This study highlights that T2DM patients are receptive to the use of a multimedia-based application for educational purposes, which could positively impact patient health education. Knowledge expansion among patients may influence their disease self-management and improve self-efficacy toward therapy. The most important aspects of this study are that educational materials should include essential topics in diabetes self-management, such as medication adherence, blood glucose monitoring, problem-solving, disease coping, risk of complications, diet modification and physical activity. A multimedia-based application for patient education must be engaging and interactive in order to enhance patients' ability to attain self-efficacy, improve their quality of life and prevent diabetes complications. The multimedia applications developers should also consider including doctors, pharmacists, nutritionists and psychologists who are experts in their fields to promote behavioral modification techniques among patients. Future research is needed in designing more user-friendly mobile applications, especially for elderly patients, with engaging content, interactive video or audio, comprehensible content, clear instructions, individualized diet recommendations and motivational content, tailored to this particular group of patients in order to maximize the impact on knowledge and self-efficacy among them.

Acknowledgments
We extend our heartfelt appreciation to the patients who participated in the semi-structured qualitative interviews. Their willingness to share their experience and insights has been invaluable in providing a deeper understanding of the educational content and features required for developing an interactive multimedia-based application for T2DM management.

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

CRediT Author Statement (based on Author Form)
NS: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Visualization, Project administration; **TM:** Conceptualization, Methodology, Validation, Formal Analysis, Resources, Data Curation, Writing – review and editing, Visualization, Supervision, Project Administration; **EH:** Conceptualization, Methodology, Validation, Formal Analysis, Resources, Data Curation, Writing – review and editing, Visualization, Supervision, Project Administration; **HA:** Methodology, Investigation, Resources; **NA:** Methodology, Investigation, Resources

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

Sociodemographic and Lifestyle Factors Associated with Undiagnosed Diabetes in Indonesia: Findings from the Basic Health Research Work of Riskesdas 2018

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Abstract

Background. As a developing nation, there has been an increasing trend in non-communicable diseases, including diabetes mellitus (DM) in Indonesia. However, a remarkable proportion of DM cases in this archipelagic country is likely undiagnosed.

Objective. This study assessed the sociodemographic and lifestyle factors related to undiagnosed DM in Indonesians.

Methodology. This cross-sectional study analyzed secondary data from the 2018 Indonesian Basic Health Research (Riskesdas). It involved 3,755 study subjects, 3,619 individuals with high blood glucose levels meeting the DM criteria and 136 individuals with controlled DM. Multivariable regression analysis examined the associations between sociodemographic and lifestyle factors and undiagnosed diabetes.

Results. The study revealed that 80% of the DM cases among the subjects were undiagnosed. Multivariable analysis confirmed that age group, area of residence, employment, wealth quintiles and physical activity were significantly associated with higher odds of undiagnosed diabetes. Notably, sex, smoking status and vegetable consumption did not show any association with the diagnosis status of diabetes.

Conclusion. A significant portion of DM cases in Indonesia remain undiagnosed, especially among young adults, rural residents, agricultural workers and lower socioeconomic groups. Improved healthcare access, targeted screening and enhanced health education are essential to ensure early diagnosis and effective management of diabetes.

Key words: undiagnosed diabetes, diabetes mellitus, non-communicable diseases, diabetic

INTRODUCTION

According to the International Diabetes Federation (IDF), almost one out of two adults with diabetes mellitus (DM) are unaware they have the condition.[1] There are various types of diabetes, but most of the undiagnosed cases are Type 2 Diabetes Mellitus (T2DM), comprising up to 95% of all diabetes incidence.[2] The symptoms of diabetes are often not prominent or noticeable, leading to delayed diagnosis for several years after onset when complications have already occurred.[3] Some may present with the classic symptoms of polyuria, polydipsia and polyphagia with associated weakness and weight loss. However, many people with T2DM are asymptomatic and remain silent for many years, such that at diagnosis, they may already have features of long-term complications like neuropathy, retinopathy or even nephropathy.[4] This makes early detection and timely treatment essential in preventing long-term damage and managing the disease effectively.[5,6]

The burden of undiagnosed diabetes has profound implications on both individual health and national healthcare systems. Delayed diagnosis often leads to an increased risk of severe complications, including cardiovascular diseases, kidney failure and nerve damage. These, in turn, increase healthcare costs and strain health services. Moreover, individuals unaware of their condition cannot take the necessary steps to control their blood glucose levels through lifestyle changes or medication, further exacerbating the progression of their disease.[1,6]

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 5, 2024. Accepted: September 24, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.21

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Globally, Indonesia ranks fifth in terms of the highest number of individuals affected by DM, and this prevalence is projected to rise significantly in the coming years.[1] As almost three-quarters of DM cases are undiagnosed, this archipelagic country ranks third in the total number of undiagnosed diabetes cases.[1] This data poses a challenge to increasing DM awareness among Indonesian citizens. Without diagnosis, unaware patients with diabetes will not be able to seek adequate treatment or modify their lifestyle to control their blood glucose.

Earlier studies have assessed the prevalence of DM and identified its potential risk factors in Indonesia.[7–9] Yet, there remains a significant gap in understanding the risk factors specifically associated with undiagnosed diabetes in the country. Few studies have explored this issue nationally, making identifying interventions for those most at risk difficult. Therefore, this study aims to fill this knowledge gap using nationwide data from the Riskesdas 2018 data to assess the sociodemographic and lifestyle factors associated with undiagnosed diabetes. By identifying the patient characteristics that delineate those diagnosed with DM from those undiagnosed, this research will provide crucial insights that can inform targeted screening and prevention strategies in Indonesia.

METHODOLOGY

Study design

This study analyzed secondary data from the Indonesian Basic Health Research (Riset Kesehatan Dasar or Riskesdas, the abbreviation in Indonesian) 2018. Riskesdas is a nationwide survey conducted by the Ministry of Health of Indonesia every five years. The samples were selected through a two-stage stratified cluster sample drawn nationwide.[10] The population of interest in this study was Indonesians with diabetes, regardless of the diagnosis status. The inclusion criteria were non-pregnant subjects aged >15 years who were detected as having blood glucose levels corresponding with DM in the survey and those with controlled DM. The subjects with controlled DM were those whose blood glucose levels during the survey were normal but had been diagnosed with DM. Data will be excluded if any missing values are found in any of the analyzed variables.

Riskesdas' study participants were selected from the general population of Indonesia using probability proportional to size and linear systematic sampling methods. The survey achieved a 95% interview response rate at the national level. Biomedical data collection, including blood glucose measurements, was conducted on a subsample basis in 26 provinces for individuals aged 15 years and older. Data were obtained from 25,000 households, with a response rate of 77.7%.[10]

Three thousand six hundred nineteen individuals with high blood glucose levels were identified during the survey and included in the analyzed dataset. In addition, the dataset also consists of 136 individuals with controlled DM. Therefore, this study included 3,755 subjects, with the details of subject selection outlined in Figure 1. The sample size calculation/ power analysis was conducted post-hoc using G*Power software. The results indicate that the number of subjects used in this study far exceeds the required minimum sample size, providing robust statistical power to detect significant associations in the analysis.

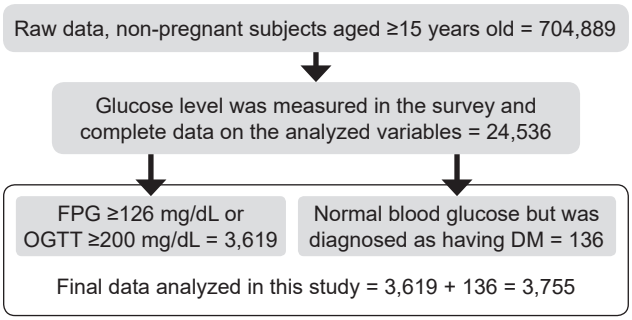

Figure 1. Data selection process.

Variables

The selection of the subjects was based on their diabetes status during the survey. The subject was considered to have diabetes if, at the time of the survey, the fasting plasma glucose (FPG) was >126 mg/dL or the 2-hour oral glucose tolerance test (OGTT) was >200 mg/dL, which followed the consensus of the Indonesian Society of Endocrinology.[11] Subjects are defined as having undiagnosed diabetes when their blood glucose levels correspond to the diagnostic criteria for diabetes, but a doctor has not confirmed the diagnosis.[1]

The data on the diagnosis history relies on the survey item asking the subjects whether they had ever been diagnosed with DM by a health professional. The diagnosis status of diabetes is the dependent variable of this study. The independent variables in this study consist of several sociodemographic, lifestyle, and physical characteristics. The sociodemographic characteristics include sex, age group, area of residence, educational level, employment and wealth quintile. The area of residence is classified following the official regulations established by Statistics Indonesia, which considers several criteria, including population density and the proportion of households engaged in agriculture within the administrative area.[12] Wealth quintiles were adopted from data on average monthly expenditure as determined by Statistics Indonesia. They were categorized into five levels, with Q1 representing the lowest level of wealth and Q5 the highest.[13]

Lifestyle characteristics used as the independent variables include behaviors related to smoking, physical activity, and fruit and vegetable consumption. Physical activities are categorized into "active" and "inactive" based on the modified Global Physical Activity Questionnaire,

a component of the WHO STEPS instrument.[10] Simple questionnaires and food cards were used to ask about the consumption frequency of several food groups. The fruit and vegetable consumption frequency was also asked and then categorized into ≥5 days/week and ≤5 days/week. Smoking status was categorized into daily, non-daily and never smoked. All those data and body weight and height measurements were collected using a validated questionnaire delivered by trained enumerators.[10]

Ethical consideration

The primary data collection of Riskesdas 2018 received ethical approval, with the reference number LB.02.01/2/KE.267/2017, from the Ethical Committee of Health Research, NIHRD, Ministry of Health of Indonesia. Before participating in the survey, all subjects signed informed consent forms. Secondary analysis of the obtained data required no additional ethical clearance.

Statistical analysis

Descriptive statistics were performed to characterize the study population and to compare the prevalence of diagnosed and undiagnosed DM. Bivariate analyses were conducted to obtain crude odds ratio (OR) and their 95% confidence intervals (CI). Subsequently, with the factors that obtained a value of p <0.25, a multivariable regression model was estimated to obtain adjusted odds ratios (aOR) with their 95% CI. Significance is determined at p <0.05. A complex sample technique incorporating stratification, clustering, and weighting for unequal selection probabilities was used to ensure accurate population estimates and valid statistical measures in line with the study's design. The statistical analysis used the International Business Machines Statistical Package for the Social Sciences (IBM SPSS) version 25.

RESULTS

Overall, the majority (80%) of DM cases among the study subjects were undiagnosed. Since all subjects in this study had DM, the fasting plasma glucose and the 2h postprandial glucose averages are higher than normal (Table 1). The average age of the study subjects was 51.39, and most of them were within the 50-59 age range.

The association between the dependent variable (undiagnosed diabetes) and each independent variable was explored by bivariate analysis. Based on this analysis, some variables were shown to have a statistically significant relationship with undiagnosed DM with a p-value <0.05. They include age group, area of residence, employment status, educational level, wealth quintile, physical activity, fruit consumption, and BMI (Table 2). All these variables were then included in the multivariable analysis. Meanwhile, gender, smoking status, and vegetable consumption were not showing statistically significant differences between the diagnosed and undiagnosed DM.

Among the analyzed sociodemographic characteristics, the only variable in the bivariate analysis that does not have a statistically significant relationship with undiagnosed DM is gender. On the other hand, smoking status and vegetable

Table 1. Mean of age, BMI, and blood glucose of the study subjects

Characteristics	Mean (95% CI)	Standard Error
Age	51.39 (50.83-51.95)	0.285
BMI	25.53 (25.32-25.74)	0.106
Fasting plasma glucose	143.97 (141.36-146.58)	1.331
2-hour post prandial glucose	232.71 (229.45-235.97)	1.663

Table 2. Distribution of subjects based on DM status

Characteristics	N	DM status (%)	
		Diagnosed	Undiagnosed
Overall	3755	20.0	80.0
Age group (years)			
15-29	218	1.6	98.4
30-39	455	8.8	91.2
40-49	973	17.7	82.3
50-59	1071	26.6	73.4
≥60	1038	24.3	75.7
Sex			
Male	1209	20.9	79.1
Female	2546	19.6	80.4
Area of residence			
Urban	2266	25.3	74.7
Rural	1489	12.1	87.9
Employment status			
Employed in public/private sectors	274	21.6	78.4
Entrepreneur	558	25.1	74.9
Farmer/fisherman	737	9.9	90.1
Informal worker	533	17.7	82.3
In school/not employed	1653	23.4	76.6
Educational level			
Graduated high school	880	25.9	74.1
Not graduated high school	2875	18.2	81.8
Wealth quintile (IDR)			
Q1 (0 – 378,350)	711	10.6	89.4
Q2 (>378,350 – 593,859)	654	14.9	85.1
Q3 (>593,859 – 838,710)	657	15.9	84.1
Q4 (>838,710 – 1,220,660)	741	22.0	78.0
Q5 (>1,220,660 – 2,592,001)	992	31.4	68.6
Smoking status			
Yes, daily	669	17.8	82.2
Yes, not daily	291	23.0	77.0
Never	2795	20.3	79.7
Physical activity			
Active	2716	16.9	83.1
Inactive	1039	38.9	24.9
Fruit consumption			
≥5 days/week	864	27.9	72.1
<5 days/week	2891	17.7	82.3
Vegetable consumption			
≥5 days/week	2511	20.1	79.9
<5 days/week	1244	20.0	80.0
BMI			
Underweight	252	12.8	87.2
Normal	1565	20.5	79.5
Overweight/obese	1938	20.6	79.4

consumption are the lifestyle characteristics that did not have relationships with undiagnosed DM.

Table 3 presents a multivariable logistic regression analysis examining the relationship between the diagnosis status of diabetes (DM) and various independent variables. This analysis considers multiple factors simultaneously. The results showed that age group, employment status, area of residence, wealth quintile, physical activity, and BMI remain significantly associated with undiagnosed DM.

The odds ratios for age groups suggest that younger individuals are less likely to be diagnosed with DM, corroborating the bivariate analysis. The association between rural residence and having undiagnosed DM remains significant in the multivariable analysis. Farmers and fishermen are still more likely to have undiagnosed DM. The lower wealth quintiles are consistently associated with a higher likelihood of undiagnosed DM. The association between being physically inactive and having undiagnosed DM remains significant. The U-shaped relationship between BMI and DM diagnosis also persists in the multivariable analysis.

DISCUSSION

Various factors contribute to a lack of awareness about diabetes, leading to late detection and potential complications. Since diabetes does not exhibit early signs, people with it typically ignore its symptoms until they become a problem in their daily lives.[14] Data from Riskesdas 2018 revealed that most (80%) diabetes cases in Indonesia were undiagnosed.

Socio-demographic factors influencing diabetes diagnosis

Biological and psychosocial factors influence gender differences in diabetes risk and outcomes. Women are more likely to experience psychosocial stresses and increases in their BMI. Hormonal processes, like menstrual cycle syndrome and post-menopause, can facilitate fat accumulation, increasing the risk of developing type 2 diabetes.[15] Accordingly, Riskesdas showed that more women than men in Indonesia have diabetes. Another Indonesian study reported that gender is not statistically associated with DM.[9] Our analysis showed no difference between the two genders regarding the diagnostic status.

The current guidelines from the Indonesian Society of Endocrinology recommend that diabetes screening begin at age 40 for the general population.[11] Indeed, we found that diabetes is more prevalent among people aged 40 and over. However, analysis of Indonesia Family Life Survey (IFLS) data showed that respondents over 35 are already at a 5.6 risk of diabetes compared to respondents younger than 35.[7]

Moreover, the age-group-specific proportion of undiagnosed diabetes cases follows a pattern that differs from the overall diabetes prevalence in Indonesia. It is observed that DM cases in Indonesian young adults (15-29 years) are less likely to be diagnosed. This indicates that older individuals

Table 3. Results from the bivariate analysis

Variables		OR	*P*-value
Age group (years) (reference = 15-29)	30-39	0.172 (0.03-1)	<0.001
	40-49	0.078 (0.014-0.42)	
	50-59	0.046 (0.009-0.248)	
	60 or more	0.052 (0.01-0.281)	
Sex (reference = Male)	Female	1.08 (0.871-1.341)	0.713
Area of residence (reference = Urban)	Rural	2.471 (2.009-3.04)	<0.001
Employment status (reference = In school/not employed)	Employed in public/private sectors	1.107 (0.756-1.621)	<0.001
	Entrepreneur	0.911 (0.671-1.236)	
	Farmer/fisherman	2.773 (2.096-3.67)	
	Informal worker	1.414 (1.023-1.955)	
Education (reference = Graduated high school)	Not graduated high school	1.567 (1.236-1.986)	<0.001
Wealth quintile (reference = Q5)	Q1	3.872 (2.808-5.338)	<0.001
	Q2	2.614 (1.838-3.716)	
	Q3	2.418 (1.766-3.309)	
	Q4	1.624 (1.23-2.143)	
Smoking status (reference = Never)	Yes, daily	1.17 (0.891-1.538)	0.442
	Yes, not daily	0.851 (0.598-1.211)	
Physical activity (reference = Active)	Inactive	0.52 (0.418-0.647)	<0.001
Fruit consumption (reference = ≥5 days/week)	<5 days/week	1.848 (1.459-2.34)	<0.001
Vegetable consumption (reference = ≥5 days/week)	<5 days/week	1.004 (0.803-1.256)	0.517
BMI (reference = Normal)	Underweight	1.764 (1.143-2.722)	0.020
	Overweight/obese	0.996 (0.801-1.238)	

are more likely to be aware of their diabetes status and have received a medical diagnosis. Our analysis showed that developing diabetes at a young age (under 30 years) significantly increases the risk of going undiagnosed when compared to developing it later in life.

Countries with high incomes tend to have a higher prevalence of diabetes compared to poorer countries.[16] On the other hand, people from lower socioeconomic backgrounds may face challenges in accessing healthcare and health education, potentially leading to delayed detection of diseases such as diabetes. A previous study reported that socioeconomic status influences the prevalence of DM in Indonesia.[8] Our analysis reveals that factors such as type of employment, area of residence, and wealth index also affect the diagnosis status of diabetes. The inverse relationship between socioeconomic factors and diabetes diagnosis status observed in our study mirrors findings from Bangladesh,[17] where the wealthy are more likely to have diabetes. Still, the poor are less likely to be diagnosed and treated.

Although diabetes is more prevalent in urban areas, rural residents have a significantly higher percentage of undiagnosed cases in Indonesia. Our results show that rural residents are at least 1.5 times more likely to have undiagnosed diabetes compared to urban residents (Table 4). This disparity may be due to the limited access to healthcare services in rural areas, leading to fewer diagnoses among rural residents. While individuals in rural areas are less likely to develop diabetes compared to urban dwellers,[9] they may have a poorer understanding of diabetes screening and management due to limited access to healthcare centers.[14] This lack of accessibility, coupled with the perception that diabetes is an urban issue, may contribute to rural communities' reluctance to undergo diabetes screening, resulting in a higher proportion of undiagnosed cases in rural areas.

Another survey reported a higher risk of getting DM among unemployed Indonesians compared to those employed,[9] which aligns with the results from Riskesdas 2018. Notably, asymptomatic patients are typically diagnosed during routine health check-ups for LIC policy, job recruitment, or before surgery.[4] Meanwhile, agricultural field workers in Indonesia do not typically access such facilities. Occupations such as farming and fishing, which are common in lower wealth quintiles, are associated with a higher likelihood of undiagnosed diabetes, according to our analysis. This could be due to limited healthcare access and lower health awareness among these populations.

It was reported that low educational attainment is associated with diabetes occurrence in urban areas of Indonesia,[7] contrasting findings from multiple low and middle-income countries where higher education levels were linked to increased diabetes vulnerability.[18] In our study, not graduating from high school is only seen as being associated with undiagnosed DM in bivariate analysis but not in the multivariable analysis. This may suggest that the contribution of educational level is not as significant as financial and employment status for undiagnosed diabetes. Nevertheless, health illiteracy is known as an important barrier to seeking healthcare.[14]

Lifestyle and undiagnosed diabetes

Previous studies show that lack of physical activity is associated with diabetes incidence. Thus, many health promotion activities are directed to the increase of physical

Table 4. Multivariable logistic regression analysis between the diagnosis status of DM and the independent variables

Variables		OR	*P*-value
Age group (years) (reference = 15-29)	30-39	0.176 (0.03-1.043)	<0.001
	40-49	0.08 (0.014-0.444)	
	50-59	0.048 (0.009-0.267)	
	≥60	0.055 (0.01-0.306)	
Area of residence (reference = Urban)	Rural	1.557 (1.228-1.973)	<0.001
Employment status (reference = In school/not employed)	Employed in public/private sectors	1.283 (0.804-2.048)	<0.001
	Entrepreneur	1.015 (0.73-1.413)	
	Farmer/fisherman	1.942 (1.418-2.661)	
	Informal worker	1.387 (0.991-1.941)	
Education (reference = Graduated high school)	Not graduated high school	1.111 (0.826-1.495)	0.485
Wealth quintile (reference = Q5)	Q1	2.373 (1.667-3.378)	<0.001
	Q2	1.715 (1.174-2.505)	
	Q3	1.616 (1.156-2.259)	
	Q4	1.248 (0.935-1.665)	
Physical activity (reference = Active)	Inactive	0.654 (0.517-0.828)	<0.001
Fruit consumption (reference = ≥5 days/week)	<5 days/week	1.24 (0.976-1.577)	0.079
BMI (reference = Normal)	Underweight	1.374 (0.851-2.218)	0.139
	Overweight/obese	1.239 (0.973-1.577)	

activity.[19–22] Our study, however, shows that diabetic Indonesians who are physically active also have a higher risk of undiagnosed diabetes. Similar results were observed in a study from Bangladesh,[23] indicating a potential misconception that physical activity alone can safeguard against diseases.

Results from our study show that people with sufficient physical activity have a higher proportion of undiagnosed diabetes compared to those with less physical activity. The perception that physical activity reduces the risk of diabetes may lead individuals who are already physically active to skip blood sugar tests, potentially contributing to the progression of diabetes. Nevertheless, physical activity is a fundamental therapeutic aid in managing type 2 diabetes.[24] Additionally, inactive individuals with more screen time may exhibit a higher prevalence of diagnosed diabetes due to increased health awareness through information accessed through their gadgets.

Moreover, high physical activity levels can be job-related. It was reported that rural women tend to engage in more physical activity than urban women.[25] Our analysis shows that farmers and fishermen, the typical rural jobs that also require high physical activity for their work, are among the most at risk for undiagnosed diabetes. On the other hand, having a BMI beyond the normal range is found to increase the odds of undiagnosed diabetes, although the relationship was not statistically significant.

Cigarette smoking is known to exacerbate diabetes risk by impairing glucose tolerance and insulin sensitivity.[26–28] However, there is no association between smoking status and the prevalence of diabetes in urban Indonesia.[7] Similarly, our analysis did not reveal a significant relationship between smoking status and the diagnosis status of diabetes among diabetic Indonesians.

Dietary adherence poses challenges in diabetes care, especially amid cultural barriers.[14] Our study suggests that while fruit consumption initially appears associated with undiagnosed diabetes, this relationship diminishes in multivariable analysis, highlighting the complexity of dietary influences on diabetes outcomes. Nevertheless, a diet rich in fruits and vegetables is vital to prevent type 2 diabetes.[29]

An Indonesian study has suggested considering social support when designing dietary interventions for patients with type 2 DM, especially in rural settings.[30] As proposed by a study from another ASEAN country, internationally recommended diabetes prevention interventions may not be directly applicable here; instead, a localized program such as reducing rice consumption and considering prevailing health beliefs should be encouraged.[31] In the United States, the proportion of undiagnosed diabetes has declined drastically in the past decades. The undiagnosed cases comprise only a minor proportion (<5 %) of all diabetes cases in the country.[5] This is, of course, a contrasting difference with undiagnosed diabetes in Indonesia. While developing as a nation, trends of NCDs, including diabetes, continue to increase, but the healthcare system still needs to catch up to detect diabetes cases.

Our findings have important implications for public health strategies and clinical practice. First, addressing undiagnosed diabetes in Indonesia requires a multifaceted approach, combining improved access to healthcare with better public awareness of diabetes risks. Screening programs should target younger adults, rural populations, and those in lower socioeconomic groups, where the risk of undiagnosed diabetes is highest. Second, public health campaigns must continue to promote routine screenings, even for individuals with active lifestyles or those who perceive themselves as low risk.

An ecological study across Asian countries demonstrated that more robust healthcare governance is associated with higher rates of diabetes, potentially due to improved and earlier detection of diabetic patients.[32] Accurate identification of individuals with diabetes is crucial for initiating proper blood glucose control and preventing complications.[33] Early detection of type 2 diabetes allows for patient-centred management to enhance glycaemic control and reduce complications.[34] The Indonesian healthcare system should prioritize strengthening primary healthcare services, particularly in rural areas, to improve access to diagnostic tools and diabetes treatment.

Limitations

Our study's cross-sectional design limits our ability to establish causal relationships between the diagnosis status of diabetes and the independent variables, calling for future longitudinal investigations. Additionally, the lack of other potential risk factors, such as marital status, family history, comorbidities, or access to healthcare, may have overlooked essential influences on undiagnosed DM.

This study did not account for individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), which are high-risk conditions for type 2 diabetes. The Riskesdas dataset needed more specific questions on these conditions, limiting our ability to include them in the analysis. We also acknowledge the absence of HbA1c measurements, a more objective indicator of DM, and the lack of distinction between type 1 and type 2 DM, which could have enriched our insights into disease dynamics. Future research with more detailed data on glucose metabolism is recommended to capture the entire burden of undiagnosed diabetes better.

However, our study offers significant strengths, particularly in estimating the prevalence of undiagnosed diabetes in Indonesia using Riskesdas, a nationally representative survey. Using odds ratios to identify risk factors for undiagnosed DM enhances the robustness of our findings. Despite limitations, the nationwide sampling approach

employed in our study bolsters the generalizability of our results and provides valuable insights for public health strategies targeting undiagnosed diabetes in Indonesia.

CONCLUSION

As a developing nation, Indonesia is experiencing a continual rise in diabetes prevalence, reflecting an epidemiological transition towards non-communicable diseases. This trend significantly strains the country's healthcare system, which is challenged to detect more diabetes cases. Unfortunately, our analysis indicates that many diabetes cases remain undetected, highlighting the current limitations in our healthcare system's ability to diagnose this particular public health issue. Despite governmental campaigns against NCDs, including diabetes, it appears that these programs have not effectively reached vulnerable populations, such as rural communities, the economically disadvantaged, and workers in agriculture and informal sectors.

Ensuring all patients are accurately diagnosed and detected is essential for meaningful disease control. Identifying the unequal distribution of undiagnosed diabetes among different socioeconomic groups is crucial for setting priorities and resource allocation. The findings of our study will aid policymakers by highlighting disparities in undiagnosed diabetes distribution, guiding targeted interventions and resource allocation. Our analysis recommends initiating diabetes screening at a productive age, focusing on those in rural areas, agricultural and informal workers, and those from lower economic classes. By targeting screenings for high-risk groups and improving health literacy, Indonesia can move toward more equitable and effective diabetes management.

Acknowledgments
The authors thank the Ministry of Health of Indonesia for providing data from Riskesdas 2018.

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

CRediT Author Statement
ARF: Conceptualization, Methodology, Formal Analysis, Writing – original draft preparation, Writing – review and editing; **J**: Writing – original draft preparation; **WTY**: Writing – original draft preparation; **BS**: Formal analysis, Writing – review and editing; **DEP**: Formal analysis.

Data Availability Statement
The Riskesdas 2018 data used in this study was supplied by the Health Development Policy Agency of the Ministry of Health of Indonesia under license. Requests for access to these data should be directed to the Health Development Policy Agency of the Ministry of Health of Indonesia.

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

Validation of the Filipino Version of the Diabetes Distress Scale for Adult Patients with Diabetes seen at the Outpatient Department of a Tertiary Government Hospital in Quezon City, Philippines

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Abstract

Introduction. Caring for persons with diabetes involves a holistic approach. Addressing diabetes distress is crucial to achieve optimal health outcomes for persons with diabetes. This study aims to validate a Filipino version of the diabetes distress scale (DDS).

Methodology. We conducted forward and backward translations to construct a Filipino version from the validated English questionnaire. We performed statistical analysis to check internal consistency and validation and to correlate diabetes distress with glycemic control based on the subjects' HbA1c levels.

Results. We included one hundred and seventy patients (170) seen at the Outpatient Diabetes Clinic in the analysis. Of the participants, 13 (7.6%) have Type 1 Diabetes Mellitus (T1DM), while the rest have Type 2 (T2DM). We found physician distress (PD) to be significantly associated with having T1DM. All domains in the Filipino DDS showed good internal consistency, ranging from 0.81 to 0.85. We used factor analysis to extract four factors similar to the original diabetes distress scale. We did not find any significant correlation between diabetes distress and HbA1c level.

Conclusion. The Filipino DDS showed good internal reliability and had consistent results similar to the original diabetes distress scale. However, we did not find a significant correlation between diabetes-related distress and the HbA1c level.

Key words: emotional distress, Filipino, diabetes self-management questionnaire, validation

INTRODUCTION

Diabetes Mellitus poses a heavy burden worldwide, affecting a significant number of people. As of 2021, the Federation (IDF) reports that 66 million adults worldwide have diabetes, with a local prevalence of 7.5%, or 4.3 million adults.[1] Consequently, deaths due to diabetes mellitus have increased, making it the fifth leading cause of death in 2024.[2] In the Philippines, there is a greater prevalence of diabetes in urban compared to rural areas.[3]

Among Filipino patients, a study done by Bernabe-Dela Victoria and Dampil showed the prevalence of depression to be higher among patients with T2DM, at 19.9%.[4] However, it is important to note that diabetes distress does not equate to clinical depression.[5] Diabetes distress results from the emotional burden in the management of diabetes.[6] However, depression is a risk factor for diabetes and is associated with poor glycemic control and a higher rate of microvascular complications.[6,7] Among patients with T1DM, those with poor glycemic control and higher HbA1c levels have higher diabetes distress scores.[6,8] Lee et al., found that there is a positive correlation between depressive symptoms and heightened diabetes awareness but with further inadequacy in glycemic control.[9] In a local cross-sectional study by Totesora et al., which utilized the Problem Areas In Diabetes (PAID-20) and Diabetes Self-management Questionnaire (DSMQ) to screen for diabetes-related emotional distress and diabetes-reported self-care, respectively, the authors found that majority of patients who reported emotional distress had higher HbA1c levels. Moreover, those with poor self-care were likely to have poor glycemic outcomes.[10]

It is important to consider not only the physical but also the psychological well-being of individuals affected by diabetes. It is crucial to provide comprehensive psycho-social care to identify interpersonal and intrapersonal barriers to diabetes-related health and develop effective intervention strategies.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: April 30, 2024. Accepted: June 27, 2024.
Published online first: April 20, 2025.
https://doi.org/10.15605/jafes.040.01.05

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Furthermore, since diabetes management relies heavily on the patient's adherence to a treatment regimen, factors affecting self-care, such as diabetes distress, must be identified, addressed, and monitored. As such, the American Diabetes Association suggests including psychological assessment of patients, periodic assessment, and standardized or validated tools to gauge psychosocial wellness.[11]

The most commonly used validated tools to assess diabetes distress are Problem Areas in Diabetes (PAID) and Diabetes Distress Scale (DDS). PAID focuses more on the emotional concerns that can affect health-related quality of life.[12] On the other hand, the DDS evaluates emotional distress related to clinicians, treatment, and personal factors impacting glycemic control, such as behavior and motivation. Developed by William Polonsky, the DDS is applicable for patients with both T1DM and T2DM, provided that these patients do not have severe cognitive impairment.[13] The original DDS comprises 17 questions grouped into four domains as follows: interpersonal distress (ID), emotional burden (EB), regimen-related distress (RR), and physician-related distress (PD). Participants are asked to rate the items listed using a 6-point Likert scale based on their experiences regarding diabetes over the past month. They can indicate whether each item was "not a problem" or if it was considered "a very serious problem."[13] We used DDS in this study as Schmitt et al., found that the psychometric results of the DDS are more precise and more cross-culturally replicable.[14]

In a study by Farm et al., where the authors translated and validated a Bahasa-Indonesian diabetes distress scale, they found that the translated tool provided the necessary factor structure and internal consistency to assess distress among outpatients with T2DM.[15] Similarly, Batais et al., evaluated an Arabic version of the DDS. The results were similar: the Arabic version proved reliable for assessing diabetes distress among outpatients with T2DM.[16] Chew et al., conducted a similar study that found a significant correlation between the score categories of the Malay Diabetes Distress Scale and HbA1c levels among patients with T2DM in the Malay population.[17]

Providing holistic care for patients with diabetes includes identifying areas requiring psychosocial intervention; hence, we aimed to pinpoint those specific areas for our adult diabetic patients seen in the outpatient department. Understanding differences in the patterns of diabetes distress between patients with T1DM and T2DM can help identify which specific psychosocial areas we need to address to aid these patients. As there was a lack of existing literature comparing diabetes distress using the original DDS among adult Filipinos with T1DM and T2DM, this study aimed to fill that knowledge gap. Additionally, even though the Philippines ranks 2nd among Asian countries in the English proficiency index, the ranking did not account for participants without access to the internet since the proficiency index test is administered online.[18] Tagalog or Filipino remains the most widely spoken language,[19] and developing a Filipino version of the Diabetes Distress Scale could help physicians better assess and communicate with patients.

OBJECTIVES

General objective

To determine the validity of the translated, revised DDS tool among Filipino patients with diabetes.

Specific objectives

- To describe the sociodemographic and clinical characteristics of the population
  - Characteristics of interest include age, sex, body mass index, marital status, educational attainment, employment status, duration of diabetes, smoking history, intake of alcohol-containing beverages, HbA1c, antidiabetic medication, and presence of complications such as retinopathy, neuropathy, and nephropathy.
- To determine the correlation of diabetes distress as measured by the DDS tool with glycemic control among adult Filipinos with diabetes.

METHODOLOGY

Study design

This study was conducted in two phases. The first phase involved translating and initially validating the Filipino Version of the Diabetes Distress Scale. The second phase involved collecting data to validate the finalized questionnaire and to assess the correlation between diabetes distress and poor glycemic outcomes.

Translation and validation

The translation process consisted of a forward and backward translation per the recommended guidelines.[20] With permission from the original author, the validated English tool was translated into a Filipino version by two bilingual translators recommended by the Center of the Filipino Language. The forward translations were then reviewed by the researchers and merged into a single document, then translated back to English (back translation) by two bilingual translators. These back translators were professional bilingual (English and Filipino) teachers at a university. Afterward, we compared the back translations to the original DDS. We used the final questionnaire as the initial DDS in Filipino.

The initial DDS was then assessed for content validity by eight respondents (four endocrinologists, two psychiatrists, a family medicine physician, and a nurse practitioner) based on the COSMIN criteria for content validity.[21] From these respondents, we gathered feedback on whether the questions were relevant, comprehensive, and easily under-

stood by the target population. We asked the following questions from the respondents:

COSMIN criteria for content validity[21]

Item	Question
Relevance	
1	Are the items relevant to the construct of interest (Diabetes Distress Scale)?
2	Are the items relevant to the target population of interest (patients with diabetes)?
3	Are the items relevant for the context of use of interest (To develop a Filipino version of the diabetes distress scale)?
4	Are the response options appropriate?
5	Are there other issues that need to be addressed?
Comprehensiveness	
6	Are there any missing key concepts 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?

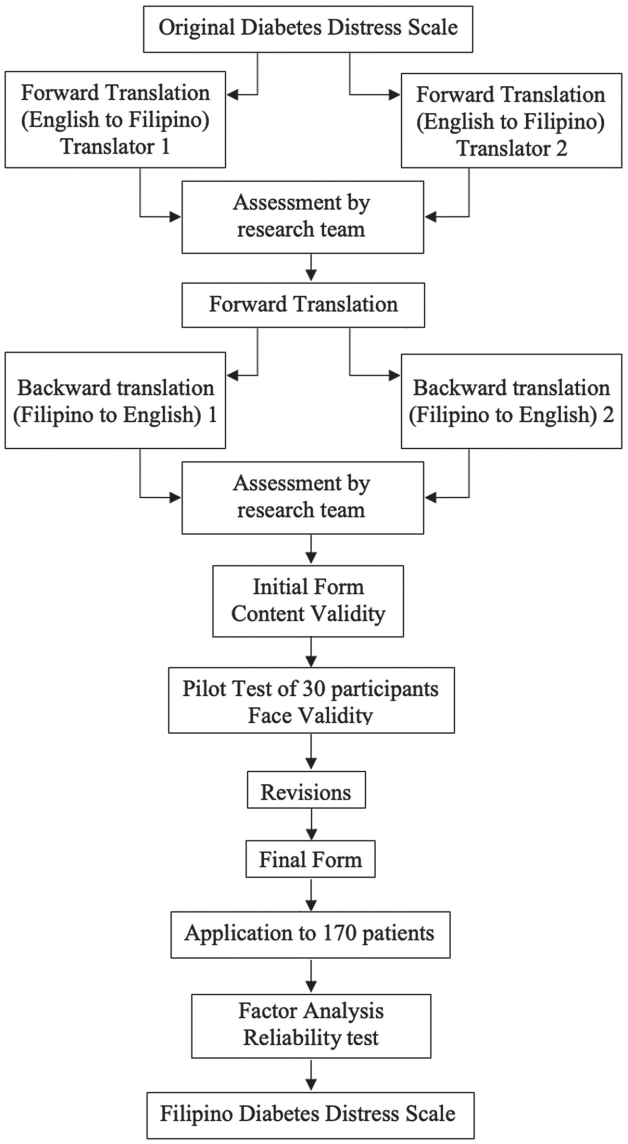

Figure 1. Flow diagram of study procedure.

We computed the item-level content validity index (I-CVI), the proportion of experts who agree that the item is either quite or highly relevant. The accepted I-CVI should be greater than 0.8. The investigators and the expert panel reviewed and discussed items with scores lower than 0.8.

After content validity and final revisions, we pilot-tested the Filipino DDS among 30 participants by convenience random sampling at the OPD. For face validity, we gathered feedback from the pilot testing on whether the subjects thought the specific item was essential and if the item was understandable or needed to be rephrased. We also asked the participants whether they had any difficulty answering each question and if there were statements that needed to be rephrased.[21,22] We administered the final questionnaire to 170 participants who have diabetes, either Type 1 or Type 2.

Study subjects

The participants were patients with diabetes being seen at the Outpatient Department of the East Avenue Medical Center. We employed convenience sampling to select the participants.

Inclusion criteria

- Patients diagnosed with diabetes based on American Diabetes Association (ADA) criteria ≥19 years of age.
  - ADA criteria for diabetes: fasting blood sugar ≥126 mg/dl (7.0 mmol/L), 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during a 75 g oral glucose tolerance test, or HbA1c ≥6.5%;
- Patients diagnosed with T1DM from childhood who have transferred to the adult endocrinology clinic or diagnosed in the adult endocrinology clinic by having a positive anti-GAD test or with C-peptide levels less than the laboratory-specific normal value.
- Patients already taking antidiabetic medications.
- Patients who gave informed consent.
- Patients who can understand, read, and write in the Filipino language.

Exclusion criteria

- Patients with neurological or psychological impairment or on antipsychotic medications or mood stabilizers.
- Patients with gestational diabetes mellitus.

Procedure

The researchers collected data by asking patients to answer the questionnaire during their actual visit to the outpatient department. After obtaining the participant's informed consent, the researchers provided the questionnaire for the participant to fill out independently to minimize attention and interviewer bias. On average, participants spent 13 minutes completing the questionnaire (minimum of 8 minutes, maximum of 20 minutes).

Sample size

According to Krabbe, a validation study should ideally have a minimum sample size of 10 participants for each item in the questionnaire under evaluation. The Diabetes Distress Scale has 17 items; hence, the minimum required sample size is 170. Excluding the initial 30 participants recruited for pilot testing, we enrolled 170 eligible patients who met the inclusion and exclusion criteria.

Description of outcome measures

Primary outcome measure

- Content validity – Feedback was gathered from experts as to whether the question is relevant, comprehensive, and easily understood by the target population. Item-level content validity index (I-CVI) was computed wherein the proportion of experts who agree that the item is either quite or highly relevant should outweigh the total number of experts that the accepted I-CVI should be greater than 0.8. An item with a lower score will be subject to review and discussion by the investigators and the expert panel.
- Face validity – Feedback was gathered from the pilot testing as to whether they
- think the specific item is important and if the item is understandable or needed to be rephrased.
- Construct analysis – measured using factor analysis which will be used to verify the scale construction.
- Internal Consistency – the diabetes distress scale measures 4 subsets related to distress with several questions per set. Cronbach alpha is a measure of internal consistency to assess how the questions are interrelated to assess the general distress of interest.

Secondary outcome measure

- Correlation of glycemic control with diabetes distress scale

Ethical considerations

The institutional ethical research board approved this study. We secured patient confidentiality by using a participant code to withhold patient identifiers.

Data analysis

We used descriptive statistics to summarize the general and clinical characteristics of the participants. We used frequency and proportion for categorical variables (nominal/ordinal), mean and standard deviation for normally distributed interval/ratio variables, and median and range for non-normally distributed interval/ratio variables. We used independent T-test, Mann-Whitney U test, and Fisher's Exact/Chi-square test to determine differences in mean, median, and frequency between groups, respectively.

We used Spearman's rank correlation to determine the correlation between HbA1c and distress scores. We performed factor analysis to assess the consistency of the questions concerning construct validity when translated into Filipino. We used Cronbach α to measure internal reliability.

We included all valid data in the analysis. We did not replace or estimate missing variables. We rejected the null hypothesis if the α-level of significance was less than 0.05. We used R 4.2.2 (Free Software Foundation, Inc., Boston, MA, USA) for data analysis.

RESULTS

Phase I: Questionnaire Formulation

Based on the feedback from the eight respondents, the results of the content validity assessment of the Filipino Diabetes Distress Scale indicated that the items were highly rated as relevant (Appendix Table 1). We received no comments concerning the comprehensiveness of the scale. However, one participant did mention that a word in the translation might not be commonly used. Nonetheless, the initial participants in the pilot testing did not encounter any issues with the original prototype, so it was used for the study.

During the pilot testing, we performed an initial internal reliability test to assess the consistency of the results with the translated questions. A measure of 0.7 – 0.8 was deemed acceptable, with results within 0.8-0.9 deemed good. The initial results for the first 30 participants fell between 0.78 and 0.85, the lowest being interpersonal distress and the highest regimen distress (Appendix Table 2). Aside from this, we conducted face validity to collect feedback on the scale and the questions. All items were perceived as important and understandable (Appendix Table 3).

Phase II: Validation

No additional modifications were made to the initial DDS since there were no further comments from the participants. One hundred seventy (170) diabetic patients were analyzed for this study: 13 patients had T1DM, and the rest had T2DM (Table 1). The mean age was 53.64 (+ 12.18) years old, with the T2DM group significantly older (55.72 ±_9.91 vs 28.46 ± 8.32, p <0.001). The majority were males (58.82% vs. 41.81%) and overweight (60%), with the median BMI values significantly higher among patients with T2DM (24.07, IQR 21.64-26.72 vs 20.67 IQR 19.61-23.22; p = 0.012). Notably, underweight patients were more frequently seen among patients with T1DM (23.08% vs 6.37%, p = 0.026). Most patients (61.76%) were married, which was more frequently noted in patients with T2DM (64.33% vs 30.77%, p = 0.003). Most patients were high school graduates (58.82%) and unemployed (61.76%). The median duration of diabetes was six years (IQR 3-10 years). Patients with T1DM had a longer median diabetes duration than those with T2DM (10 years, IQR 8-14 years vs six years, IQR 3-10 years). Thirteen (7.65%) patients were smokers, while 18 (10.59%) were alcoholic beverage drinkers. The median HbA1c levels of

Table 1. Clinical characteristics of the study population (n=170)

	Total (n=170)	T1DM (n=13)	T2DM (n=157)	*p*-value
Age in years (mean ± SD)	53.64 ± 12.18	28.46 ± 8.32	55.72 ± 9.91	<0.001*
Gender n (%)				0.931†
Male	70 (41.81)	6 (46.15)	64 (40.76)	
Female	100 (58.82)	7 (53.85)	93 (59.24)	
BMI Median (IQR)	23.88 (21.31-26.68)	20.67 (19.61-23.22)	24.07 (21.64-26.72)	0
Underweight n (%)	13 (7.65)	3 (23.08)	10 (6.37)	0.026‡
Normal n (%)	55 (32.35)	6 (46.15)	49 (31.21)	
Overweight n (%)	102 (60)	4 (30.77)	98 (62.42)	
Civil status n (%)				0.003‡
Single	39 (22.94)	9 (69.23)	30 (19.11)	
Married	105 (61.76)	4 (30.77)	101 (64.33)	
Separated	5 (2.94)	0	5 (3.18)	
Widowed	21 (12.35)	0	21 (13.38)	
Educational attainment n (%)				0.686‡
Elementary	22 (12.94)	1 (7.69)	21 (13.38)	
High school	100 (58.82)	7 (53.85)	93 (59.24)	
College	38 (22.35)	4 (30.77)	34 (21.66)	
Vocational	10 (5.88)	1 (7.69)	9 (5.73)	
Employment status n (%)				0.068‡
Unemployed	105 (61.76)	12 (92.31)	93 (59.24)	
Employed	33 (19.41)	1 (7.69)	32 (20.38)	
Retired	32 (18.82)	0	32 (20.38)	
Duration of diabetes, years median (IQR)	6 (3-10)	10 (8-14)	6 (3-10)	0.005§
Smoking n (%)	13 (7.65)	1 (7.69)	12 (7.64)	>0.999‡
Alcoholic beverage drinker, n (%)	18 (10.59)	1 (7.69)	17 (10.83)	>0.999‡
HbA1c % median (IQR)	8.3 (6.61-10.2)	9.6 (9-11.2)	8.2 (6.6-10.07)	0.015§
Antidiabetic medication, n (%)				
Oral	146 (85.88)	0	146 (92.99)	<0.001‡
Insulin	91 (53.53)	13 (100)	78 (49.68)	<0.001‡
Others	1 (0.59)	0	1 (0.64)	>0.999‡
Complications n (%)				
Retinopathy	113 (66.47)	11 (84.62)	102 (64.97)	0.223‡
Neuropathy	105 (61.76)	7 (53.85)	98 (62.42)	0.564‡
Nephropathy	38 (22.35)	3 (23.08)	35 (22.29)	>0.999‡
DDS score (total scale) Median (IQR)	1.706 (1.191-2.632)	2.176 (1.529-2.941)	1.647 (1.176-2.588)	0.085§
High ≥3 n (%)	32 (18.82)	3 (23.08)	29 (18.47)	0.713‡
Low n (%)	138 (81.18)	10 (76.92)	128 (81.53)	

Statistical tests used: * – Independent Sample T-test; § – Mann-Whitney U test; † – Chi-square test; ‡ – Fisher's exact test

patients with T1DM were significantly higher than those with T2DM (9.60, IQR 9-11.20 vs 8.20 IQR 6.60-10.07; p = 0.015). Ninety-three percent (93%) of patients with T2DM were on oral antidiabetic medications alone, while 50% were on insulin. Most of the patients had retinopathy (66.47%) as a complication and a low DDS score (81.18%), which notably were not different based on DM type.

Among patients with T2DM, low emotional burden (r = 0.31; p-value <0.001), low regimen distress (r = 0.39; p-value <0.001), and low physician distress (r = 0.27; p-value = 0.004) showed weak and direct correlations with HbA1c level. Among patients with T1DM, only high emotional burden was seen to have a perfect and direct relationship, although it was not statistically significant (p-value >0.999) (Table 2).

Among distress score domains, physician distress was significantly associated with the diabetes subset (p-value = 0.008). Patients with T1DM had significantly higher physician distress scores (median 3.25, IQR 2.25-3.50) than those with T2DM (median 1.75, IQR 1.25-3). Patients with T1DM (n = 13) were 3.25 times more likely (53.85% with high scores) to have physician distress. Patients with T1DM and patients with T2DM had low distress scores for emotional burden, regimen distress, and interpersonal distress (Table 3).

As seen in Table 4, all instrument domains presented good internal reliability. The highest internal consistency was seen for regimen distress, with a Cronbach alpha of 0.877. This domain includes items 5, 6, 10, 12, 16. Meanwhile, the lowest Cronbach alpha was seen for physician distress with a value of 0.81. These are items 2, 4, 9, and 15.

In the factor analysis, we identified four factors that align with the original diabetes distress scale. Factor 1 is linked to emotional burden, factor 2 is associated with regimen distress, factor 3 seems to correlate with interpersonal distress, and factor 4 is tied to physician-related distress. Items 15 and 16 show cross-loading for two factors, with

Table 2. Correlation and comparison between high- and low- distressed patients on hemoglobin A1C (HbA1c) (n=170)

	HbA1c (Mean ± SD)	Correlation coefficient	Interpretation	*p*-value
Type 1				
Emotional burden				
High ≥3	10.05 ± 1.63	1	Perfect, direct	>0.999
Low	10.56 ± 3.16	-0.1160	Very weak, indirect	0.734
Regimen distress				
High ≥3	9.62 ± 0.98	0.1160	Very weak, direct	0.827
Low	11.21 ± 3.87	-0.4077	Moderate, indirect	0.364
Interpersonal distress				
High ≥3	11.20 ± 0	-	-	-
Low	10.42 ± 3.05	0.2281	Weak, direct	0.476
Physician distress				
High ≥3	10.16 ± 1.68	0.2594	Weak, direct	0.574
Low	10.85 ± 4.10	0.2648	Weak, direct	0.612
Type 2				
Emotional burden				
High ≥3	8.36 ± 2.19	0.1166	Very weak, indirect	0.625
Low	8.59 ± 2.48	0.3054	Weak, direct	<0.001
Regimen distress				
High ≥3	9.36 ± 2.30	-0.0372	Very weak, indirect	0.808
Low	8.24 ± 2.43	0.3856	Weak, direct	<0.001
Interpersonal distress				
High ≥3	8.56 ± 2.45	-0.0944	Very weak, indirect	0.692
Low	8.56 ± 2.44	0.1404	Very weak, direct	0.102
Physician distress				
High ≥3	9.10 ± 2.34	-0.0248	Very weak, indirect	0.874
Low	8.36 ± 2.45	0.2654	Weak, direct	0.004

Interpretation of correlation coefficients: (+) – direct, (-) – indirect; 0 – no correlation; (0-0.2] – very weak, (0.2- 0.4] – weak, (0.4-0.6] – moderate, (0.6-0.8] – strong, (0.8-1.0) – very strong, 1.0 – perfect.

Table 3. Comparison of distress scores between patients with T1DM and T2DM (n=170)

	Total (n=170)	T1DM (n=13)	T2DM (n=157)	*p*-value
	Frequency (%); Median (IQR)			
Emotional burden	1.40 (1-2.20)	1.40 (1.20-2.40)	1.40 (1-2.20)	0.576§
High ≥3	22 (12.94)	2 (15.38)	20 (12.74)	0.677‡
Low	148 (87.06)	11 (84.62)	137 (87.26)	
Regimen distress	2.10 (1.20-3.20)	2.60 (1.80-4.20)	2 (1.20-3.20)	0.206§
High ≥3	119 (70)	6 (46.15)	45 (28.66)	0.213‡
Low	51 (30)	7 (53.85)	112 (71.34)	
Interpersonal distress	1 (1-2)	1 (1-2.667)	1 (1-2)	0.548§
High ≥3	21 (12.35)	1 (7.69)	20 (12.74)	>0.999‡
Low	149 (87.65)	12 (92.31)	137 (87.26)	
Physician distress	2 (1.25-3)	3.25 (2.25-3.50)	1.75 (1.25-3)	0.008§
High ≥3	120 (70.59)	7 (53.85)	43 (27.39)	0.058‡
Low	50 (29.41)	6 (46.15)	114 (72.61)	

Statistical tests used: § – Mann-Whitney U test; ‡ – Fisher's exact test

Table 4. Measure of internal reliability using Cronbach α (n=170)

Domain (Item number)	Cronbach α
Emotional burden (1, 3, 8, 11, 14)	0.855
Physician distress (2, 4, 9, 15)	0.818
Regimen distress (5, 6, 10, 12, 16)	0.877
Interpersonal distress (7, 13, 17)	0.848

Interpretation of Cronbach α: >0.9 and up – Excellent; 0.8 to <0.9 – Good; 0.7 to <0.8 – Acceptable; 0.6 to <0.7 – Questionable; 0.5 to ≤ 0.6 – Poor; <0.5 – Unacceptable.

Item 15 relating to interpersonal and physician-related distress and Item 16 relating to regimen and interpersonal distress. Each item has a uniqueness value of less than 0.60, indicating that it is explained in conjunction with the other items in the subset (Table 5).

DISCUSSION

Our main objective was to validate a Filipino version of the Diabetes Distress Scale. The Filipino version showed good internal reliability and was able to extract four factors similar to the original diabetes distress scale [interpersonal distress (ID), emotional burden (EB), regimen-related distress (RR), and physician-related distress (PD)].

Table 5. Factor analysis of questions per subset of the Diabetes Distress Scale (n = 170)

Item	Domain	Description	Four extracted factors of DDS				
			1	2	3	4	Uniqueness
17	ID	Feeling that friends or family don't give me the emotional support that I would like.	0.1778	0.1576	0.6823	0.2991	0.3885
13	ID	Feeling that friends or family don't appreciate how difficult living with diabetes can be.	0.4008	0.0678	0.6208	0.2872	0.3669
7	ID	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).	0.3210	0.2047	0.5675	0.3937	0.3780
14	EB	Feeling overwhelmed by the demands of living with diabetes.	0.6047	0.3063	0.4541	0.0549	0.3313
3	EB	Feeling angry, scared, and/or depressed when I think about living with diabetes.	0.6690	0.1033	0.1269	0.3435	0.4076
1	EB	Feeling that diabetes is taking up too much of my mental and physical energy every day.	0.5790	0.3765	0.1499	0.1283	0.4841
11	EB	Feeling that I will end up with serious long-term complications, no matter what I do.	0.5597	0.3019	0.2307	0.2196	0.4942
8	EB	Feeling that diabetes controls my life.	0.6273	0.3228	0.3208	0.1903	0.3632
15	PD	Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	0.1485	0.2557	0.4511	0.4135	0.5381
2	PD	Feeling that my doctor doesn't know enough about diabetes and diabetes care.	0.1709	0.1469	0.1590	0.7293	0.3920
9	PD	Feeling that my doctor doesn't take my concerns seriously enough.	0.0572	0.2431	0.3868	0.5994	0.4287
4	PD	Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.	0.2478	0.0332	0.1473	0.7613	0.3362
5	RD	Feeling that I am not testing my blood sugars frequently enough.	0.1638	0.7006	0.0209	0.3278	0.3744
12	RD	Feeling that I am not sticking closely enough to a good meal plan.	0.3138	0.6259	0.3829	0.0069	0.3632
16	RD	Not feeling motivated to keep up my diabetes self-management.	0.3412	0.5233	0.5726	0.0389	0.2803
6	RD	Feeling that I am often failing with my diabetes routine.	0.2779	0.7961	0.1855	0.1577	0.2298
10	RD	Not feeling confident in my day-to-day ability to manage diabetes.	0.4959	0.5424	0.2819	0.1030	0.3698

Note: cut-off = 0.40; blank means <0.40; Uniqueness <0.6 – related within the subset
Abbreviations: ID – interpersonal distress; EB – emotional burden; PD – physician distress; RD – regimen distress

The study recruited 170 participants, excluding the 30 participants in the pilot test. This was more than the minimum required for a factor analysis, which was 100.[23] This also met the sample required for validation testing of 5-10 participants per item to be validated.[24]

Contrary to the study of Chew et al., which used the Malay version of the DDS for individuals with T2DM, our results showed a weak correlation between glycemic control (HbA1c level) and diabetes distress. Low emotional burden, regimen distress, and physician distress have shown weak and direct correlations with HbA1c levels. Filipinos are colloquially known to be easy-going, and that culture of *"bahala na,"* or leaving things up to fate or the divine, further promulgates indifference and accepting things as they are.[25] The majority of the respondents in this study, despite poor glycemic control and the presence of comorbidities, responded to the items on the scale as "not a problem," which accounts for low distress scores in the results. Our results were similar to the local study by Totesora et al., where they did not find a statistically significant association between emotional distress and glycemic control.

We did not find a significant association between poor glycemic outcomes and high distress score domains for patients with T1DM and T2DM. Our findings contrast with a study by Cechetti in Brazil, which found that 53% of patients with T1DM and HbA1c levels >7.6% experienced high emotional distress.[26]

Physician variability may be a factor for the significant difference in distress scores between patients with T1DM and T2DM. Our institution is part of a government-subsidized healthcare system, and patients often cannot choose their attending physician. Additionally, the patients with T1DM included in our study have just transitioned from the pediatric clinic. Compared to when their pediatric endocrinologists constantly saw them, they have just started seeing adult endocrinologists. This may be a contributing factor as to why physician distress emerged as the significant factor for patients with T1DM.

All domains showed good internal reliability with the resulting Cronbach α greater than 0.8, ranging from 0.81 to 0.87 for all four domains. This result is in line with the original DDS17. It is also comparable to the Malay version, which has a high internal consistency of 0.94.[17] the Thai DDS with Cronbach alpha of 0.95[27] and the Bahasa version, which has an internal consistency of 0.78 to 0.83.[15]

We were able to extract four factors during factor analysis: Factor 1 appeared to represent the emotional burden domain, Factor 2 included those in the regimen distress, Factor 3 contained items related to interpersonal distress, and Factor 4 contained items regarding physician-related distress. The extracted four factors were similar to the original DDS17. Most of the items with cross-loading are evident in items related to physician and regimen distress. Item number 15, "Feeling that I don't have a doctor who I can see regularly enough about my diabetes," has been factored under both interpersonal distress and physician-related distress. This phenomenon could be explained by the institution's system, which often does not allow patients to choose their attending physician. This is comparable to what was reported in China by Ting et al., wherein they had cross-loading of item number 12, "Feeling that I am not sticking closely enough to a good meal plan, and 15, "Feeling that I don't have a doctor who I can see regularly enough about my diabetes."[28] These findings were also seen

Table 6. Comparison of the Filipino, Malay, Indonesian, and Thai Diabetes Distress Scales

	Filipino Diabetes Distress Scale	Malay Diabetes Distress Scale[17]	Indonesian Diabetes Distress Scale[15]	Thai Diabetes Distress Scale[27]
Participants	170 outpatients	262 outpatients	324 outpatients (246 from the hospitals and 78 from the primary health care centers)	170 (particularly elderly outpatients)
Internal Consistency (Cronbach alpha)	0.81 - 0.87 lowest: 0.818 (Physician Distress), highest 0.87 (Regimen Distress)	0.93, lowest: 0.823 (physician-related distress), highest: 0.925 (regimen distress and interpersonal distress)	0.78 - 0.83, lowest value - 0.78 regimen distress, highest 0.83 (interpersonal distress and physician distress)	0.95, highest item correlation with Emotional and regimen-related burden, lowest with Physician-related distress
Construct Validity (Factor Analysis)	Extracted four factors similar to the original diabetes distress scale: Factor 1 – Emotional burden, factor 2 – regimen distress, factor 3 – interpersonal distress, factor 4 – physician-related distress	Extracted three factors – combined regimen and interpersonal distress, emotional burden, physician-related distress	Extracted four similar factors	Three extracted factors – emotional & regimen-related burden, physician distress, interpersonal distress.

in the Malay version, wherein they merged interpersonal and regimen-related distress. Similarly for the Thai DDS, the emotional burden and regimen-related distress were considered as a single factor.[27] Socio-economic and cultural factors must be considered particularly for items relating to regimen distress: number 16, "Not feeling motivated to keep up my diabetes self-management," as our respondents mostly belong to the financially challenged sector, and the majority are unemployed.[5] Diabetes management entails not only medical but also behavioral and lifestyle changes. Given the background of the participants in this study, the financial cost of management can be considered a factor, and it can add further distress. Aside from the cost, the Filipino culture of having "*fiestas*" or having celebrations with food can be challenging for patients to manage their diet.[29] Furthermore, item 16 had cross-loading with factors 2 and 3 for regimen and interpersonal distress. Based on a content analysis by Francisco et al., one of the prevalent themes to be considered in the Filipino population should be socio-economic factors, as the cost of medications and lifestyle changes are key factors to consider in management. Additionally, Filipino families are closely knit and can act as patients' caregivers. Depending on their approach to the patient, they can aggravate or alleviate distress by monitoring patient adherence to diet and medication.[29]

CONCLUSIONS AND RECOMMENDATIONS

The Filipino DDS showed good internal reliability and consistent results compared to the original diabetes distress scale. However, it did not reveal a significant correlation between high levels of diabetes-related distress and poor glycemic outcomes.

Subsequent research should focus on individuals with T2DM, as they represent a distinct subset of patients. For those with T1DM, evaluations using a specialized scale are appropriate, indicating the need for further studies to explore and understand this particular group of patients more comprehensively.

Limitations

A limitation of our study was that we did not compare our tool to other diabetes-related health measures or any other tool for depression. Further analysis may also be done to correlate subsets with complications contributing to high distress scores. A focus-group discussion may also be done in subsequent studies to explore other socio-cultural factors that may contribute to diabetes-related distress. Another limitation of our study was that test-retest reliability could have been measured to further determine the construct's stability. Additionally, the researchers only specified the ability to read, write, and understand the Filipino language in the inclusion criteria. Further assessment of fluency in the Filipino language was not done. As this study only included diabetic patients from the outpatient department, the sample can be considered to represent those with better health-seeking behavior. Another study should assess those in the community for potentially different results.

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

CRediT Author Statement
MRP: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing -review and editing, Visualization, Supervision. Project administration, Funding analysis; **IJG:** Conceptualization, Methodology, Writing – review and editing, Visualization, Supervision, Project administration

Author Disclosure
The authors declared no conflict of interest.

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

Funding Source
None.

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APPENDICES

Table 1. Content validity of the Diabetes Distress Scale(n=8)

Question Items	Item Relevance Rating				I-CVI	Decision
	Not Relevant	Somewhat Relevant	Quite Relevant	Highly Relevant		
1. Pakiramdam na ang Diyabetes ay kinukuha ng labis ang aking mental at pisikal na enerhiya araw-araw	0%	0%	0%	8 (100%)	1	Accept
2. Pakiramdam na walang sapat na kaalaman ang aking Doktor tungkol sa Diyabetes at sa pangangalaga nito.	0%	0%	1 (12.5%)	7 (87.5%)	1	Accept
3. Nakakaramdam ng galit, takot, o panlulumo kapag naiisip ko ang pagkakaroon ng Diyabetes.	0%	0%	0%	8 (100%)	1	Accept
4. Pakiramdam na hindi ako binibigyan ng aking Doktor ng sapat at malinaw na direksyon kung paano aaksyonan ang aking Diyabetes.	0%	0%	1 (12.5%)	7 (87.5%)	1	Accept
5. Pakiramdam na hindi ako nagtetest ng aking asukal madalas at sapat.	0%	0%	0%	8 (100%)	1	Accept
6. Pakiramdam na hindi ko nasusundan ang aking diabetes routine	0%	0%	0%	8 (100%)	1	Accept
7. Pakiramdam na ang aking mga kaibigan o pamilya ay walang suporta sa mga pangangalaga ng sarili (hal. Pagplano ng mga aktibidad na salungat sa aking schedule, pagkain ng “maling” pagkain)	0%	0%	0%	8 (100%)	1	Accept
8. Pakiramdan na kinokontrol ng diabetes ang aking buhay	0%	0%	0%	8 (100%)	1	Accept
9. Pakiramdam na hindi sineseryo ng aking doctor ang aking mga pag-aalala	0%	0%	0%	8 (100%)	1	Accept
10. Walang kompyansa sa aking sarili sa pang-araw-araw na kakayahan i-manage ang aking diabetes	0%	0%	0%	8 (100%)	1	Accept
11. Pakiramdam na magkakaron parin ako ng malubhang pang-matagalang komplikasyon ng diabetes kahit anong gawin ko	0%	0%	0%	8 (100%)	1	Accept
12. Pakiramdam na hindi ako sumusunod ng masinsinan sa isang mabuting meal plan	0%	0%	0%	8 (100%)	1	Accept
13. Pakiramdam na hindi naaappreciate ng mga kaibigan o pamilya kung gaano kahirap ang mabuhay nang may diabetes	0%	0%	0%	8 (100%)	1	Accept
14. Pakiramdam na nalulula sa mga dapat sundin sa isang pamumuhay na may diabetes	0%	0%	0%	8 (100%)	1	Accept
15. Pakiramdam na wala akong doctor na maaari kong pag-followup na madalas para sa aking diabetes	0%	0%	0%	8 (100%)	1	Accept
16. Hindi nararamdaman ang pagkagana na panatilihin ang pansariling pamamahala ng diabetes.	0%	0%	0%	8 (100%)	1	Accept
17. Pakiramdam na ang aking mga kaibigan at kamag-anak ay hindi nagbibigay ng emosyon na suporta na aking gusto.	0%	0%	0%	8 (100%)	1	Accept

Table 2. Initial assessment of internal reliability (n=30)

Domain (Item Number)	Cronbach α
Emotional burden (1,3,8,11,14)	0.802
Physician distress (2, 4, 9, 15)	0.828
Regimen distress (5,6,10,12,16)	0.851
Interpersonal distress (7, 13, 17)	0.782

Table 3. Face validity of the Filipino Diabetes Distress Scale (n=30)

Items	Important	Difficulty in understanding (Frequency %)	Comment
1. Pakiramdam na ang Diyabetes ay kinukuha ng labis ang aking mental at pisikal na enerhiya araw-araw		100% Important	The item is very clear and understandable
2. Pakiramdam na walang sapat na kaalaman ang aking Doktor tungkol sa Diyabetes at sa pangangalaga nito.		100% Important	The item is very clear and understandable
3. Nakakaramdam ng galit, takot, o panlulumo kapag naiisip ko ang pagkakaroon ng Diyabetes.		100% Important	The item is very clear and understandable
4. Pakiramdam na hindi ako binibigyan ng aking Doktor ng sapat at malinaw na direksyon kung paano aaksyonan ang aking Diyabetes.		100% Important	The item is very clear and understandable
5. Pakiramdam na hindi ako nagtetest ng aking asukal madalas at sapat.		100% Important	The item is very clear and understandable
6. Pakiramdam na hindi ko nasusundan ang aking diabetes routine		100% Important	The item is very clear and understandable
7. Pakiramdam na ang aking mga kaibigan o pamilya ay walang suporta sa mga pangangalaga ng sarili (hal. Pagplano ng mga aktibidad na salungat sa aking schedule, pagkain ng “maling” pagkain)		100% Important	The item is very clear and understandable
8. Pakiramdan na kinokontrol ng diabetes ang aking buhay		100% Important	The item is very clear and understandable
9. Pakiramdam na hindi sineseryo ng aking doctor ang aking mga pag-aalala		100% Important	The item is very clear and understandable
10. Walang kompyansa sa aking sarili sa pang-araw-araw na kakayahan i-manage ang aking diabetes		100% Important	The item is very clear and understandable
11. Pakiramdam na magkakaron parin ako ng malubhang pang-matagalang komplikasyon ng diabetes kahit anong gawin ko		100% Important	The item is very clear and understandable
12. Pakiramdam na hindi ako sumusunod ng masinsinan sa isang mabuting meal plan		100% Important	The item is very clear and understandable
13. Pakiramdam na hindi naaappreciate ng mga kaibigan o pamilya kung gaano kahirap ang mabuhay nang may diabetes		100% Important	The item is very clear and understandable
14. Pakiramdam na nalulula sa mga dapat sundin sa isang pamumuhay na may diabetes		100% Important	The item is very clear and understandable
15. Pakiramdam na wala akong doctor na maaari kong pag-followup na madalas para sa aking diabetes		100% Important	The item is very clear and understandable
16. Hindi nararamdaman ang pagkagana na panatilihin ang pansariling pamamahala ng diabetes.		100% Important	The item is very clear and understandable
17. Pakiramdam na ang aking mga kaibigan at kamag-anak ay hindi nagbibigay ng emosyon na suporta na aking gusto.		100% Important	The item is very clear and understandable

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Beyond Glycaemia: Socioeconomic Factors and Diabetes Distress are Associated with Health-Related Quality of Life in People with Type 2 Diabetes

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Abstract

Background. Diabetes is a complex multifactorial disease. Therapy focused only on managing glycaemia does not yield optimal health outcomes. Health-related Quality of Life (HRQOL) is a broad, subjective, and multidimensional concept gaining significance in diabetes care. The complex interplay of HRQOL and other factors must be addressed to achieve optimal health outcomes.

Objective. We aim to describe the factors associated with HRQOL in type 2 diabetes.

Methodology. A single-center cross-sectional short messaging service (SMS) survey invited adults with type 2 diabetes (T2D) with ≥1 clinic attendance in the past year. Participants completed the Problem Areas in Diabetes-5 (PAID-5), Diabetes Distress Scale-17 (DDS17), and European Quality of Life Score (EQ-5D-5L). Demographic and diabetes-related data were retrieved from electronic medical records. Multiple regression models were created with EQ-5D-5L Index score (HRQOL) as the dependent variable.

Result. A total of 1406 people with T2D participated, 46.4% women, mean (SD) age 61.1 (13.4) years, BMI 27.1 (5.4) kg/m^2, and HbA1c 8.0 (1.4)%. Of these, 60.9% had ≥1 microvascular and 23.8% had ≥1 macrovascular complication. Mean (SD) of EQ-5D-5L Index score was 0.81 (0.27), EQ5D Visual Analog Score (VAS) was 77.4 (23.8), total mean DDS17 score was 1.87 (0.93) and PAID-5 score was 5.04 (4.5). 26.9% and 11.3% had significant diabetes distress (DD) based on PAID-5 ≥8 and DDS17 ≥3. Multiple regression models revealed diabetes distress, a lower class of housing type, presence of macrovascular complication, higher BMI, older age, and female sex to be associated with a poorer EQ-5D-5L Index Score.

Conclusion. Multiple non-glycemic factors like sociodemographic, socioeconomic, diabetes distress, impact health-related QoL in people with type 2 diabetes.

Key words: diabetes mellitus type 2, quality of life, mental health

INTRODUCTION

Quality of Life (QoL) is a broad, subjective, and multi-dimensional concept gaining importance in healthcare.[1] Dimensions of life like physical well-being, interpersonal relations, social, community, and civic activities, personal development, fulfilment and recreation affect QoL.[2] Health remains an important factor, as poor health has a ripple effect on multiple dimensions of life. Health-related QoL (HRQOL) is defined as aspects of the overall QoL that can be clearly shown to affect physical or mental health.[3] The impact of diabetes on HRQOL has gained greater significance due to the potential early onset and associated lifelong disease burden. The American Diabetes Association recommends that psychosocial care be provided for people with diabetes to optimise HRQOL.[4]

Diabetes affects HRQOL in multiple ways. For example, micro- and macrovascular complications of diabetes could impact physical well-being. Healthcare expenditure could impact the financial domain. Necessary self-care routines related to medications such as insulin administration may impact the freedom of spontaneity and interpersonal relationships. Mental health can be affected by diabetes

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 4, 2024. Accepted: September 17, 2024.
Published online first: April 22, 2025.
https://doi.org/10.15605/jafes.040.01.19

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distress (DD), depression, and the stigma of living with diabetes.[5] Diabetes distress refers to the emotional and cognitive stress of living with diabetes.[5] Individuals may feel overwhelmed by the demands of adhering to the recommended medications, diet and lifestyle. Diabetes distress is estimated to be prevalent in approximately 36% of people with T2D.[6] Further, diabetes distress affects self-care and self-efficacy.[7] People with high diabetes distress are less likely to engage in optimal self-care, resulting in poor glycaemia. In addition, depression and anxiety are associated with suboptimal glycaemia in young people with diabetes.[8] Diabetes distress has been associated with poor glycaemic control, increased diabetes complications, work productivity loss and all-cause mortality.[9–11] Fortunately, targeted intervention with cognitive behavioural therapy and mindful self-compassion have improved both glycaemic and psychological outcomes of people with DD.[12,13] Equally important is the environment in which a person lives, which significantly impacts their health and quality of life. Aspects of the environment, like the economic, environmental, political, and social conditions, are defined as Social determinants of health (SDOH).[14]

The definition of and the factors comprising SDOH have been described in various frameworks.[15] Factors working at a societal and national level could also influence health. However, for evaluation at the healthcare setting, socioeconomic position as defined by the World Health Organisation, includes factors such as social class, gender, ethnicity, education, occupation, and income, which can be readily assessed by the health care providers during the comprehensive evaluation of a person with diabetes.[15]

In summary, factors beyond glycaemia could affect the HRQOL of a person with diabetes. Socioeconomic factors, diabetes distress and perceived health status could all impact HRQOL. The ADA recommends routine screening for HRQOL, SDOH and diabetes distress in diabetes care. A better understanding of the complex dynamics will enable focused intervention to improve physical and psychosocial outcomes related to diabetes care. Our study aimed to describe the association between HRQOL, HbA1c and non-glycemic factors in people with type 2 diabetes in Singapore. We hypothesised that factors beyond glycaemia would be associated with HRQOL.

METHODOLOGY

This study was conducted at the SingHealth Duke-NUS Diabetes Centre, Singapore General Hospital. Singapore General Hospital is a tertiary care referral centre in Singapore. The data was collected from June 2021 to July 2021. SingHealth Institutional Review Board approved the waiver of informed consent for this research project (CIRB No: 2022/2616).

Study design

This was a cross-sectional observational study.

Study population

People with diabetes who attended the outpatient clinic at Singapore General Hospital.

Inclusion and exclusion criteria

Inclusion criteria

All people with diabetes who attended the clinic at least once in the past year (June 2020-May 2021) were invited.

Exclusion criteria

People with types of diabetes other than type 2 were excluded.

Study procedures

All eligible participants received a link via SMS, and they completed the following patient-reported outcome measures (PROM): Diabetes-Distress 17 (DDS17) score, Problem Areas in Diabetes (PAID) score, and European Quality of Life score – 5 dimensions – 5 levels (EQ-5D-5L). We used validated translations in English, Chinese, Malay, and Tamil. The participant could choose the preferred language.

Measures

We retrieved demographic and diabetes-related data from the Electronic Medical records (EMR). Demographic data were age, sex, ethnicity, BMI, and housing type. Housing type was used as a surrogate to determine socioeconomic status. Data from Singapore shows that the average monthly income per household member increases progressively across the housing classes: one/two/studio apartments, three-room, four-room, five-room/executive, condominium, non-landed, and landed houses.[16] Diabetes-related data collected were diabetes duration (year of diabetes diagnosis), type of glucose-lowering therapy (all prescribed medications), the presence of micro- and macrovascular complications, and HbA1c. All available diagnostic codes until the latest visit were retrieved. The presence of micro and macrovascular complications was discerned based on the relevant diagnostic codes. All data were extracted from the latest clinic visit.

We used two scales to measure DD in our study: the Diabetes Distress Scale (DDS17) and the Problem Areas in Diabetes (PAID-5) scale. The DDS17 is a 17-item questionnaire developed by Polonsky that studies diabetes distress over the preceding four weeks.[5] Each item is measured on a Likert scale of 1 (not a problem) to 6 (a very serious problem), and a total mean score is determined. Diabetes distress measured on DDS17 is divided into four subscales. These subscales are emotional distress (EB), regimen distress (RD), interpersonal distress (ID), and physician distress (PD). This provides a comprehensive assessment of diabetes distress. A total mean DDS17 score, calculated as the sum of all items divided by 17, ≥3 is considered significant.[5] PAID is a 20-item questionnaire, while the PAID-5 score

comprises five emotional-distress questions of the total PAID items (PAID-5, with items 3, 6, 12, 16, 19). The PAID-5 has satisfactory sensitivity (94%) and specificity (89%) for recognising diabetes-related emotional distress.[17] For the PAID-5 score, a score ≥5 indicates possible distress, and ≥8 indicates clinically significant diabetes-related emotional distress. Although the PAID-5 score was developed initially from Western (mainly European) populations with T2D, it has accepted validity in Asian populations (such as Korean people with diabetes).[18]

The European Quality of Life (EQoL) score, EQ-5D-5L, was used to measure HRQOL and is used for various diseases.[19] Respondents describe their HRQOL in 5 dimensions (EQ-5D descriptive system): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and rate across five levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). Combining these scores provides a 5-dimensional and 5-level description of health status defined by a 5-digit number (EQ-5D self-reported health state, 11111 – best health state, 55555 – worst health state). EQ-5D utility value was derived from the 5L to 3L crosswalk of Singapore using the time-trade-off and crosswalk techniques.[20,21] The EQ-5D Index score represents the HRQOL for each participant, and it can range from 0 (dead) to 1 (full health). A value less than 0 indicates a state worse than death. The respondents also rate their overall health (Health Status) on a visual analog scale (EQ-VAS), between 0 (worst imaginable health) and 100 (best imaginable health). The EQ-VAS score depicts their perceived health status.

PROM data was anonymised and combined with sociodemographic and diabetes-related data from EMR. Data extraction and anonymisation were done by the Health Services Research Unit at Singapore General Hospital. The primary outcome was the association between HRQOL as assessed by EQ-5D Index score and other variables.

Sample size considerations

This study invited all people with diabetes who attended the clinic in the past year via an SMS link. Given the nature of this study, no sample size estimation was done.

Data analysis

All variables were screened for implausible values, and none were found. Data distribution was assessed using density plots and the Shapiro-Wilk test for normality. All univariate analysis results were expressed as mean (standard deviation, SD) for continuous variables as they were normally distributed and counts with percentages for categorical variables. A multiple linear regression model was built with EQ5D Index score as the dependent variable and socioeconomic and sociodemographic factors (age, gender, ethnicity, housing type, BMI), diabetes-related factors (HbA1c, diabetes duration, microvascular complication, macrovascular complication, insulin use), and diabetes distress (Model 1 = PAID-5, Model 2 = Total Mean DDS17 score) as independent variables. The presence of diabetic retinopathy, neuropathy or nephropathy was classified as a microvascular complication, and the presence of any atherosclerotic cardiovascular disease was classified as a macrovascular complication. The above variables were chosen based on the authors' consensus and current available literature suggesting that each of the above variables may have an impact on the quality of life for people with diabetes. Crude estimates from simple regression models for each predictor variable as well as adjusted estimates from multivariable models (with all variables included), are presented. Corresponding 95% confidence intervals were also presented. A two-sided p-value of less than 0.05 was considered to be statistically significant. As missing values were not replaced, complete case analyses were performed. Data manipulation and statistical analysis were done using Excel (Version 2302) and R (Version 4.3.1).

RESULTS

A total of 1406 with type 2 diabetes responded to the survey that was sent out to 6219 people. The response rate varied across the instruments (DDS17-737, 11.9%, PAID -769, 12.4%, EQ5D-5L -1008, 16.2%). The mean age of the cohort was 61.1(13.4) years, approximately half were female (46.4%). The predominant ethnicity was Chinese (67.1%), followed by Indian (16.9%) and Malay (12.3%). The average duration of diabetes in the study population was 16.2 (9.6) years, and the majority (74%) of the participants lived in public housing. The mean BMI was 27.1 (5.4) kg/m^2, and 55.2% were on insulin therapy. More than half (60.9%) of the participants had one or more microvascular complications, and 23.8% had one or more macrovascular complications. The mean HbA1c was 8.0 (1.4) %. The characteristics of the study population are shown in Table 1.

The mean (SD) of the EQ5D Index score adjusted for Singapore in this sample was 0.81(0.27). It ranged from -0.77 to 1, and the mean EQ-VAS score was 77.4 (23.8). An EQ5D Index score of 1 represents the HRQOL, and the EQ-VAS score of 100 represents the perceived health status, both corresponding to the best possible health state. A EQ5D Index Score less than 0 represents a state worse than death. The mean (SD) total mean DDS17 score for the whole cohort was 1.87 (0.93). Emotional distress subscale had the highest mean (SD) score [2.10 (1.09)], while physician distress had the lowest mean (SD) score [1.59 (1.13)]. The mean (SD) PAID-5 score was 5.04 (4.5). The proportions with clinically significant diabetes distress defined by the DDS17 total mean Score ≥3 and a PAID-5 score ≥8 was 11.3% and 26.9%, respectively (Table 2). About half of the participants (46.9%) described a perfect health state depicted by "11111" and only one participant (0.1%) described the worst health state depicted by "55555." The proportions for health states in between are shown in Table 3.

In the analyses using simple linear regression, housing type had the highest association with HRQOL. Living in a non-

Table 1. Participant characteristics

Characteristic	Type 2 (N = 1406)
Age, years, mean (SD)	61.1 (13.4)
Sex	
Female, n (%)	653 (46.4%)
Male, n (%)	753 (53.6%)
Ethnicity	
Chinese	932 (67.1%)
Malay	171 (12.3%)
Indian	235 (16.9%)
Others	51 (3.7%)
Housing	
One-room/two-room/studio	53 (4.0%)
Three room	212 (16.0%)
Four room	362 (27.4%)
Five/exec	352 (26.6%)
Condo non-landed	192 (14.5%)
Landed	150 (11.4%)
Unknown	85
BMI, kg/m², mean (SD)	27.1 (5.4)
Diabetes Duration, years, mean (SD)	16.2 (9.6)
Type of Glucose lowering treatment	
Oral with sulfonylureas	292 (22.2%)
Oral without sulfonylureas	298 (22.6%)
Insulin premixed	230 (17.5%)
Insulin basal only	160 (12.2%)
Insulin basal bolus	269 (20.4%)
Insulin bolus only	67 (5.1%)
Unknown	90
Microvascular complications, any	856 (60.9%)
Nephropathy	694 (49.4%)
Retinopathy	346 (24.6%)
Neuropathy	70 (5.0%)
Macrovascular complications, any	335 (23.8%)
Ischemic heart disease	274 (19.5%)
Cerebrovascular disease	52 (3.7%)
Peripheral vascular disease	50 (3.6%)
HbA1c (%), mean (SD)	8.0 (1.4)
HbA1c (mmol/mol), mean	64

BMI – Body Mass Index

Table 2. Patient-reported outcome measures

Patient-reported outcome measure	Type 2 diabetes
EQ-5D-5L	Mean (SD) (N=879)
EQ-VAS health status score	77.4 (23.8)
EQ5D 5L index score	0.81 (0.27)
Anxiety/depression	1.33 (0.64)
Mobility	1.34 (0.73)
Self-care	1.13 (0.53)
Usual activities	1.27 (0.68)
Pain	1.58 (0.76)
Diabetes Distress Score (DDS 17)	Mean (SD) (N=637)
Total mean score	1.87 (0.93)
Physician distress subscale mean score	1.59 (1.13)
Emotional distress subscale mean score	2.10 (1.09)
Regimen distress subscale mean score	1.99 (1.07)
Interpersonal distress subscale mean score	1.65 (1)
Proportion with total score ≥3	72 (11.3%)
PAID-5 score	Mean (SD) (N=676)
Total Score	5.04 (4.5)
Proportion with total score ≥8	182 (26.9%)

EQ-5D-5L – European Quality of Life 5 Dimension 5 Level, VAS – Visual Analog Score, PAID – Problem Areas in Diabetes

Table 3. EQ-5D health states

Health states (n = 879)	Frequency (%)	Cumulative frequency (%)
11111	412 (46.9)	46.9
11112	116 (13.2)	60.1
11122	39 (4.4)	64.5
11121	35 (4)	68.5
21112	35 (4)	72.5
21212	15 (1.7)	74.2
11123	10 (1.1)	75.3
21111	10 (1.1)	76.5
21122	10 (1.1)	77.6
11212	9 (1)	78.6
21222	8 (0.9)	79.5
11132	7 (0.8)	80.3
11222	7 (0.8)	81.1
21213	5 (0.6)	81.7
21223	5 (0.6)	82.3
22222	5 (0.6)	82.8
.....		
55555	1 (0.1)	100.0

landed condominium was associated with a higher HRQOL (Crude β, [95% CI] = 0.17 [0.07 – 0.27]) compared to living in a one/two/studio apartment. Other variables associated with a lower HRQOL found in simple linear regression were the presence of macrovascular complications, Indian ethnicity compared to Chinese ethnicity, insulin use, presence of microvascular complications, female sex, a higher PAID score, longer diabetes duration, higher BMI, and older age, in decreasing strengths of association. The total mean DDS score and HbA1c did not show any significant association with HRQOL in simple linear regression. Multiple linear regression models with HRQOL defined by EQ5D Index score as the dependent variable were generated. In a fully adjusted model with the PAID score for diabetes distress, only a lower class of housing type, a higher BMI, presence of macrovascular complication, higher PAID score, and older age remained significantly associated with lower HRQOL. In the fully adjusted model with total mean DDS score for diabetes distress, it was shown that the female sex, a lower class of housing type, lower HbA1c, higher BMI and presence of macrovascular complications were significantly associated with a lower HRQOL (Table 4).

DISCUSSION

This study found that HRQOL in people with type 2 diabetes is associated with multiple nonglycemic factors. Diabetes distress as described by PAID score, living in a lower class of housing type, older age, female sex, higher BMI, and the presence of macrovascular complications were associated with lower HRQOL.

Our findings are largely concordant with published data on HRQOL in diabetes. Our mean (SD) EQ-5D-5L index score of 0.81 is the same as the finding of 0.81 (95% CI: 0.81-0.82) for people with T2D in a meta-analysis of nine studies using EQ-5D-5L.[22] It also falls within the range of 0.78 to 1.00 found in people with T2D in East and Southeast Asian countries.[23] Our mean EQ-VAS score of 77.4 is slightly higher than the upper bound of its range from 72.3 to 76.3 for people with T2D but without complications.[23] Thus, the

HRQOL of the participants in this study sample is very typical of people with T2D in the general population.

A recent systematic review summarised all the cross-sectional studies between 2012 and 2022 on adults with T2D investigating the factors associated with HRQOL.[24] Eight different instruments were used across 35 studies on HRQOL in diabetes. The review found various factors like sociodemographic factors (age, marital status, gender, monthly income, education, area of residence, and religiosity), person-centered factors (diabetes knowledge and self-efficacy), disease characteristics (HbA1c, comorbidities, duration of diabetes and insulin treatment), self-management behaviors (physical activity, medication adherence, and frequent glucose checks) and family support to be predictors of HRQOL.[24] More specifically, multiple studies have reported a lower HRQOL in females with diabetes compared to males.[25–27] This could be due to multiple factors like a higher propensity for mental health disorders in females, differences in financial status, and their reduced sense of control over life circumstances.[28] Studies from Indonesia and Malaysia found that DD was associated with poorer HRQOL, similar to our findings.[29–31] A high BMI has also been reported to have a negative effect on HRQOL.[32]

A higher HbA1c is associated with a lower HRQOL in prior studies.[24] A possible reason for the lower HRQOL with a higher HbA1c is the perceived worse diabetes disease state and fear of complications triggered by a higher HbA1c result. This could have a couple of implications. Firstly, studies show that many people with T2D forget their recent HbA1c. Hence, the timing of the administration of a PROM survey may affect its relationship with HbA1c. Our study did not administer the PROM questionnaires during a clinic visit. Instead, all eligible participants received an SMS one day, irrespective of their upcoming appointments. This could be a reason for the lack of a relationship between HbA1c and HRQOL, even in simple regression. Secondly, the type of diabetes distress scale included in a regression model could modify the impact of HbA1c on HRQOL. For example, the PAID-5 scale has 2/5 items related to diabetes complications, which could reduce the effect of HbA1c on HRQOL when the PAID-5 scale is included as an independent variable. However, DDS17 has only 1/17 items directly related to diabetes complications. Prior studies from Singapore in the primary care setting reported that higher HbA1c, a higher DD, and younger age were associated with lower HRQOL.[33] However, when fully adjusted with diabetes distress (PAID) and other variables, no association existed between HbA1c and EQ-5D-5L Index score, similar to our findings.[34] In Model 2 using DDS17,

Table 4. Simple and multiple linear regressions of factors associated with EQ-5D-5L scores

	Simple linear regression (Crude estimates)			Multiple linear regression Model 1: PAID-5 Score [Adjusted]			Multiple linear regression Model 2: Total DDS17 Score		
Adjusted R²				0.176			0.125		
p-value				<0.001			<0.001		
Characteristic	**Beta**	**SE[1]**	***p*-value[2]**	**Beta**	**SE[1]**	***p*-value[2]**	**Beta**	**SE[1]**	***p*-value[2]**
PAID-5 Score	-0.02	0.00	<0.01***	-0.02	0.00	<0.01***			
Total Mean DDS Score	-0.01	0.02	0.5				-0.02	0.00	>0.9
Age	0.00	0.00	<0.01***	0.00	0.00	<0.01**	-0.00	0.00	0.02*
Male	—	—		—	—		—	—	
Female	-0.05	0.02	<0.01**	-0.04	0.02	0.06	-0.09	0.03	<0.01**
Ethnicity									
Chinese	—	—		—	—		—	—	
Indian	-0.08	0.03	<0.01**	-0.04	0.03	0.15	-0.07	0.04	0.08
Malay	-0.04	0.03	0.11	0.04	0.03	0.2	-0.05	0.05	0.4
Others	0.03	0.05	0.6	0.02	0.06	0.8	-0.00	0.09	>0.9
Housing Type									
One/Two/Studio	—	—		—	—		—	—	
Three Room	0.07	0.05	0.13	0.08	0.05	0.12	0.30	0.08	<0.01**
Four Room	0.14	0.05	<0.01**	0.13	0.05	<0.01**	0.35	0.08	<0.01***
Five/Executive	0.12	0.05	<0.01**	0.12	0.05	0.01*	0.31	0.08	<0.01***
Condo non-landed	0.17	0.05	<0.01***	0.15	0.05	<0.01**	0.35	0.09	<0.01***
Landed	0.14	0.05	<0.01**	0.13	0.06	0.02*	0.38	0.09	<0.01***
BMI	0.00	0.00	0.03*	-0.01	0.00	<0.01**	-0.01	0.00	0.02*
HbA1c	-0.01	0.01	0.3	0.01	0.01	0.2	0.02	0.01	0.03*
Diabetes duration	0.00	0.00	<0.01***	0.00	0.00	0.08	-0.00	0.00	0.3
Microvascular complication									
No	—	—		—	—		—	—	
Yes	-0.06	0.02	<0.01**	-0.02	0.02	0.5	0.00	0.04	>0.9
Macrovascular complication									
No	—	—		—	—		—	—	
Yes	-0.10	0.02	<0.01***	-0.06	0.03	0.03*	-0.09	0.04	0.04*
Insulin Use									
No	—	—		—	—		—	—	
Yes	-0.08	0.02	<0.01***	-0.01	0.02	0.6	-0.03	0.04	0.4

[1]SE = Standard Error, [2]*p<0.05; **p<0.01; ***p<0.001. DDS- Diabetes Distress Scale, PAID- Problem Areas in Diabetes, BMI- Body Mass Index

we found a weak positive association between HbA1c and HRQOL (i.e., a higher HbA1c improves HRQOL). We are unable to explain this discordant finding in Model 2.

The presence of macrovascular complications was consistently associated with a lower HRQOL. This was expected as, in clinical practice, people with cardiovascular complications like myocardial infarction or stroke are more concerned about health implications compared to those with microvascular complications like neuropathy, retinopathy, or nephropathy. The acute nature of the presentation of macrovascular complications with immediate life-changing consequences versus the insidious onset and slow progression of microvascular complications may explain this.

Diabetes distress was a significant factor associated with HRQOL. Diabetes is a chronic condition with multifactorial aetiology and drivers. Despite the emergence of newer classes of medications, achieving optimal glycaemia to limit diabetes-related complications is still elusive, with only about half achieving an HbA1c of <7%.[35] Treatment success in diabetes requires the right medication and adherence to medication, lifestyle changes, and observation of several diabetes self-care habits. The psychological burden of living with diabetes, diabetes distress, has a bidirectional impact on diabetes.[36] Studies have shown that diabetes distress is associated with anxiety, depression, and reduced self-efficacy, which leads to poor self-care, lower HRQOL, and, ultimately, a vicious cycle leading to poor glycaemia and diabetes-related complications.[36] Prior studies from Singapore have shown a high prevalence of severe diabetes distress (31.4%, using a PAID score >40) in the primary care setting.[37] Similarly, our study found a prevalence of 26.9% for significant diabetes distress (PAID-5 ≥8). Interestingly, significant DD, as assessed by DDS17 (Total mean score ≥3), was lower at only 11.3%. Although both PAID and DDS17 are reliable instruments, there are significant differences. PAID covers more emotional concerns and is related to coping styles; hence, it correlates better with HRQOL. DDS17, instead, is more related to aspects of diabetes treatment, motivational and behavioural aspects, and, therefore, has a better correlation to metabolic outcomes.[38] Our findings were concordant with this in that only PAID-5 was significantly associated with HRQOL and not DDS17. PAID-5 may be a better determinant for identifying the emotional burden and QoL in people with T2D.

Socioeconomic status is well recognised as a determinant of health. Although Singapore is a developed country, income disparity and relative poverty are prevalent based on the OECD's (Organization for Economic Cooperation and Development) definition of relative poverty.[39] In Singapore, healthcare is not free but subsidised according to 'means testing'. The principle of means testing is to provide a higher degree of financial subsidy for those in the lower economic strata, thereby attempting to reduce the financial inequity in healthcare.[40] The Ministry of Health further refined means testing by changing the assessment parameter from average individual monthly income to per capita household income, as per capita household income would better represent the financial burden in situations where all family members may not be earning.[40] Further, the Agency of Care Effectiveness (ACE),[41] established in 2015, aims to improve the access of Singaporeans to clinically effective medicines and medical technology. This agency has played a vital role by conducting health technology assessments on medications' clinical effectiveness and cost-effectiveness, informing subsidy decisions, and fixing value-based pricing for clinically effective drugs and technologies.[42] However, despite these existent measures, our data shows that the type of housing, a surrogate measure of average monthly income,[16] was a significant factor associated with poorer HRQOL of people with diabetes in Singapore. Since all healthcare expenditure is "out-of-pocket" in Singapore, the economic impact of diabetes could be significant, especially for those in the lower socioeconomic strata, with potential financial implications even to aspects of QOL beyond health. The economic burden could also directly impact health via medication nonadherence. Medication nonadherence among newly diagnosed people with diabetes in Singapore has been reported to be as high as 35%.[43] Studies have shown that the most common reason for medication nonadherence is cost-related.[44] This is consistent with data that socioeconomic factors may have a high impact on health outcomes, even higher than self-care behaviours and clinical care.[45]

Non-glycemic factors as discussed above significantly impact HRQOL. A lower HRQOL leads to lower self-efficacy and suboptimal self-care. It becomes imperative that healthcare providers address these factors in all people with diabetes.[4] Socioeconomic and sociodemographic factors and diabetes distress, if left unaddressed, could have a significant stalling effect on diabetes care. Hence, clinicians must periodically assess these aspects. Apart from optimising the medications according to the risk profile of a person with T2D, optimising their psychosocial care must also become a priority. Short, validated instruments like DDS2 and PAID-5 serve as quick screening tools during consults, with the administration of more comprehensive tools reserved for those with suspected diabetes distress.[46]

Once identified, the management of diabetes distress depends on individual needs. For example, education on diabetes may allay irrational fears about complications, instruction on skills required to manage diabetes may reduce the burden of self-care, and introducing technology could reduce diabetes-specific burdens like glucose monitoring and insulin injections. For more complex situations, cognitive behavioural therapy, mindfulness therapy, and motivational interviewing techniques administered by a trained healthcare professional or diabetes psychologist have improved psychological and metabolic outcomes.[47] Addressing the unfavourable socioeconomic factors is equally crucial in enhancing diabetes health outcomes. Social prescribing is an intervention to improve well-being by linking individuals to community assets to optimise

their health.[48] It moves beyond the biomedical model of diabetes care to involve non-medical community resources and interventions to address the social factors.[49] Social prescribing needs to be improved and integrated with diabetes care in Singapore to educate and empower healthcare providers tackling complex multifactorial conditions like type 2 diabetes.

The strengths of our study include the relatively large number of people who participated in the survey. However, the response rates for our SMS survey were relatively low. Nevertheless, the demographic data of our participants was comparable to unpublished data from the SingHealth diabetes registry.[35] People with type 2 diabetes consulting at Singapore General Hospital have a mean age of 63.4 years, 48.1% are female, and have an ethnicity distribution of 68.7% Chinese, 12% Malays, 15.1% Indians and 4.2% other ethnicities. This is comparable to the demographic features of our study participants, suggesting representativeness from a sociodemographic perspective. We also retrieved relevant factors from the SingHealth Diabetes Registry to study their association with HRQOL. The limitations of our study include the fact that there were missing data among the instruments administered. We did not have measures of self-efficacy or diabetes self-management, which were both identified in prior studies as important parameters. We used only the diagnostic codes to determine diabetes complications; hence, the reported complication rates are likely underestimated. The proportion of insulin users was higher in this cohort than in the whole cohort of people with type 2 diabetes in Singapore General Hospital (31.7%, unpublished data). Furthermore, as stated earlier, the response rate to the SMS survey was also relatively low; hence, any generalisation of study findings must be cautious. Timing the SMS survey before or during a clinic visit might improve response rates in future studies. This cohort may not be representative of people with type 2 diabetes in primary care.

CONCLUSION

Factors beyond glycaemia, like socioeconomic and sociodemographic factors, and diabetes distress, are significantly associated with health-related quality of life in people with T2D.

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

CRediT Author Statement
SRC: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, visualisation, Supervision, Project administration. **GSKK:** Methodology, Software, Validation, Formal Analysis, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, visualisation. **NNBMS:** Software, Validation, Formal Analysis, Resources, Data curation, Writing – review and editing, visualisation. **XX:** Conceptualization, Methodology, Formal Analysis, Resources, Writing – review and editing, visualisation. **GHL:** Conceptualisation, Methodology, Formal Analysis, Resources, Writing – review and editing, visualisation. **DG:** Investigation, Resources, Writing – review and editing, visualisation. **SG:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review and editing, visualisation, 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
The Singapore General Hospital funded pilot clinical service program led to the generation of data for this study.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Association of Nutritional Status using the Short Nutritional Assessment Questionnaire (SNAQ) and Malnutrition Risk using the Malnutrition Screening Tool (MST) with In-Hospital Mortality and Intensive Care Unit Admission Among Non-Critically-Ill Patients: A Single Center, Prospective Cohort Study

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Abstract

Background and Objective. Although nutritional assessment tools have been available internationally, local data for their use in foreseeing adverse outcomes among admitted patients are currently unavailable. The primary objective of this study was to determine the association of nutritional status using Short Nutritional Assessment Questionnaire (SNAQ) and malnutrition risk using the Malnutrition Screening Tool (MST) with intensive care unit (ICU) admission and in-hospital mortality.

Methodology. This was a prospective-cohort study which included 122 purposively-selected adult participants who were non-intubated, admitted for medical and surgical management, stayed for at least 24 hours, had no COVID-19 infection, and were not admitted in any critical care unit. The SNAQ and MST questionnaires, which are validated tools and consists of two to three easy-to-answer questions, were used among the participants and their scores were tallied in order to get their nutritional status and malnutrition risk. Primary endpoints measured were the length of hospital stay, incidence of mortality, and ICU admission rate. Comorbidities were taken into account using the Charlson Comorbidity Index.

Results. Categorizing the SNAQ scores showed 33.61% were severely malnourished, which was similar when using the MST classification, wherein 34.43% were at risk of malnutrition. None of the participants were admitted to the ICU. Malnutrition risk and nutritional status was not significantly associated with 30-day in-hospital mortality ($p > 0.05$). On the other hand, results of the Cox proportional hazards showed that SNAQ and MST significantly predicted the hazard of 30-day in-hospital mortality, increasing the hazard of mortality by 2.58 times and 3.67 times, respectively, for every 1-unit increase in SNAQ and MST scores. Similarly, nutritional status using the SNAQ classification indicated the severely malnourished category significantly predicted the hazard of mortality, increasing it by 9.22 times for those who are severely malnourished. Also, malnutrition risk using the MST classification indicated that those who were at risk of malnutrition were 9.80 times greater hazard of mortality than those who were not at risk of malnutrition.

Conclusion. The MST and SNAQ classification are screening tools for nutritional status (SNAQ) and malnutrition risk (MST) that can be administered at the onset of the patient's hospital course and have been demonstrated in this study to predict 30-day in-hospital mortality. It is important to note that none of the patients included in this study required intensive care unit admission.

Key words: malnutrition, surveys and questionnaires, mortality, ICU

INTRODUCTION

An optimal dietary intake of the required nutrients contributes to the person's immune system leading to a conclusion that a person must strengthen his or her own immune system in order to achieve a sustainable way to survive. In order to determine one's nutritional status, various tools have been developed and one of which is the Short Nutritional Assessment Questionnaire (SNAQ). This is a nutrition assessment tool that has been validated by Kruizenga et al.,[1] and has been stated to be among the validated tools in the Netherlands for use among hospitalized patients. Another tool available to determine the risk of malnutrition among patients is the Malnutrition

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 7, 2024. Accepted: October 8, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.20

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Screening Tool (MST). This is a simple and quick nutrition screening tool that is based on weight loss and appetite changes and is validated in the acute hospital setting.[2,3] Both of these tools are easy and fast to use and involve only 2 questions for the MST and 3 questions for the SNAQ. This study determined the association of nutritional status using the SNAQ and malnutrition risk using the MST scoring when used for ICU admission rate and in-hospital mortality among non-critically ill patients. This helped us better identify patients who would benefit from more aggressive nutritional intervention. In a study by Barker et al.,[4] it was said that along with the adverse outcomes associated with malnutrition, referrals and assessment of malnutrition per se is in fact suboptimal. This therefore increases the risk of hospitalized patients for more occurrences of muscle wasting, impaired wound healing, and higher treatment costs. Furthermore, malnutrition prevalence in the acute hospital setting has been reported to be as high as 20-50% and as high as 23% among randomly assessed patients on admission indicating the prevalence of malnutrition in the hospital;[5,6] however, identification of these cases is at the minimum. In another study,[7] referrals for malnutrition to dietitians also were noted at only 15% among an identified malnutrition rate of 42%. Among these studies, malnutrition rates were associated with a longer length of hospital stay, higher incidence of complications, and higher mortality rates as also seen in the study by Braunschweig et al.[8]

OBJECTIVE

The primary objective of this study was to determine the association of nutritional status using the SNAQ and malnutrition risk using the MST with in-hospital mortality and ICU admission among non-critically ill patients.

METHODOLOGY

Study design and setting

This was a prospective cohort study conducted at the non-COVID wards of Chinese General Hospital and Medical Center from May 2022 to December 2022.

Participants of the study

Patients included in the study were all adult patients of age 19 years and above, both males and females, non-intubated and admitted for medical and surgical management.

Patients excluded from the study were patients with hospital stay of less than 24 hours, with COVID-19 infection, and patients admitted at the ICU/CCU/NICU.

Data collection

Data and informed consent were solely collected by the primary investigator. Age and sex data were obtained from the patients' charts and by interviewing the patients. The primary investigator was also the one to administer the tests to the patients. Collection started with the approval of the protocol and was done for 8 months (May 2022 to December 2022). The primary investigator collected the responses of the patients included in the study from the forms provided (using the SNAQ and MST tools) by total enumeration from the start of approval until 7 months after the start of the study. Patients included in the study were all medical and surgical patients. Data collected included data that were part of the questionnaires used (SNAQ and MST). The Charlson Comorbidity Index (CCI) was used to assess and document the participant's current comorbidities. The SNAQ and MST scoring sheets were used and were retrieved thereafter, with their scores being tallied. Their outcomes were followed up until the date of their discharge. For those patients who were still at the wards once the study was terminated, they were classified as still admitted and were still included in the study and considered as non-ICU/non-mortality data as an outcome assessment. The data was encoded and compiled using Microsoft Excel in only one laptop of the primary investigator. Data protection was done by ensuring password protection on the file before access which was only known by the primary investigator and their co-author. The compiled data that was garnered through the interview was only accessed by the primary investigator and their co-author. Data privacy and confidentiality were reiterated to the patients. Data sheets, questionnaires, and files will be destroyed once no longer needed for the study.

Sample size

A sample size computation for binary logistic regression analysis was conducted using GPower version 3.1.9.4. According to the study of Bernardino and Llido,[9] the odds ratio of mortality for patients with an mSGA score of >5.00 (high risk malnutrition) was 2.98 with a confidence interval of 2.01 to 4.45. The lowest limit of the odds ratio (2.01) was utilized. In addition, the odds ratio for admission in critical care units was 2.986. Furthermore, in the same study above,[9] the prevalence of mortality was 20.60% while ICU admission had a prevalence of 23.89%. With these parameters and with a minimum power of 80% at a significance level of 5% (two-tailed), a minimum of 109 respondents was necessary for the analyses for mortality and 50 participants was needed for the analyses for ICU admission. From these two estimates, the largest sample size was inflated by 10% to account for possible attrition. Hence, the final sample size for the study was a total of 122 respondents.

External validation

The MST and the SNAQ tool were translated from English to Tagalog by three (3) physicians who were fluent in English and Tagalog. This was further verified by a Filipino Language Expert to determine the appropriateness of the translation. The tools subsequently underwent a pilot study among 10-15 participants that were not included in the study. This then underwent validation using one-sample

t-test and Spearman correlation to determine the difference and association, respectively, of the items in English and Filipino languages. There were no significant differences in all items between the two languages and the correlations were high to excellent (r_s = 0.764 to 1.000), hence they were used in the study. The tools obtained rights for usage via Elsevier website using Rights Link for use in the study.

Nutritional status and malnutrition risk

The Short Nutritional Assessment Questionnaire (SNAQ) is a nutrition screening tool created by the Dutch Malnutrition Screening Group to identify risk for malnutrition in hospitalized patients which consists of three questions namely: presence and degree of unintentional weight loss, changes in appetite and use of supplemental drinks or tube feeding. Scores are from zero to three based on severity and patients with a score of two or more are classified as moderately malnourished and patients with a score of three or more are identified as severely malnourished.[1]

The Malnutrition Screening Tool (MST) is a simple and valid tool developed for use in adult hospitalized patients and consists of two items namely: Decreased intake due to poor appetite and amount of recent unintentional weight loss. The sum obtained in this tool results in a score between zero and five and patients are considered to be at risk for malnutrition if they receive a score of two or more.[2]

Mortality assessment and ICU admission

Administration of the two tools was conducted within 48 hours of admission. Their in-hospital course was monitored for the outcomes (in-hospital mortality and ICU admission rate). The comorbidities of the target population were taken into account using the Charlson Comorbidity Index. Participants were followed up on the hospital electronic medical record system at the time of termination of the study in order to record mortality outcomes and ICU admission rates. All deaths and ICU admissions from the time of hospitalization until the date of discharge or mortality were recorded as binary outcome.

Statistical analysis

Statistical analyses were conducted using STATA Statistical Software, Version 13, College Station, TX: StataCorp LP. A *p*-value of 0.05 was considered statistically significant. Missing data were imputed using variable mean imputation; however, variables with more than 10% missing data were excluded. Data normality was analyzed using Shapiro-Wilk's Test.

Descriptive statistics involved mean and standard deviation for normally distributed, continuous data; median and interquartile range (IQR) for ordinal and non-normally distributed, continuous data; and frequency and percentage for categorical data.[10] The incidence rate of 30-day in-hospital mortality, alongside its 95% confidence intervals, was also estimated. Comparative analyses of the different demographic and clinical characteristics according to malnutrition risk, using both the SNAQ and MST classifications, were performed using independent *t*-test and one-way Analysis of Variance (ANOVA) for normally-distributed, continuous data; Mann-Whitney U Test and Kruskall-Wallis H Test for ordinal and non-normally-distributed, continuous data; and, Chi-Square Test of Homogeneity or Fisher's Exact test, if the assumption of at least 5 expected observations per cell was not met, for categorical data.[10]

To address the questions and hypotheses on the associations of nutritional status using the SNAQ and malnutrition risk using MST with ICU admission and in-hospital mortality, binary logistic regression analyses were performed. In addition, Kaplan-Meier survival curve analyses were utilized to determine the survival rates or estimates according to nutritional status using the SNAQ and malnutrition risk using the MST. Moreover, Cox proportional hazards regression analyses were employed to determine the hazards of 30-day in-hospital mortality. Data were censored at the time participants were discharged or expired. Crude estimates were initially determined (crude odds ratios and hazards ratio). Afterwards, the estimates were adjusted after controlling confounders or covariates using a 10% change-in-estimate criterion and were represented as adjusted odds ratio (aOR) or adjusted hazards ratio (aHR).[11] Finally, survival estimates according to malnutrition risk, using both SNAQ and MST classifications, were compared using the log-rank test.[12]

Ethical considerations

There was strict adherence to ethical considerations set in relevant guidelines such as the Declaration of Helsinki, data privacy act, voluntary participation, informed consent, anonymity, confidentiality, potential for harm, and results communication. Ethical approval was granted by the Ethics Review Board of the Chinese General Hospital and Medical Center with RERB Protocol No. 2022 F-16.

RESULTS

Demographic characteristics

The comparative analyses of the demographic and clinical characteristics according to malnutrition risk are depicted in Table 1. The mean age of the participants was 55.08 years old (SD =16.43), with most of them being <50 years old (36.89%). In addition, majority of the participants were females (57.38%), and the most prevalent comorbidities were uncomplicated diabetes mellitus (31.97%), congestive heart failure (10.66%), and hemiplegia (9.84%). Results also showed that the mean Charlson Comorbidity Index (CCI) was 2.84 (SD = 2.37). Comparative analyses of the demographic characteristics according to malnutrition risk using the SNAQ classification showed that age, sex, and all comorbidities were not significantly different (*p*

Table 1. Comparative analyses of the demographic and clinical characteristics according to Malnutrition Risk, using the Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Screening Tool (MST), among the participants (N = 122)

Characteristics	Total (N = 122)	Malnutrition risk						
		SNAQ classification				MST classification		
		Well nourished (n = 70)	Moderately malnourished (n = 11)	Severely malnourished (n = 41)	*p*-value (two-tailed)	Not at risk (n = 80)	At risk (n = 42)	*p*-value (two-tailed)
Age (Years; x̄, SD)	55.08 (16.43)	53.43 (16.50)	49.00 (15.71)	59.54 (15.83)	0.098	51.78 (15.37)	61.38 (16.72)	0.002†
<50 Years Old	45 (36.89%)	28 (40.00%)	6 (54.55%)	11 (26.83%)	0.587	35 (43.75%)	10 (23.81%)	0.029*
50 to 59 Years Old	31 (25.41%)	17 (24.29%)	2 (18.18%)	12 (29.27%)		19 (23.75%)	12 (28.57%)	
60 to 69 Years Old	27 (22.13%)	17 (24.29%)	2 (18.18%)	8 (19.51%)		18 (22.50%)	9 (21.43%)	
70 to 79 Years Old	10 (8.20%)	4 (5.71%)	1 (9.09%)	5 (12.20%)		6 (7.50%)	4 (9.52%)	
≥80 Years Old	9 (7.38%)	4 (5.71%)	0 (0.00%)	5 (12.20%)		2 (2.50%)	7 (16.67%)	
Sex (f, %)					0.512			0.133
Male	52 (42.62%)	33 (47.14%)	4 (36.36%)	15 (36.59%)		38 (47.50%)	14 (33.33%)	
Female	70 (57.38%)	37 (52.86%)	7 (63.64%)	26 (63.41%)		42 (52.50%)	28 (66.67%)	
Comorbidities (f, %)								
Myocardial Infarction	5 (4.10%)	4 (5.71%)	1 (9.09%)	0 (0.00%)	0.195	5 (6.25%)	0 (0.00%)	0.163
Congestive Heart Failure	13 (10.66%)	6 (8.57%)	1 (9.09%)	6 (14.63%)	0.560	7 (8.75%)	6 (14.29%)	0.346
Peripheral Vascular Disease	8 (6.56%)	5 (7.14%)	1 (9.09%)	2 (4.88%)	0.866	5 (6.25%)	3 (7.14%)	1.000
Cerebrovascular Disease	9 (7.38%)	6 (8.57%)	0 (0.00%)	3 (7.32%)	0.884	5 (6.25%)	4 (9.52%)	0.493
Dementia	2 (1.64%)	1 (1.43%)	0 (0.00%)	1 (2.44%)	1.000	1 (1.25%)	1 (2.38%)	1.000
Chronic Obstructive Pulmonary Disease	6 (4.92%)	4 (5.71%)	0 (0.00%)	2 (4.88%)	1.000	4 (5.00%)	2 (4.76%)	1.000
Connective Tissue Disease	5 (4.10%)	3 (4.29%)	0 (0.00%)	2 (4.88%)	1.000	4 (5.00%)	1 (2.38%)	0.659
Peptic Ulcer Disease	5 (4.10%)	1 (1.43%)	0 (0.00%)	4 (9.76%)	0.107	1 (1.25%)	4 (9.52%)	0.047*
Liver Disease					0.495			0.654
None	116 (95.08%)	68 (97.14%)	11 (100.00%)	37 (90.24%)		77 (96.25%)	39 (92.86%)	
Mild	4 (3.28%)	1 (1.43%)	0 (0.00%)	3 (7.32%)		2 (2.50%)	2 (4.76%)	
Moderate to severe	2 (1.64%)	1 (1.43%)	0 (0.00%)	1 (2.44%)		1 (1.25%)	1 (2.38%)	
Diabetes mellitus					0.359			0.206
None or diet-controlled	77 (63.11%)	48 (68.57%)	6 (54.55%)	23 (56.10%)		53 (66.25%)	24 (57.14%)	
Uncomplicated	39 (31.97%)	20 (28.57%)	5 (45.45%)	14 (34.15%)		25 (31.25%)	14 (33.33%)	
End-organ damage	6 (4.92%)	2 (2.86%)	0 (0.00%)	4 (9.76%)		2 (2.50%)	2 (2.50%)	
Hemiplegia	12 (9.84%)	9 (12.86%)	1 (9.09%)	2 (4.88%)	0.330	9 (11.25%)	3 (7.14%)	0.542
Moderate to severe CKD	8 (6.56%)	3 (4.29%)	0 (0.00%)	5 (12.20%)	0.214	3 (3.75%)	5 (11.90%)	0.122
Solid tumor					0.095			0.024*
No tumor	109 (89.34%)	66 (94.29%)	10 (90.91%)	33 (80.49%)		75 (93.75%)	34 (80.95%)	
Localized	10 (8.20%)	4 (5.71%)	1 (9.09%)	5 (12.20%)		5 (6.25%)	5 (11.90%)	
Metastatic	3 (2.46%)	0 (0.00%)	0 (0.00%)	3 (7.32%)		0 (0.00%)	3 (7.14%)	
Leukemia	2 (1.64%)	0 (0.00%)	1 (9.09%)	1 (2.44%)	0.069	1 (1.25%)	1 (2.38%)	1.000
Lymphoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	0 (0.00%)	0 (0.00%)	–
AIDS/HIV	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	0 (0.00%)	0 (0.00%)	–
Charlson Comorbidity Index (x̄, SD)	2.84 (2.37)	2.41 (2.20)	2.09 (1.45)	3.78 (2.59)	0.014*	2.29 (2.04)	3.90 (2.61)	0.001†

*Significant at 0.05; †Significant at 0.01

>0.05); however, the mean Charlson Comorbidity Index was significantly higher (z = 8.57, p = 0.014) among those who were severely malnourished ($\bar{x}$ = 3.78, SD = 2.59) compared to those who were well-nourished ($\bar{x}$ = 2.41, SD = 2.20) or only moderately malnourished ($\bar{x}$ = 2.09, SD = 1.45). On the other hand, between-group comparisons of these characteristics using the MST classification indicated that age and most comorbidities were not significantly different (p >0.05) except for age, peptic ulcer disease, and Charlson Comorbidity Index. For age, those who were classified as at risk of malnutrition ($\bar{x}$ = 61.38, SD = 16.72) had a significantly higher mean age (t = –3.18, p = 0.002) than those who were not at risk of malnutrition ($\bar{x}$ = 51.78, SD = 15.37). Similarly, the proportion of participants who were at risk of malnutrition was significantly higher (χ^2 = 10.87, p = 0.029) among those who were ≥80 years old (16.67% vs. 2.50%) and was significantly lower among those who were <50 years old (23.81% vs. 43.75%). For peptic ulcer disease, results showed that those who were at risk of malnutrition (9.52% vs. 1.25%) have a significantly higher (χ^2 = 4.80, p = 0.047) proportion of peptic ulcer disease than those who were not at risk of malnutrition. The mean Charlson Comorbidity Index of those who were at risk of malnutrition ($\bar{x}$ = 3.90, SD = 2.61) was also significantly higher (z = –3.18, p = 0.001) than those who were not at risk ($\bar{x}$ = 2.29, SD = 2.04).

The descriptive statistics of the prevalence of malnutrition risk, using Short Nutritional Assessment Questionnaire (SNAQ) and Malnutrition Screening Tool (MST), are presented in Table 2. Results showed that the mean SNAQ and MST scores were 1.52 (SD = 1.62) and 1.02 (SD = 1.09), respectively. Categorizing the SNAQ scores showed 33.61% were severely malnourished, 9.02% were moderately malnourished, and most of the participants (57.38%) were well nourished. Similarly, 34.43% of participants were classified to be at risk of malnutrition.

Table 2. Descriptive statistics on the prevalence of malnutrition risk, using the Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Screening Tool (MST), among the participants (N = 122)

Malnutrition Risk	Mean (SD)	Frequency (%)	95% CI
SNAQ score	1.52 (1.62)		1.23 to 1.81
SNAQ classification			
Well nourished		70 (57.38%)	48.10% to 66.28%
Moderately malnourished		11 (9.02%)	4.59% to 15.63%
Severely malnourished		41 (33.61%)	25.72% to 42.52%
MST score	1.02 (1.09)		0.82 to 1.21
MST classification			
Not at risk of malnutrition		80 (65.57%)	56.43% to 73.94%
At risk of malnutrition		42 (34.43%)	26.06% to 43.57%

95% CI = 95% Confidence Intervals

Table 3. Descriptive statistics of the study outcomes [Intensive Care Unit (ICU) admission, in-hospital mortality, and length of hospital] among the participants according to malnutrition risk (N = 122)

Outcomes	Malnutrition risk							
		SNAQ classification				MST classification		
	Total (N = 122)	Well nourished (n = 70)	Moderately malnourished (n = 11)	Severely malnourished (n = 41)	*p*-value (two-tailed)	Not at risk (n = 80)	At risk (n = 42)	*p*-value (two-tailed)
Intensive Care Unit admission (ICU; f, %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	0 (0.00%)	0 (0.00%)	–
30-day in-hospital mortality (per 1,000 person-day)	0.007	0.000	0.006	0.015	0.009†	0.001	0.016	0.007†
Duration of hospital stay (Days; Md, IQR)	6.00 (4.00 – 12.00)	5.00 (3.00 – 9.00)	6.00 (4.00 – 30.00)	7.00 (5.00 – 16.00)	0.029*	8.86 (8.23)	10.57 (9.16)	0.212

*Significant at 0.05; †Significant at 0.01

Comparison of intensive care unit admission, in-hospital mortality, and length of hospital stay according to malnutrition risk

Table 3 illustrates descriptive statistics of the study outcomes according to malnutrition risk using the SNAQ and MST score classifications. Results showed that none of the participants were admitted in the intensive care unit (ICU), and the overall incidence rate of 30-day in-hospital mortality was 7 per 1,000 person-day. In addition, the median duration of hospital stay was 6.00 days (IQR = 4.00 – 12.00). Comparative analyses of the duration of hospital stay showed that the median duration of hospital stay was statistically higher among those who were severely malnourished (Md = 7.00, IQR = 5.00 – 16.00). In addition, results indicated that the incidence of 30-day in-hospital mortality was significantly higher (p = 0.009) among those who were severely malnourished (15 per 1,000 person-day), using the SNAQ classification. Likewise, the incidence of 30-day in-hospital mortality was significantly higher (p = 0.007) among those who were at risk of malnutrition (16 per 1,000 person-day), using the MST classification, compared to those who were not at risk of malnutrition (1 per 1,000 person-day).

Associations of demographic characteristics and malnutrition risk

Table 4 presents the univariate binary logistic regression analyses of the associations of demographic and clinical characteristics with malnutrition risk. Classifying malnutrition risk using the SNAQ classification, results indicated that age, sex, and all comorbidities were not significantly associated with malnutrition risk (p >0.05). However, the Charlson Comorbidity Index significantly predicted the likelihood of severe malnutrition (cOR = 1.28, p = 0.005, 95% CI = 1.08 – 1.52), denoting that every 1-unit increase in the Charlson Comorbidity Index leads to a 28% increase in the odds of developing severe malnutrition.

On the other hand, analyses of the association of the demographic and clinical characteristics with malnutrition risk using the MST classification indicated that sex and all comorbidities were not significantly associated (p >0.05) except for age and Charlson Comorbidity Index. Age (cOR = 1.04, p = 0.003, 95% CI = 1.01 – 1.07), for this part, positively predicted the likelihood of being at risk for malnutrition, with every 1-year increase in age leading a 4% increase in the odds of being at risk for malnutrition. Likewise, results showed that those who were 70 to 79 years old (cOR = 12.25, p = 0.004, 95% CI = 2.19 – 68.51) were 12.25 times more likely to be at risk for malnutrition than those who were <50 years old. For Charlson Comorbidity Index (cOR = 1.35, p=0.001, 95% CI = 1.13 – 1.61) showed a positive association, indicating a 35% increase in the odds of being at risk for malnutrition for every 1-unit increase in Charlson Comorbidity Index.

Associations and hazards of 30-day in-hospital mortality and malnutrition risk

The associations and the hazards of 30-day in-hospital mortality with malnutrition risk are presented in Table 5. Crude analyses of the associations of SNAQ (cOR = 3.56,

p = 0.002, 95% CI = 1.57 – 8.03) and MST scores (cOR = 5.39, p = 0.001, 95% CI = 1.94 – 14.93) with 30-day in-hospital mortality indicated that every 1-unit increase in SNAQ and MST scores lead to a 3.56 times and 5.39 times increase in the likelihood of 30-day in-hospital mortality, respectively. Similarly, malnutrition risk using SNAQ classification was significantly associated with 30-day in-hospital mortality. In particular, those who were severely malnourished (cOR = 16.47, p = 0.010, 95% CI = 1.95 – 139.06) were 16.47 times more likely to expire within 30 days compared to those who were not severely malnourished. Likewise, malnutrition risk using the MST positively predicted 30-day in-hospital mortality (cOR = 15.80, p = 0.011, 95% CI = 1.87 – 133.32), which denote that those who are at risk of malnutrition were 15.80 times more likely to develop 30-day in-hospital mortality than those who were not at risk of malnutrition. After adjusting for the significant confounders, results showed that malnutrition risk, using both SNAQ and MST scores and classifications, were not significantly associated with 30-day in-hospital mortality (p >0.05).

On the other hand, results of the Cox proportional hazards showed that SNAQ (cHR = 2.58, p = 0.009, 95% CI = 1.27 – 5.26) and MST scores (cHR = 3.67, p=0.001, 95% CI = 1.67 – 8.05) significantly predicted the hazard of 30-day in-hospital mortality, increasing the hazard of mortality by 2.58 times ad 3.67 times, respectively, for every 1-unit increase in SNAQ and MST scores. Similarly, malnutrition risk using the SNAQ classification indicated the severely malnourished category (cHR = 9.22, p = 0.038, 95% CI =

Table 4. Univariate binary logistic regression analyses of the associations of the demographic and clinical characteristics on malnutrition risk, using the Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Screening Tool (MST), among the participants (N = 122)

Characteristics	Malnutrition risk[a]								
	SNAQ classification						MST classification (at risk)		
	Moderately malnourished			Severely malnourished					
	cOR	95% CI	*p*-value (two-tailed)	cOR	95% CI	*p*-value (two-tailed)	cOR	95% CI	*p*-value (two-tailed)
Age (years)	0.98	0.94 – 1.02	0.388	1.02	1.00 – 1.05	0.061	1.04†	1.01 – 1.07	0.003
Age categories									
<50 Years Old	Referent	–	–	Referent	–	–	Referent	–	–
50 to 59 Years Old	0.55	0.10 – 3.04	0.492	1.80	0.65 – 4.96	0.258	2.21	0.81 – 6.06	0.123
60 to 69 Years Old	0.55	0.10 – 3.04	0.492	1.20	0.40 – 3.57	0.746	1.75	0.60 – 5.08	0.303
70 to 79 Years Old	1.16	0.11 – 12.38	0.898	3.18	0.72 – 14.09	0.127	2.33	0.55 – 9.92	0.251
≥80 Years Old	1.00	–	0.988	3.18	0.72 – 14.09	0.127	12.25†	2.19 – 68.51	0.004
Sex (Female)	1.56	0.42 – 5.81	0.507	1.55	0.70 – 3.41	0.280	1.81	0.83 – 3.94	0.135
Comorbidities									
Myocardial infarction	1.65	0.17 – 16.30	0.668	1.07	0.92 – 1.12	0.984	1.00	–	–
Congestive heart failure	1.07	0.12 – 9.82	0.955	1.83	0.55 – 6.10	0.326	1.74	0.54 – 5.55	0.351
Peripheral vascular disease	1.30	0.14 – 12.31	0.819	0.67	0.12 – 3.60	0.638	1.15	0.26 – 5.08	0.850
Cerebrovascular disease	1.08	0.95 – 1.12	0.990	0.84	0.20 – 3.56	0.815	1.58	0.40 – 6.22	0.514
Dementia	1.06	0.95 – 1.13	0.991	1.72	0.10 – 28.32	0.703	1.93	0.12 – 31.60	0.646
Chronic obstructive pulmonary disease	1.09	0.98 – 1.16	0.991	0.85	0.15 – 4.84	0.851	0.95	0.17 – 5.41	0.954
Connective tissue disease	1.03	0.95 – 1.09	0.988	1.14	0.18 – 7.15	0.885	0.46	0.05 – 4.28	0.498
Peptic ulcer disease	1.03	0.96 – 1.11	0.993	1.07	0.80 – 69.11	0.077	8.32	0.90 – 76.97	0.062
Liver disease									
None	Referent	–	–	Referent	–	–	Referent	–	–
Mild	1.09	0.97 – 1.16	0.988	5.51	0.55 – 54.83	0.146	1.97	0.27 – 14.55	0.504
Moderate to severe	1.07	0.96 – 1.12	0.990	1.84	0.11 – 30.23	0.670	1.97	0.12 – 32.42	0.634
Diabetes mellitus									
None or diet-controlled	Referent	–	–	Referent	–	–	Referent	–	–
Uncomplicated	2.00	0.55 – 7.31	0.295	1.46	0.63 – 3.40	0.379	1.24	0.55 – 2.79	0.608
End-organ damage	1.03	0.92 – 1.11	0.991	4.18	0.71 – 24.48	0.113	4.42	0.76 – 25.79	0.099
Hemiplegia	0.68	0.08 – 5.95	0.726	0.35	0.07 – 1.69	0.191	0.61	0.16 – 2.37	0.473
Moderate to severe CKD	1.03	0.95 – 1.09	0.986	3.10	0.70 – 13.72	0.136	3.47	0.79 – 15.30	0.100
Solid tumor									
No tumor	Referent	–	–	Referent	–	–	Referent	–	–
Localized	1.65	0.17 – 16.29	0.668	2.50	0.63 – 9.93	0.193	2.21	0.60 – 8.13	0.234
Metastatic	1.04	0.95 – 1.12	1.000	1.04	0.96 – 1.09	0.986	1.00	–	–
Leukemia	1.02	0.94 – 1.07	0.993	1.06	0.97 – 1.13	0.993	1.93	0.12 – 31.60	0.646
Lymphoma	1.00	–	–	1.00	–	–	1.00	–	–
AIDS/HIV	1.00	–	–	1.00	–	–	1.00	–	–
Charlson Comorbidity Index	0.92	0.67 – 1.28	0.632	1.28†	1.08 – 1.52	0.005	1.35†	1.13 – 1.61	0.001

[a]Short Nutritional Assessment Questionnaire (SNAQ) referent or baseline outcome is the "well-nourished classification". On the other hand, the Malnutrition Screening Tool (MST) used the classification of "Not At Risk of Malnutrition" as the baseline outcome.

cOR = Crude Odds Ratio; 95% CI = 95% Confidence Intervals

*Significant at 0.05; †Significant at 0.01

1.13 – 75.09) significantly predicted the hazard of mortality, increasing it by 9.22 times for those who are severely malnourished. In a similar vein, malnutrition risk using the MST classification indicated that those who were at risk of malnutrition (cHR = 9.80, $p = 0.033$, 95% CI = 1.20 – 79.74) were 9.80 times at greater hazard of mortality than those who were not at risk of malnutrition.

It can also be seen in the covariate-adjusted Kaplan Meier survival curves (Figure 1) that the survival estimates of those who were not severely malnourished, using the SNAQ classification ($X^2 = 13.40$, $p = 0.004$), and those who were not at risk of malnutrition, using the MST classification ($X^2 = 13.57$, $p = 0.004$, have significantly higher survival estimates even after controlling for confounders.

Table 5. Binary logistic and cox-regression hazards regression on the association of malnutrition risk, using the Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Screening Tool (MST), on the 30-day in-hospital mortality of the participants (N = 122)

Characteristics	30-day in-hospital mortality (expired)							
	cOR (95% CI)	*p*-value (two-tailed)	aOR[a] (95% CI)	*p*-value (two-tailed)	cHR (95% CI)	*p*-value (two-tailed)	aHR[a] (95% CI)	*p*-value (two-tailed)
SNAQ score	3.56† (1.57 – 8.03)	0.002	2.19 (0.86 – 5.63)	0.102	2.58† (1.27 – 5.26)	0.009	1.81 (0.77 – 4.28)	0.179
SNAQ classification								
Not severely malnourished	Referent	–	Referent	–	Referent	–	Referent	–
Severely malnourished	16.47† (1.95 – 139.06)	0.010	7.45 (0.58 – 95.05)	0.122	9.22* (1.13 – 75.09)	0.038	4.29 (0.43 – 42.24)	0.212
MST score	5.39† (1.94 – 14.93)	0.001	4.25 (0.87 – 20.79)	0.074	3.67† (1.67 – 8.05)	0.001	2.50 (0.94 – 6.68)	0.067
MST classification								
Not at risk of malnutrition	Referent	–	Referent	–	Referent	–	Referent	–
At risk of malnutrition	15.80* (1.87 – 133.32)	0.011	7.77 (0.60 – 101.34)	0.118	9.80* (1.20 – 79.74)	0.033	4.55 (0.46 – 44.94)	0.194

[a]Odds ratios were adjusted for the following confounders: liver disease, moderate to severe chronic kidney disease, solid tumor, and leukemia. On the other hand, hazards ratios were adjusted for liver disease and solid tumor.

cOR = Crude Odds Ratio; aOR = Adjusted Odds Ratio; cHR = Crude Hazards Ratio; aHR = Adjusted Hazards Ratio; 95% CI = 95% Confidence Intervals

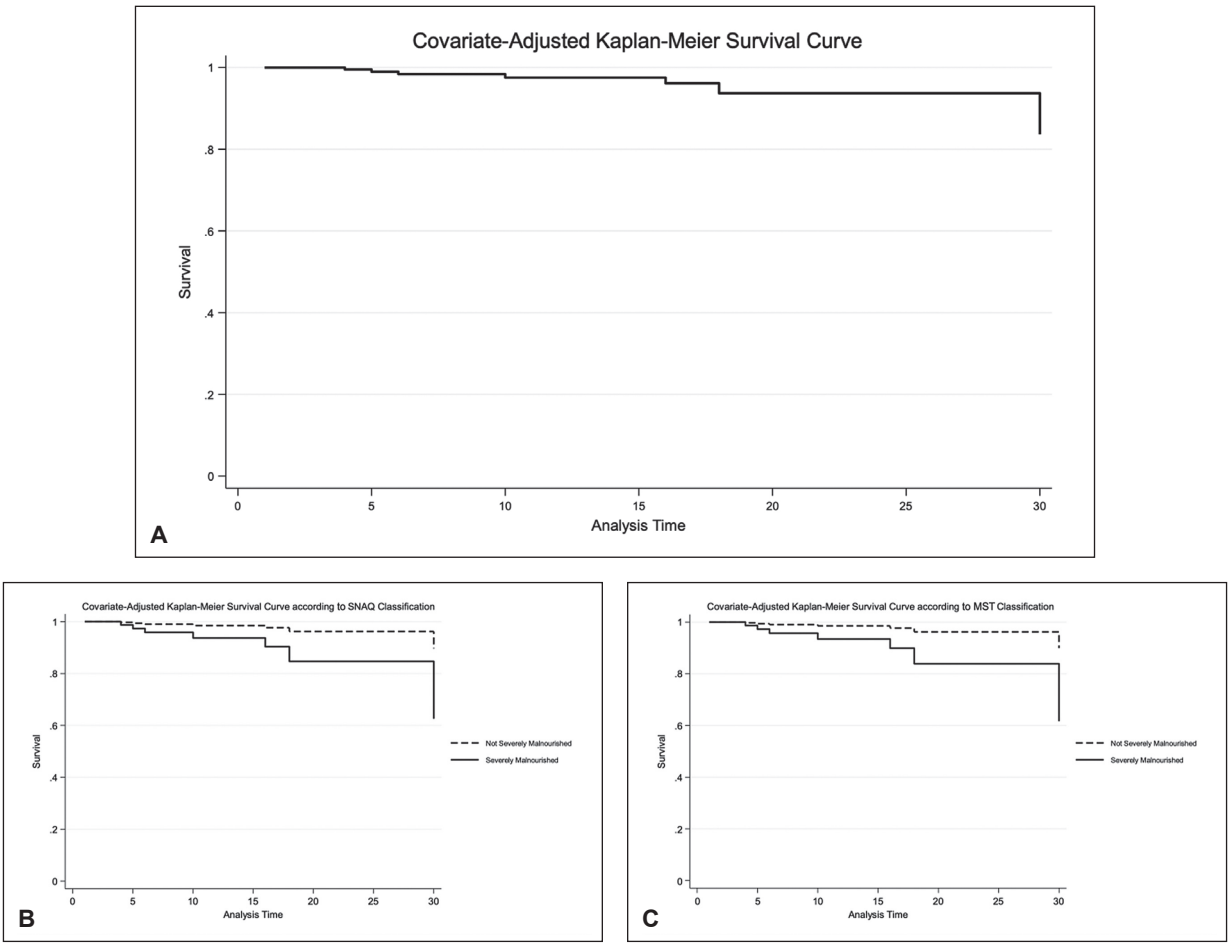

Figure 1. Covariate-adjusted Kaplan-Meier survival curves for **(A)** all the participants and according to Malnutrition Risk using the **(B)** SNAQ Classification and **(C)** MST classification.

DISCUSSION

We studied 122 patients and the mean age was 55.08 years old (SD = 16.43), with most of them being <50 years old (36.89%). In addition, majority of the participants were females (57.38%), and the most prevalent comorbidity was uncomplicated diabetes mellitus (31.97%). Their nutritional status using SNAQ and malnutrition risk using MST classification were assessed, 41 patients (33.61%) being severely malnourished using the SNAQ classification and 42 patients (34.43%) being at risk using the MST classification.

After adjusting for the significant confounders, results showed that nutritional status using SNAQ and malnutrition risk using MST, were not significantly associated with 30-day in-hospital mortality (p>0.05) which were different from a study that showed an association using similar nutrition tools and another study that used the MST.[13,14] On another note, results of the Cox proportional hazards showed that SNAQ and MST scores significantly predicted the hazard of 30-day in-hospital mortality, increasing the hazard of mortality by 2.58 times and 3.67 times, respectively, for every 1-unit increase in SNAQ and MST scores. Moreover, those who were severely malnourished (SNAQ) and at risk for malnutrition (MST) significantly predicted the hazard of mortality, increasing it by 9.22 times and 9.80 times respectively than those who were not at risk of malnutrition or those who were not severely malnourished. On the writing of this research, there seems to be no local data available that had similar results from our study which also used these two simple tools among patients admitted at the wards.

In a study by Isenring et al., malnutrition prevalence was found out to be 42.8%[15] and this is alarming since regardless of the cause of death, malnutrition and risk of malnutrition are associated with increased mortality[16] which stresses the importance for nutritional screening to identify those who may require nutritional support in order to avoid preterm death. When the MST was used to classify patients, it was found out that it is an effective predictor of nutritional risk. Also, it was found that the MST predicted patients that were at increased risk for death[17] and was also comparable with SGA in terms of sensitivity and specificity.[18] Badosa et al.,[19] used the SNAQ classification and was able to identify a higher rate of nutritionally at-risk patients, and was also present among those with a higher CCI which was similar to our study since our data revealed that a higher CCI would have a higher risk of severe malnutrition which can lead to undesirable outcomes for patients. We also found that the hazard of mortality was higher in those at risk for malnutrition risk using the MST classification or patients classified as severely malnourished using the SNAQ classification indicating the usefulness of both of these tools in assessing nutritional risk and malnutrition at the onset of their hospital course.

There is currently no gold standard among the various screening tools available, but tools with the highest evidence for validity included the SNAQ and MST.[20] Most of the studies that used the tools involved elderly patients, and those admitted at the critical care unit. Our study provides a new light on these tools since we included adults aged 19 years old and above. We also only included those who were at the regular ward of the hospital and excluded those who were critically ill at the onset. Although none of the patients were admitted at the ICU, the hazard of 30 day in-hospital mortality was still evident among those at risk for malnutrition and severely malnourished groups indicating the usefulness and predictive value of both tools. The ease and validity of administering these tools may be applied to the patients, especially at the first day of hospitalization to detect at risk patients.

This study has potential limitations. These include the accuracy of recall of some patients regarding their answers to the questionnaires provided since the questions were to be answered based on the time of admission. Also, this study was done via total enumeration sampling hence may not be fully representative of the population being studied and given the high confidence interval even adjust for confounders would mean that a larger sample size would be appropriate for future studies.

More studies may be conducted to further analyze the advantage of using one tool over the other, or by comparing these tools to what is commonly used in the institutions since there is still no gold standard when it comes to screening tools for malnutrition.

CONCLUSION

The MST and SNAQ classification are screening tools for nutritional status (SNAQ) and malnutrition risk (MST) that can be administered at the onset of the patient's hospital course and have been demonstrated in this study to predict 30-day in-hospital mortality. It is important to note that none of the patients included in this study required intensive care unit admission.

Acknowledgments
The completion of this research paper would not have been possible without the support of the consultants in my institution and the guidance from our Creator above.

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

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

Perioperative Complications Associated with Routine Preoperative Glucocorticoid Use Among Patients Undergoing Pituitary Surgery with Normal Preoperative HPA Axis: A Retrospective Cohort Study

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Abstract

Objective. This study determined the incidence of perioperative complications associated with routine preoperative glucocorticoid use in patients undergoing pituitary surgery with normal preoperative hypothalamo-pituitary-adrenal axis (HPA axis).

Methodology. From 2011-2021 retrospective chart review, 243 patients undergoing pituitary surgery with normal preoperative HPA axis were analyzed into 2 groups: 1) with preoperative steroids; and 2) without preoperative steroids. Development of postoperative complications was subsequently evaluated.

Results. Incidence of primary composite postoperative complications of in-hospital mortality, postoperative infection and postoperative diabetes insipidus (DI) was significantly increased among those who had preoperative steroids compared to those without (58.33% versus 33.33%, *p*-value 0.004) with an adjusted odds ratio of 2.90 (CI 1.29 to 6.53, *p*-value 0.010). Among the components of the composite outcome, post-operative DI was statistically higher among those who were given preoperative steroids (52.45% versus 28.21%, *p*-value 0.006) with an adjusted OR of 3.31 (CI 1.43 to 7.67, *p*-value 0.005). The incidence of postoperative adrenal insufficiency was similar between the 2 groups (20.15% with steroids versus 8.70% without steroids, *p*-value 0.258).

Conclusion. Among patients undergoing pituitary surgery with normal preoperative HPA axis, routine preoperative steroids use was associated with an increased risk of composite postoperative complications.

Key words: pituitary-adrenal system, pituitary gland / surgery, postoperative complications, glucocorticoids, steroids

INTRODUCTION

A strategy of giving routine doses of glucocorticoids preoperatively in all patients undergoing pituitary surgery started around the 1950s when studies noted that fatal outcomes occur among patients with impaired hypothalamo-pituitary-adrenal (HPA) axis undergoing pituitary surgery.[1] Those who give preoperative glucocorticoids rationalize that postoperative adrenal insufficiency (AI) remains a life-threatening condition. Some also have a notion that adrenocorticotrophic hormone (ACTH) secretion can be compromised by trauma of surgery.[2] Lastly, there is an assumption that glucocorticoids are safe to use when given for short courses. However, in 2002, Inder and Hunt et al., advocated a restrictive approach in the use of preoperative corticosteroids. They promoted a glucocorticoid-sparing regimen for those who had intact or presumed intact function of HPA axis.[3] This recommendation was from small retrospective and prospective trials revealing that postoperative AI is rare among patients with intact HPA axis preoperatively and that HPA function is not compromised during or after this procedure.[2,4,5] A meta-analysis of small studies from western countries, revealed that the incidence of postoperative AI among patients undergoing pituitary surgery with normal preoperative morning cortisol levels ranges from 0.96% – 12.9% (mean incidence of 5.55%) and therefore concluded that proof is lacking to demonstrate clinically important benefits of preoperative administration of glucocorticoids.[6] Moreover, the study of De Tomassi et al., reported that transsphenoidal surgery can be performed safely in patients with preoperative morning serum cortisol less than 9 μg/dl (250 nmol/l).[7] Despite the 2002 guidelines released by Inder and Hunt et al., high doses of glucocorticoid are still being used in patients with intact HPA axis undergoing pituitary surgery in numerous institutions worldwide. Possible reasons for

eISSN 2308-118x (Online)
Printed in the Philippines

Received: May 28, 2024. Accepted: July 25, 2024.
Published online first: April 20, 2025.
https://doi.org/10.15605/jafes.040.01.06

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this practice include difficulties in diagnosing and defining a suboptimal function of the HPA axis, local traditions and fear of inadequate pituitary function triggered by pituitary surgery.[1] Currently, there is still a gray area in the preoperative management of pituitary surgery among patients with normal preoperative HPA axis. Predicament lies on whether to give prophylactic glucocorticoid coverage perioperatively or apply a glucocorticoid-sparing method, giving only when AI ensues.[5]

Numerous factors are associated with poor perioperative outcomes among patients undergoing pituitary surgery and the physician must address each of these factors when possible. Corollary to this, there is paucity of studies that looked extensively at the perioperative complications associated with preoperative glucocorticoid use among patients undergoing pituitary surgery with normal preoperative HPA axis. Based on studies from general surgical and neurosurgical cases that revealed worse outcomes among those who were given preoperative steroids,[8,9] it is hypothesized that preoperative glucocorticoids in patients undergoing pituitary surgery are likely to be associated with an increased risk of surgical site infections, pneumonia, myocardial infarction, cardiac arrest and death, to name a few.[9]

This study aimed to determine the incidence of perioperative complications associated with routine preoperative glucocorticoids given to patients undergoing pituitary surgery with normal preoperative HPA axis. More specifically, the study determined the effects of giving preoperative glucocorticoids on the composite of overall in-hospital mortality rate, postoperative infection and postoperative diabetes insipidus (DI). The study also analyzed the effects of routine preoperative steroid use in the incidence of postoperative AI and other secondary outcomes pertinent to endocrinologists such as: perioperative hyperglycemia, perioperative uncontrolled hypertension, incidence of cardiovascular events (MI, stroke and CV death), rate of glucocorticoid use upon discharge, incidence of perioperative hypotension, postoperative hypoglycemia and hyponatremia, CSF leak and hospital length of stay.

METHODOLOGY

Setting

The study was a retrospective cohort study done at the Philippine General Hospital (PGH), Manila, Philippines. This hospital is one of the largest tertiary government hospitals in the Philippines and is a subspecialty referral center for numerous complicated cases from the entire country including pituitary cases. The study protocol was approved by the local institutional review board of the hospital (University of the Philippines Manila- Research Ethics Board) with UPM-REB code 2021-111-01 and received a research grant from the Philippine College of Endocrinology, Diabetes and Metabolism.

Study population and sampling

Medical records of adult patients 18 years old and above at PGH who underwent pituitary surgery from 2011 to 2021 with normal preoperative 8 am serum cortisol levels (138-690 nmol/L) were included in the study. Patients were included regardless of pituitary pathology or surgical approach. On the other hand, patients with confirmed preoperative AI, pituitary apoplexy and Cushing's syndrome who required perioperative steroids were excluded from the study. Patients on chronic steroid use preoperatively for other medical conditions were also excluded. By reviewing the existing databases from the Division of Endocrinology, Diabetes and Metabolism pituitary census and from logbooks of pituitary specimens submitted to the Department of Pathology, convenient purposive sampling of patients that met the eligibility criteria were included in the study.

Sample size computation

Data collection continued until the computed sample of at least 242 patients was reached. Type I error was assigned a value of 0.05 so that the confidence level is at 95% while the Type II error was assigned a value of 0.20 so that the study can have a power of 80%. The ratio of sample size (unexposed/exposed) is at 0.5 derived from the study of De Tomassi et al.[7] The percentage of patients unexposed with the primary outcome is 14.8% which was derived from previous studies [composite of in-hospital mortality (1.6%),[9] postoperative infection (7.2%)[9] and postoperative DI (6%)].[10] Moreover, the percentage of patients exposed with the primary outcome is 32.1% [composite of in-hospital mortality (6%),[9] postoperative infection (16.5%)[9] and postoperative DI (9.6%)[10]]. Using these values, a total sample size of 242 was derived.

Data collection

Databases from the Pituitary Census of the Division of Endocrinology, Diabetes and Metabolism were reviewed to identify patients who underwent pituitary surgery from 2011 to 2021. The list was verified by reviewing the pituitary specimens sent to the Division of Pathology during the same period, ensuring the inclusion of eligible patients from 2011 to 2021. These patients were selected for the study using convenient purposive sampling. Once a list of patients who underwent pituitary surgery was identified, medical records were retrieved and data collection was accomplished by the principal investigator and research assistant who was trained in the process of data collection. Individual medical records were reviewed and screening for inclusion and exclusion criteria was performed to identify eligibility to the study. Once deemed eligible, data collection proceeded using a standardized anonymized data collection form. Since review of medical records was done and no direct patient interaction was involved, obtaining informed consent was waived.

Overview of methods

Once eligibility of inclusion to the study was ascertained, standardized data collection forms were used to collect data that was used in the subsequent analysis. The following demographic information were collected: age, sex, comorbidities and year of pituitary surgery. Preoperative data gathered were: 8 am serum cortisol levels, presence or absence of Cushing's syndrome, use of glucocorticoid, presence or absence of pituitary apoplexy and hormonal functionality (if pituitary adenoma). During the perioperative period, information on occurrence of hyperglycemia or hypoglycemia and uncontrolled hypertension or hypotension were gathered. Postoperatively, tumor size, histopathologic diagnosis, surgical approach and completeness of surgical resection were assessed. Postoperative complications which include in-hospital mortality, infection (within 30 days of operation and site of infection), DI, AI, hyponatremia, CSF leak, incidence of cardiovascular events (composite of incidence of cardiovascular death, non-fatal myocardial infarction and stroke) were noted. Day 1-day 3 postoperative 8am serum cortisol levels, preoperative and postoperative (within 7 days) serum sodium levels and urine specific gravity were compared. Lastly, use of glucocorticoids as home medication and hospital length of stay in days were gathered. Data collection was accomplished by the principal investigator and research assistant who was trained regarding the process of data collection. As authorized by the local IRB (UPM-REB), proper ethical conduct of the study was observed and compliance to data privacy act was ensured.

Outcomes

The primary outcome of the study was a composite indicator comprising in-hospital mortality, postoperative infection and postoperative DI. This composite variable is binary, wherein patients who had at least 1 component of the outcome indicator was assigned a code of 1, while those who did not experience any of these outcomes were coded as 0. This was deemed as the primary outcome of interest by the investigators because these outcomes were the most common and clinically significant morbidity of pituitary surgery in the context of giving glucocorticoids based on literature review. The independent variable is the presence of preoperative steroid use while the dependent variables are the primary outcome (composite of in-hospital mortality, postoperative infection and postoperative DI). Other clinically significant secondary outcomes (dependent variable), from an endocrinologist's point of view such as incidence of postoperative AI, perioperative hyperglycemia, perioperative uncontrolled hypertension, cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, and cerebrovascular disease), perioperative hypotension, perioperative hypoglycemia, CSF leak and rate of glucocorticoid use upon discharge and lastly the hospital length of stay were included in the study. Potential confounders include age,[3,8] sex,[3] presence of DM[8], presence of CSF leak[9,11] and histopathology[5,11] for which sensitivity analysis was performed.

Operational terms

- Normal HPA axis – a basal morning serum cortisol value of 138-690 nmol/l in the absence of overt signs and symptoms consistent with hypocortisolism.[2,6]
- Post-operative infection – any infection, regardless of site, that occurs within 30 days of operation and may be related to the operation itself or the postoperative course.[12]
- Post-operative DI – presence of documented voluminous urine output (>2.5 mL/kg body weight per hour or at least 4 L per day) with a urine specific gravity of ≤1.005 or urine osmolality <200 mOsm/kg H_2O, with or without hypernatremia or hyperosmolality or, as clinically diagnosed by the attending endocrinologist, developing anytime during hospital admission following pituitary surgery.[11]
- Post-operative AI – basal serum cortisol levels below 138 nmol/L or clinically diagnosed by the attending physician based on presence of signs and symptoms of AI for patients with postoperative serum cortisol levels of 138-270 nmol/L.[6,13]
- Perioperative hyperglycemia – any capillary glucose value >200 mg/dL within 24 hours prior to and 48 hours after the operation (Turina et al.).[14]
- Perioperative uncontrolled hypertension – BP of 160/90 mm Hg or higher or an SBP elevation of at least 20% of the preoperative value that persists for longer than 15 minutes (ACC/AHA 2017).[15]
- Perioperative hypotension – systolic BP less than 90 mm Hg for a total of 10 min or more during surgery or for any duration after surgery and for which intervention was initiated (Roshanov et al.).[16]

Statistical methods

Descriptive statistics were done to analyze and compare the baseline characteristics of the patients with preoperative steroids versus without preoperative steroids. For normally distributed data, mean and standard deviation were used and were compared using Student's t-test. For non-normally distributed data, median and interquartile range (IQR) was used and 2 groups were compared using two-sample Mann-Whitney test to identify significant differences between groups. Categorical data were summarized as frequencies and percentages and compared using either Pearson's Chi-squared test or Fisher's exact test as appropriate. Data normality was assessed using Shapiro-Wilk test.

In terms of analysis of the primary outcome of the study, significant differences between the 2 groups were assessed using Pearson's Chi-squared test and Fisher's Exact test. For the analysis of incidence of postoperative AI, it was reported as frequency and its association with preoperative steroid use was analyzed using Fisher's exact test. The other

secondary outcomes were analyzed as follows: Pearson's Chi-Square test, Fisher exact test and Mann-Whitney test as appropriate.

To identify the extent by which preoperative steroid use affects the different outcomes of interest, generalized linear models with log link function was performed adjusting for possible known confounders such as age, sex, histopathology, surgical approach, completeness of surgical resection and comorbidities.

STATA 15 was used for all analyses and a *p*-value of less than 0.05 was considered significant for all the tests.

RESULTS

From the years of 2011-2021. a total of 243 patients were deemed eligible for inclusion in the study. Of these, 204 patients received routine preoperative steroids while 39 patients did not receive preoperative steroids stating that routine preoperative steroid use was the most common practice in this cohort. Demographics and baseline clinical characteristics showed no statistically significant difference between the 2 groups except solely for admission type (Table 1). Mean patient age was 44.17 years. The overall mean largest tumor diameter was 3.59 cm and with a mean tumor volume of 16.38 ml. There was no statistical difference between tumor size (both largest diameter and tumor volume) between the 2 groups (*p*-value 0.4581 and *p*-value 0.9397, respectively). In terms of surgical approach, most cases (82.2%) underwent transsphenoidal surgery (200/243) while the transcranial approach was used in 17.70% (43/243). More patients had complete surgical resection of the tumor at 54.42% (123/243). The overall mean preoperative 8 am serum cortisol was 371.66 nmol/L. Routine preoperative steroids were given to patients with mean preoperative 8 am serum cortisol of 373.73 nmol/L while those without preoperative steroids had a mean value of 361.55 nmol/L, showing no statistically significant difference at baseline (*p*-value 0.6269).

Considering the primary objective, Table 2 shows us that the primary composite outcome of in-hospital mortality, postoperative infection and postoperative DI was significantly higher among patients given routine preoperative steroids at 58.33% (119 out of 204) compared to 33.33% (13 out of 39) of those without preoperative steroids (*p*-value of 0.004). Scrutinizing the individual components of the composite outcome, the in-hospital mortality rate among those given steroids was at 5.39% (11/204) while there was no reported in-hospital mortality among those who were not given preoperative steroids though it did not reach statistical significance (*p*-value 0.220). For post-operative infection, there were higher rates among patients given steroids 12.25% (25/204) in contrast to those who were not given steroids 5.13% (2/39), although this did not reach statistical significance (*p*-value 0.270). Lastly, for postoperative DI, this individual outcome reached statistical significance as more patients developed postoperative DI among those who were given preoperative steroids at 52.45% (107 of 204) compared to 28.21% (11 of 39) patients who did not receive preoperative steroids (*p*-value of 0.006).

Table 1. Baseline characteristics of the study population

Characteristics	Without preoperative steroids (n = 39)	With preoperative steroids (n = 204)	Total (n = 243)	*p*-value
Age, Mean (SD)	44.36 (12.50)	44.14 (12.17)	44.17 (12.20)	0.92[a]
Sex				
Male	16 (41.03)	81 (39.71)	97 (39.92)	0.88[b]
Female	23 (58.97)	123 (60.29)	146 (60.08)	
Histopathology				
Others	2 (5.13)	17 (8.33)	19 (7.82)	0.82[c]
Pituitary Adenoma	37 (94.87)	185 (90.69)	222 (91.36)	
Rathke's cleft cyst	0 (0.00)	2 (0.98)	2 (0.82)	
Tumor size, Mean (SD)				
Largest diameter (cm), n = 218	3.35 (0.92)	3.64 (2.11)	3.59 (1.97)	0.46[d]
Volume (ml), n = 204	13.99 (11.88)	16.84 (19.05)	16.38 (18.09)	0.94[d]
Surgical Approach				
Transcranial	3 (7.69)	40 (19.61)	43 (17.70)	0.07[b]
Transsphenoidal	36 (92.31)	164 (80.39)	200 (82.30)	
Complete resection of tumor, n = 226	19 (55.88)	104 (54.17)	123 (54.42)	0.85[b]
Comorbidity				
Hypertension	16 (41.03)	62 (30.39)	78 (32.10)	0.19[b]
Diabetes mellitus	9 (23.08)	49 (24.02)	58 (23.87)	0.90[b]
Any cardiovascular disease	1 (2.56)	9 (4.41)	10 (4.12)	1.00[c]
Admission type				
Service	19 (48.72)	145 (71.08)	164 (67.49)	**0.01[b]**
Pay	20 (51.28)	59 (28.92)	79 (32.51)	
Preoperative systolic BP	123.38 (13.43)	120.27 (13.95)	120.77 (13.89)	0.20[a]
Preoperative diastolic BP	79.10 (7.54)	79.10 (9.69)	79.10 (9.34)	0.93[d]
Preoperative 8 am serum cortisol	361.55 (170.64)	373.73 (174.42)	371.77 (173.53)	0.63[d]
Preoperative serum sodium, n=238	139.84 (3.32)	140.86 (3.04)	140.70 (3.10)	0.06[d]
Preoperative urine specific gravity, n=222	1.02 (0.01)	1.02 (0.01)	1.02 (0.01)	0.95[d]

Statistical test: [a] Student's t-test, [b] Pearson's chi-squared test, [c] Fisher's exact test, [d] Mann-Whitney test

Regarding the effect of giving preoperative steroids on the incidence of postoperative AI, the rates of development showed no statistically significant difference between those given versus not given preoperative steroids [20.13% vs 8.70%, *p*-value 0.258 (Table 2)]. Equally important, none of the groups had in-hospital mortality attributable to postoperative AI.

For the secondary outcomes, the incidence of perioperative hyperglycemia showed no statistical significance between the 2 groups (27.98% with steroids vs. 23.08% without steroids, *p*-value 0.531). The incidence of uncontrolled hypertension also showed no statistically significant difference between groups (52.94% with steroids vs. 41.03% without steroids, *p*-value 0.173). There was no associated increase in the incidence of cardiovascular events (cardiovascular mortality, non-fatal MI and non-fatal stroke) at 4.41% occurring in those given preoperative steroids and 2.56% in those without preoperative steroids (*p*-value 1.0). Moreover, clinical features of postoperative AI namely: perioperative hypotension, perioperative hypoglycemia and postoperative hyponatremia showed no statistically significant difference between the 2 groups (*p*-value 0.065, 1.0, 0.184, respectively). The incidence of CSF leak, which may be a risk factor in one of our primary outcomes and postoperative infection also showed no statistically significant difference between the 2 groups (*p*-value 0.913). On the other hand, more of those who were given preoperative steroids were discharged on glucocorticoids at 29.41% (60/204) compared to those who were not given preoperative steroids at 12.82% (5/39), *p*-value 0.032). For the length of hospital stay, there was a longer hospital length of stay among patients who were given preoperative steroids compared to those who were not given steroids (14.25 days versus 11 days, respectively, *p*-value 0.0154).

Generalized linear models were performed to show the strength of association of preoperative steroids use with the different outcomes of interest and adjusting for the following possible confounders: age, sex, presence of DM, presence of CSF leak and histopathology (Table 3). Evidence showed that the use of preoperative steroids was associated with 1.80 times (CI 1.14, 2.83, *p*-value 0.013) increased risk of developing the primary composite outcome. There is also an associated 1.87 times increased risk of developing DI among patients given preoperative steroids (CI 1.12, 3.13, *p*-value 0.017). The risk of developing in-hospital mortality when given preoperative steroids cannot be estimated and the adjusted RR of developing postoperative infection did not reach statistical significance, likely due to few events. (Adjusted RR 2.39, CI 0.59, 9.70, *p*-value 0.220).

Furthermore, looking at the association of primary composite outcome with other various clinical subgroups and patient characteristics, it is evident that age, sex, histopathology, surgical approach, completeness of surgical resection, comorbidities and admission type did not show significant increase in the incidence of primary composite outcome, except for presence of diabetes mellitus with an adjusted RR 1.35 (CI 1.04, 1.75, *p*-value 0.026) (Table 4).

Table 2. Comparison of incidence postoperative complications among with preoperative steroids versus without preoperative steroids

Perioperative outcomes	Without preoperative steroids (n = 39)	With preoperative steroids (n = 204)	Total (n = 243)	*p*-value
Primary Outcome, composite[1]	13 (33.33)	119 (58.33)	132 (54.32)	**0.004**[b]
In-hospital mortality	0 (0.00)	11 (5.39)	11 (4.53)	0.220[c]
Postoperative infection	2 (5.13)	25 (12.25)	27 (11.11)	0.270[c]
Postoperative diabetes insipidus	11 (28.21)	107 (52.45)	118 (48.56)	**0.006**[b]
Postoperative adrenal insufficiency, n=182	2 (8.70)	32 (20.13)	34 (18.68)	0.258[c]
Perioperative hyperglycemia	9 (23.08)	57 (27.94)	66 (27.16)	0.531[b]
Perioperative uncontrolled hypertension	16 (41.03)	108 (52.94)	124 (51.03)	0.173[b]
Incidence of cardiovascular events (composite of cardiovascular disease, nonfatal MI, and stroke)	1 (2.56)	9 (4.41)	10 (4.12)	1.000[c]
Perioperative hypotension	3 (7.69)	41 (20.10)	44 (18.11)	0.065[b]
Perioperative hypoglycemia	2 (5.13)	11 (5.39)	13 (5.35)	1.000[c]
Postoperative hyponatremia	4 (10.26)	39 (19.12)	43 (17.70)	0.184[b]
CSF leak	6 (15.38)	30 (14.71)	36 (14.81)	0.913[b]
Rate of glucocorticoid use upon discharge	5 (12.82)	60 (29.41)	65 (26.75)	**0.032**[b]
Hospital length of stay (days)	11 (6.41)	14.26 (15.34)	13.74 (14.33)	**0.0154**[d]

[1]Primary Outcome, composite: in-hospital mortality, postoperative infection, and postoperative diabetes insipidus
Statistical test: [b] Pearson's chi-squared test, [c] Fisher's exact test, [d] Mann-Whitney test

Table 3. Association of routine preoperative steroid use with the primary composite outcome

Perioperative outcomes	Crude RR (95% CI)	*p*-value	Adjusted RR (95% CI)	*p*-value
Primary Outcome, composite	1.75 (1.10, 2.76)	**0.017**	**1.80 (1.14, 2.83)**	**0.013**
In-hospital Mortality*	-	-	-	-
Postoperative infection	2.38 (0.59, 9.68)	0.222	2.39 (0.59, 9.70)	0.220
Postoperative diabetes insipidus	1.86 (1.10, 3.12)	**0.019**	**1.87 (1.12, 3.13)**	**0.017**

Table 4. Primary composite outcome and its association with various clinical subgroups

Characteristics	Crude RR (95% CI)	*p*-value	Adjusted RR (95% CI)	*p*-value
Age	1.01 (0.99, 1.01)	0.267	1.01 (0.99, 1.02)	0.232
Sex				
Male	0.98 (0.77, 1.24)	0.856	1.08 (0.85, 1.38)	0.524
Female, Ref				
Histopathology				
Others, Ref				
Pituitary Adenoma	0.94 (0.62, 1.41)	0.769	1.07 (0.70, 1.62)	0.756
Rathke's cleft cyst	-	-		
Surgical Approach				
Transcranial, Ref				
Transsphenoidal	0.76 (0.60, 0.98)	**0.033**	0.78 (0.57, 1.07)	0.123
Complete resection of tumor	0.91 (0.72, 1.15)	0.414	0.82 (0.63, 1.08)	0.164
Comorbidity				
Hypertension	1.13 (0.89, 1.43)	0.305	0.91 (0.67, 1.24)	0.564
Diabetes mellitus	1.34 (1.06. 1.68)	**0.013**	1.35 (1.04, 1.75)	**0.026**
Any cardiovascular disease	1.50 (1.08, 2.10)	**0.016**	1.10 (0.71, 1.70)	0.675
Admission type				
Charity, Ref				
Pay	0.94 (0.73, 1.21)	0.604	1.02 (0.78, 1.35)	0.862

DISCUSSION

The most important finding of this study is that the use of routine preoperative steroids among patients with normal HPA axis undergoing pituitary surgery is associated with a 1.80 times increased risk of developing composite postoperative complications (in-hospital mortality, postoperative infection and DI). This refutes the hypothesis that giving preoperative steroids among those with normal HPA axis is safe and without consequent postoperative complications. The individual outcome that has driven the statistically significant result was the postoperative DI. There was a trend towards increased risk of developing post-operative infection among those given preoperative steroids, but the rare occurrence of these events in both groups likely resulted in non-statistically significant results. The increased risk of postoperative DI among those given preoperative steroids was similarly demonstrated in the study of Rajaratnam et al.,[17] and have recommended that among those with normal basal cortisol levels, intraoperative hydrocortisone is not required.[17] The increased risk of DI among those given preoperative steroids is due to the increased threshold for anti-diuretic hormone (ADH) release after administering intravenous cortisol, as was demonstrated in the study of Aubry, et al.[18] In that study, they showed that administration of intravenous cortisol showed a delayed release of ADH to a much higher osmotic threshold.[18] In relation to this, it is evident that the rates of DI is higher in this cohort compared to what is seen in literature. The investigators believed that the main reason for this is that the norm in this cohort is to routinely administer glucocorticoids (83.95%), which is not in magnitude of what is seen internationally (52.34% received steroids in the study of Hattori et al.[19]).

Equally important outcome, no in-hospital mortality occurred among those who were not given preoperative steroids. In terms of incidence of postoperative infection, there was no statistical difference between the 2 groups, but an important characteristic in this specific cohort is that, 34 out of 39 (87.17%) among those not given preoperative steroids had prophylactic antibiotics continued for more than 24 hours postoperatively and 178 out of 204 (87.25%) patients among those given preoperative steroids had their preoperative antibiotics continued for more than 24 hours translating to low rates to post-operative infection overall.

The previous justification for giving preoperative steroids even for those with normal HPA axis is that post-operative AI remains to be a life-threatening condition.[1] Our study however showed that in-hospital mortality is not increased by withholding preoperative steroids. There was no in-hospital mortality attributable to postoperative AI in both groups. The overall incidence of postoperative AI is higher in this cohort (18.68%) compared to the meta-analysis of Tohti et al., showing a mean incidence of 5.55% (0.96% to 12.90%) across 12 studies.[6] The incidence of postoperative AI in both groups showed no statistically significant difference demonstrating that the steroid-sparing method among patients with normal HPA axis is safe and does not increase the incidence of postoperative adrenal insufficiency. Four other international studies[2,19,20,21] have similar findings, therefore, the fear of postoperative AI should not be the reason to give preoperative steroids. Paradoxically, the incidence of postoperative AI was higher (not statistically significant) among those given preoperative steroids (20.13%) compared to those not given steroids (8.70%). The incidence of postoperative AI in those not given steroids was more reflective of its overall incidence globally.[6] The reason for the higher rate of postoperative AI among those given steroids is possibly the use of long-acting steroids intraoperatively (i.e., dexamethasone), which could have interfered with the postoperative 8 am serum cortisol results. Specifically, dexamethasone, which in this study was given at least once in variable doses in 45.09% (92/204), can suppress the secretion of ACTH, inducing the decreased level of serum cortisol, effects of which may last up to 36 to 72 hours postoperatively.[22] This phenomenon is

reflected in our study's results that those given preoperative steroids had a significantly lower postoperative 8 am serum cortisol at 352.20 nmol/L compared to 553.75 nmol/L seen among patients not given preoperative steroids (*p*-value 0.0124). This emphasizes a possible consequence of using preoperative steroids in patients with normal HPA axis, that is, when not clinically indicated, the steroid use can interfere with postoperative HPA axis testing. Lee et al., in 2022, had a similar observation that the practice of routinely giving preoperative steroids among those with normal HPA axis renders postoperative interpretation of the HPA axis function difficult.[21] Furthermore, there was a higher rate of patients using glucocorticoids upon discharge among those who were given preoperative steroids likely secondary to difficulty interpreting postoperative 8 am cortisol results in the context of administering preoperative steroids. On the other hand, important clinical features of postoperative AI namely: perioperative hypotension, perioperative hypoglycemia and postoperative hyponatremia were not significantly different between the treatment groups. Hence, even subtle presentations of AI are not increased whether you use preoperative steroids or not among patients with normal HPA axis.

The secondary outcomes such as the risk of perioperative hyperglycemia, perioperative hypertension and incidence of cardiovascular disease showed no statistically significant difference between groups answering the question of whether these theoretical side effects of steroid use translate to actual clinical practice. Our findings should be taken with caution, however, since this study was not adequately powered for the secondary outcomes. Lastly, one pertinent outcome is the length of hospital stay was longer in patients with preoperative steroids. This is possibly related to the increased incidence of postoperative DI in this group.

Other relevant results revealed a very variable steroids dose used in this cohort. Both dexamethasone and hydrocortisone were used singly or concomitantly in a few cases. Most commonly, 42.64% (87/204) patients received 50 mg hydrocortisone before surgery which was slowly tapered until day 3 postoperatively as per Inder and Hunt et al.,[3] the rest of the patients received higher doses of steroids with an overall mean hydrocortisone equivalent dose of 142.35 mg, with a range of 50 mg to 583.3 mg/day. Reasons for variability include different practices between endocrinologists and anesthesiologists and the development of an indication for intraoperative steroid use such as cerebral edema.

Limitations of the study include its retrospective nature. There was limited control over sampling of the population such that there were more patients with preoperative steroids compared to those without it which poses a potential bias against those with exposure. The performance of a randomized controlled trial will provide more robust evidence regarding the causal relationship between preoperative steroid use and perioperative complications, especially in-hospital mortality and postoperative infection. However, since the incidence of these individual complications is low in general, a large sample size will be necessary to power this study. As part of the recommendation, a consensus from multidisciplinary subspecialties is a must to standardize management among patients with normal HPA axis undergoing pituitary surgery.

CONCLUSION

Among patients with normal preoperative HPA axis, the routine use of preoperative steroids is associated with an increased risk of composite postoperative complications (in-hospital mortality, postoperative infection and postoperative DI). Steroid-sparing protocol is not associated with an increased risk of postoperative AI. The findings will encourage more rational use of steroids and minimize preventable complications.

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

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

Funding Source
This research was supported by a grant from the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM)

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CASE REPORT

Paraganglioma in Pregnancy with Recurrent Pregnancy Loss: A Case Report

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Abstract

Due to its rarity, pheochromocytoma or paraganglioma (PPGL) in pregnancy is often not timely diagnosed, thus resulting in high materno-fetal complications. We report a 28-year-old female who presented with paroxysmal symptoms and severe hypertension during early pregnancy. Biochemical confirmatory tests and localization imaging were delayed due to multiple factors. She suffered from two pregnancy losses before she had resection of the paraganglioma.

Key words: paraganglioma, pheochromocytoma, pregnancy, catecholamine, fetal demise

INTRODUCTION

Pheochromocytomas are rare but treacherous neuro-endocrine tumours arising from adrenal medullary chromaffin cells, while paragangliomas are mainly from extra-adrenal sympathetic or parasympathetic chromaffin tissues. Pheochromocytoma or paraganglioma (PPGL) in pregnancy is rare, with estimated incidences varying between 1 in 15,000 and 1 in 300,000 pregnancies.[1] The majority of mothers with functioning PPGL in pregnancy were symptomatic, with more than 75% presenting with hypertension in early pregnancy, allowing antepartum detection.[2] A high index of suspicion and prompt diagnosis are essential for timely management by a multi-disciplinary team to prevent disastrous maternal and fetal complications.

CASE

A 28-year-old female was first admitted on her ninth week of period of amenorrhea (POA) with a complaint of worsening headache and vomiting. During admission, her systolic blood pressure was 200 to 220 mm Hg, and her diastolic blood pressure was 100 to 130 mm Hg. Despite adequate hydration, she remained tachycardic with the highest documented pulse rate of 170 beats per minute. She reported intermittent chest heaviness, palpitation and unprovoked nervousness for the past few months. She was treated with labetalol 300 mg thrice daily, aspirin 100 mg OD and haematinics. She had no known comorbidities and was a non-smoker and teetotaller, with no significant family history of hypertension in the young or inheritable diseases.

Clinically, she had no syndromic features, and her body mass index was 20.3 kg/m^2. Blood cell counts, electrolytes and functional parameters for the liver, kidneys and thyroid were normal. Normal echocardiogram with ejection fraction of 65% excluded coarctation of the aorta or intracardiac shunts. Urine analysis was negative for albumin, red cells and casts. A 24-hour urine excretion of fractionated metanephrines confirmed a raised normetanephrine excretion of 4.2 umol/day [N: <2.13 umol/day]. Urine metanephrine excretion of 0.2 umol/day (N: <1.62 umol/day) and 3-methoxytyramine excretion of 0.4 umol/day (N: 0.1 – 1.79 umol/day) were both normal. Renal Doppler ultrasound reported normal-sized kidneys without arterial stenosis but noted the presence of a suspicious solitary left paraaortic lesion. She was at 15 weeks of gestation and refused computed tomography (CT) imaging for further assessment.

A detailed fetal scan by a feto-maternal specialist at 19 weeks of gestation reported early-onset intrauterine growth restriction with reversed end-diastolic flow on the umbilical artery and middle cerebral arterial. Serial charting on the fetal growth chart showed alarming downward percentile-crossing (Figure 1). Repeated fetal scan at 24 weeks confirmed fetal demise. She underwent second-trimester termination of pregnancy with gemeprost (Cervagem). Psychiatric expert input was sought to help her cope with the traumatic period. Postpartum, her blood pressure

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 7, 2024. Accepted: September 2, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.09

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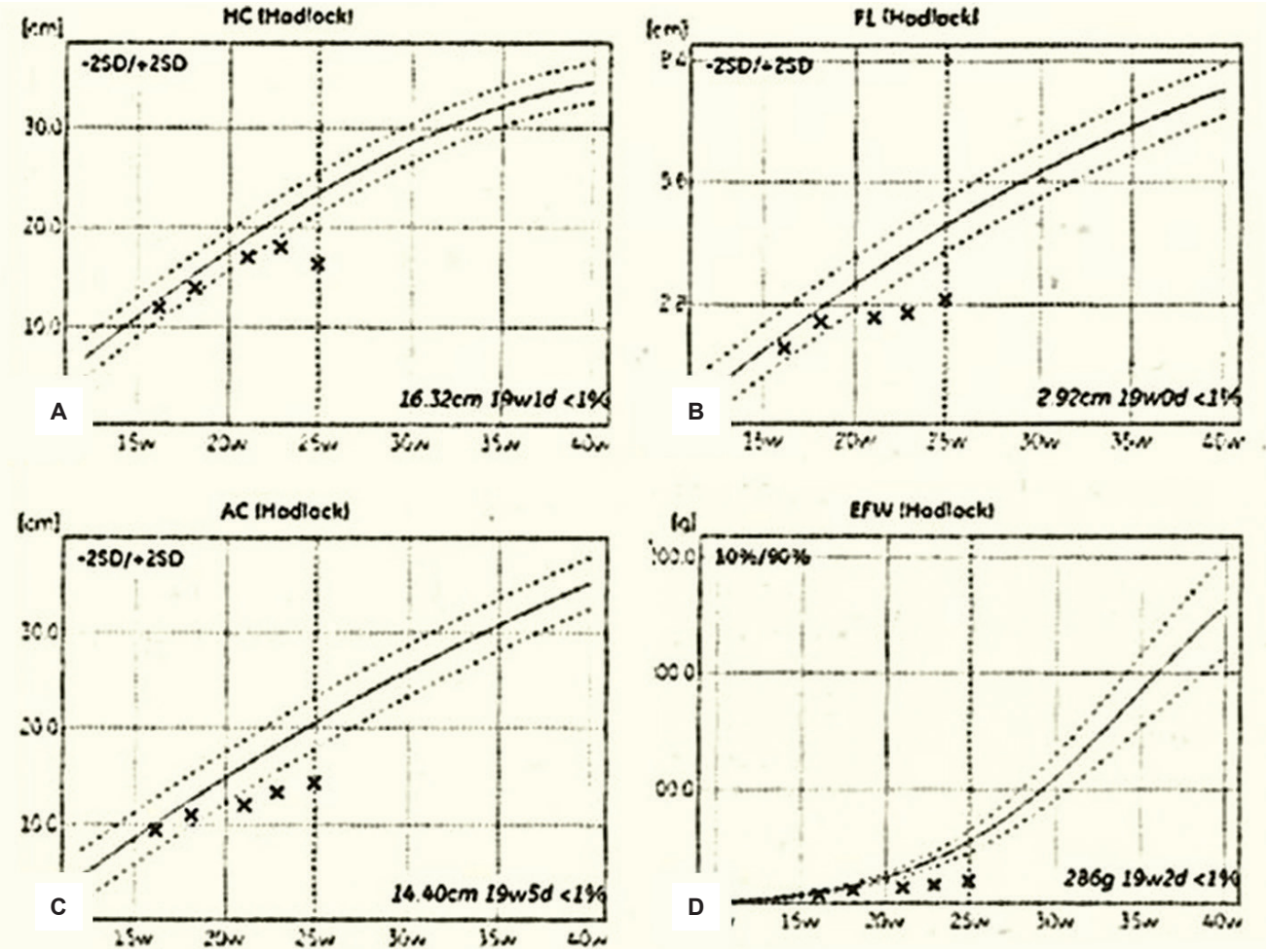

Figure 1. Fetal growth chart for first pregnancy. **(A)** HC – Head circumference; **(B)** FL – femur length; **(C)** AC – Abdominal circumference; **(D)** EFW – estimated fetal weight.

remained labile, ranging from 110 to 182 mm Hg systolic and 86 to 115 mm Hg diastolic.

Subsequently, a contrasted CT scan localized well-defined heterogeneously enhancing retroperitoneal mass or para-aortic lesion measuring 3.6 cm x 4.3 cm x 3.4 cm (AP x W x CC). The iodine-131 metaiodobenzylguanidine (^{131}I-MIBG) scan confirmed the increased tracer uptake at the medial aspect of the left paraaortic mass consistent with the CT scan findings (Figure 2). Unexpectedly, she had a positive urine pregnancy test three weeks later, with an abdominal ultrasound confirming eight weeks of pregnancy. She was on a barrier method of contraception after the first pregnancy loss. Retrospectively, she was already in early pregnancy when she had the MIBG scan, although the urine pregnancy test was negative on the day of the scan.

The nuclear medicine physician, endocrinologist and obstetrician conducted a multidisciplinary meeting amongst themselves. Concerns about radioactive exposure in early pregnancy and risk of pregnancy loss with an unresected paraganglia were discussed. The couple decided on elective termination of the second pregnancy. An intrauterine contraceptive device (IUCD) was inserted after pregnancy termination. She was prescribed phenoxybenzamine, which was titrated up to 20 mg TDS, bisoprolol 5 mg OD and amlodipine 5 mg OD to achieve a target BP of 130/80 mm Hg and heart rate of 80 beats/min prior to her scheduled left paraaortic paraganglioma excision.

During anaesthetic induction, there were BP fluctuations with the highest reading of 171/111 mm Hg and pulse rate of 99 beats/min. A well-encapsulated left paraaortic paraganglioma measuring 5 cm x 5 cm near the bifurcation of inferior mesenteric arteries (IMA) was identified and resected (Figure 3). After tumour removal, she became hypotensive with 66/37 mm Hg, requiring noradrenaline infusion, attributing it to a bleeding from the small IMA tear with an estimated blood loss of 400 ml. Noradrenaline support was discontinued 4 hours post-surgery. She remained normotensive and normoglycemic in the intensive care unit. The histopathological report confirmed extra-adrenal paraganglioma with Ki67 proliferative index of 2% and Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) score of 3. Succinate dehydrogenase (SDHB) immunohistochemical staining was performed and showed retained staining.

Table 1. Comparison on pertinent parameters before and after paraganglioma resection

	Before resection	6 months post resection
Main symptoms	Headache, palpitation, unprovoked nervousness	Intermittent headache
BP range	200-220/100-130 mm Hg	112-128/80-86 mm/Hg
Medications	Phenoxybenzamine 20 mg TDS Bisoprolol 5 mg OD Amlodipine 5 mg OD	None
24 hours urine metanephrine		
Normetanephrine (<2.13 umol/L)	4.2 umol/L (1.97x ULN)	0.20 umol/L
Metanephrine (<1.62 umol/L)	0.2 umol/L	0.10 umol/L
3-Methoxytyramine (<1.79umol/L)	0.4 umol/L	0.20 umol/L

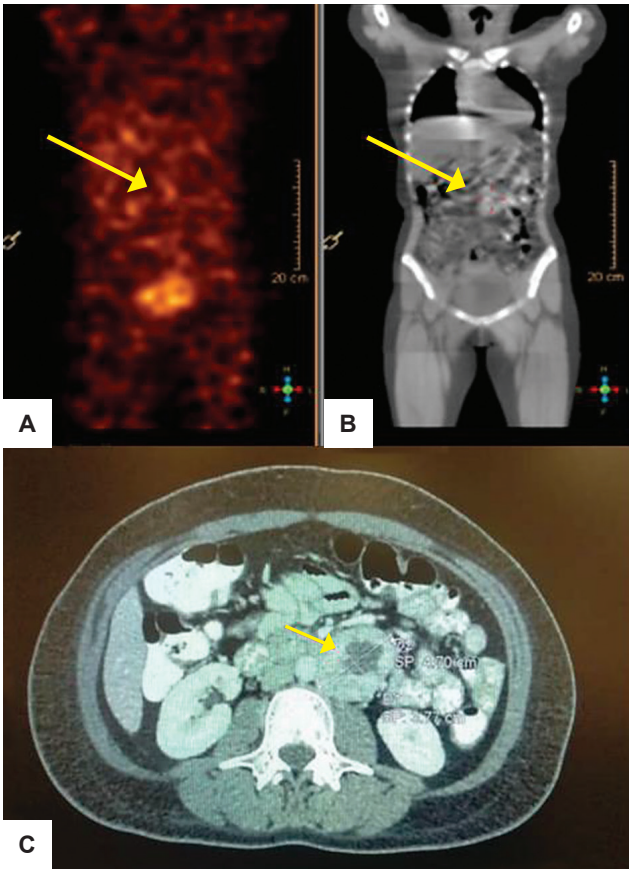

Figure 2. (A, B) ^{131}I-MIBG scan faint focal increased tracer uptake *(yellow arrows)*; **(C)** Cross Section CECT abdomen. Well-defined enhancing mass with central hypodensity at the left para-aortic region *(yellow arrow)*.

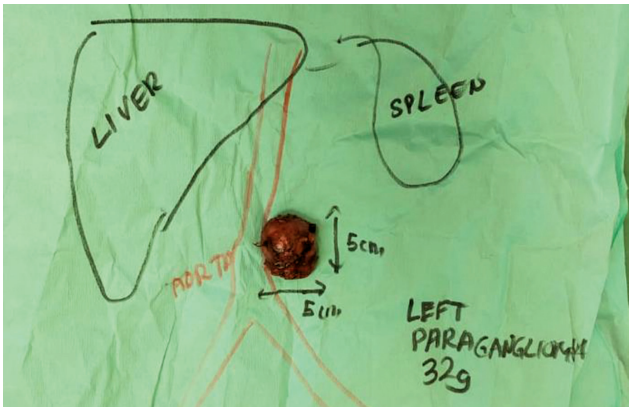

Figure 3. Left paraaortic paraganglioma resected.

Postoperatively, she was well without antihypertensive medication. 24-hour urine metanephrine repeated post-operatively was normal (Table 1). We recommended genetic testing for long-term prognostication. She was co-managed with an obstetrician to optimally prepare for subsequent pregnancies.

DISCUSSION

Diagnosing PPGL in pregnancy requires a high index of suspicion as it is rare but a significant cause of secondary hypertension in pregnancy. Mothers were mostly treated as pregnancy-induced hypertension or pre-eclampsia until recurrent admissions raised suspicion to workup for secondary hypertension (Figure 4). The overlapping features between pre-eclampsia and pheochromocytoma cause a delay in the diagnosis of PPGL in pregnancy.[3] Sustained hypertension diagnosed beyond 20 weeks of gestation associated with milder headache, pedal oedema, proteinuria and liver transaminitis will favour preeclampsia.[3] On the contrary, PPGL should be considered if mothers had paroxysmal hypertension with severe headache, flushing, palpitation and worsening glucose control.[3]

In a large case series of 249 pregnancies with PPGL, they were diagnosed during pregnancy in 134 (54%) patients at a median of 24 weeks gestation.[4] Two-thirds of reported PPGL in pregnancy were unilateral pheochromocytomas, while paragangliomas were primarily localized in the abdominopelvic area.[2,4] Functioning PPGL with higher metanephrine levels leads to more florid signs and symptoms, thus facilitating earlier suspicion and detection. Like our patient, most of them do not have relevant family history.

Fetal mortality was devastatingly high at 54.4% back in the 1970s,[5] but with increasing awareness and early treatment, pregnancy outcomes had improved significantly. In the two systemic reviews, maternal mortality was 4 to 9%, and fetal mortality was 7 to 14% if the condition was diagnosed antepartum.[2,4] However, if left undiagnosed and untreated, maternal and fetal mortality will increase to 29.3% and 25%, respectively.[2]

Excess catecholamine state can cause substantial dysregulation of physiological systems, leading to detrimental multisystemic effects. Pregnancy is a stressful state with

multiple hormonal changes that may worsen the PPGL course of disease. These changes, coupled with the growing fetus in pregnancy, may precipitate acute catecholamine crisis, especially those with abdominopelvic functioning PPGL (Figure 5). However, the placenta acts as a protective barrier for the fetus from the high maternal catecholamine level. Monoamine oxidase and catechol-o-methyltransferase (COMT) activity in the placenta will metabolically inactivate high circulating maternal catecholamine.[6] Dahia et al., found that the cord blood norepinephrine level of a fetus delivered by a mother with pheochromocytoma was only 7% of the mother's norepinephrine level.[7] Thus, fetal compromise is possibly due to haemodynamic changes in the placenta.[7] High circulating maternal catecholamine will induce a profound vasoconstrictive effect on maternal uterine arterial circulation.[8] This effect, coupled with blood pressure fluctuations, will further compromise uteroplacental circulation.[8] Reversed flow on the umbilical

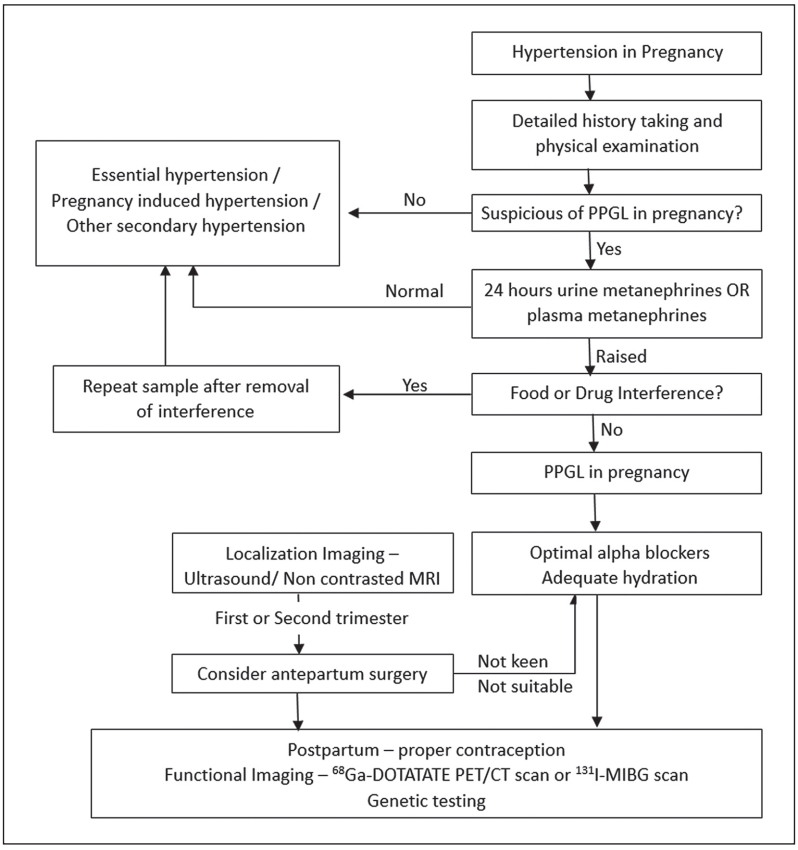

Figure 4. Algorithm of workup for of PPGL in pregnancy.

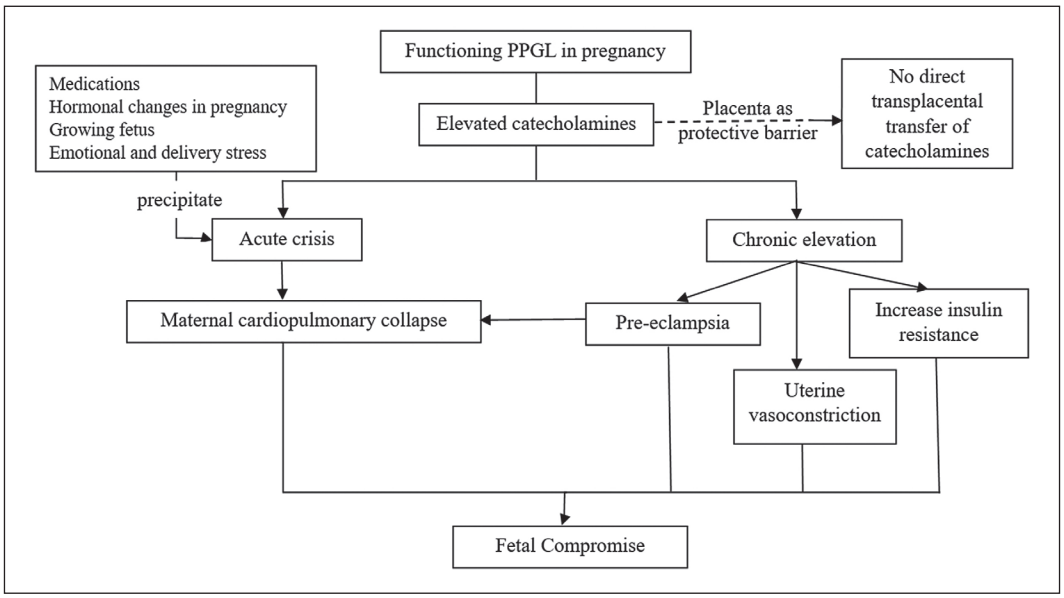

Figure 5. Conceptual framework on effect of functioning PPGL in pregnancy on fetus.

artery, as seen in our patient, is a strong indicator of placental insufficiency, which may translate into stunted fetal growth and eventually, intrauterine death.[9]

Most of the untreated PPGL were diagnosed in primigravida who are otherwise young and healthy.[4] Unfortunately, our patient had her second pregnancy before definitive resection. Elective termination of pregnancy is rarely an option and should only be considered after a multidisciplinary discussion on maternal or the problematic location of pelvic and bladder paragangliomas.[10] Our patient requested the termination of the unplanned pregnancy as she was psychologically stressed from the traumatic first pregnancy and wished for an optimal health condition before embarking on another pregnancy. Furthermore, there was radioactive exposure in early pregnancy when ^{131}I-MIBG was done. Although ^{123}I-MIBG is preferable to ^{131}I-MIBG due to lower energy photon emission and, thus, lower patient radiation, it is not yet available in Malaysia.

CT scan is essential for anatomical localization of PPGL, but radiation exposure is a major concern in pregnancy. Non-contrasted magnetic resonance imaging (MRI) is preferred.[11] Functional studies with various radioisotopes similarly have drawbacks of radioactive risk. ^{68}Ga DOTATATE PET/CT scan has higher sensitivity, higher spatial resolution and lower effective radiation dose, thus superior to ^{131}I-MIBG.[12,13] Radioactive iodine used in MIBG readily crosses the placenta, has a half-life of 8 days and emits gamma rays directly to the maternal bladder to the uterus and embryo.[11] For mothers who were found pregnant after radioactive exposure, it is important to consult medical physicists to estimate in-utero-induced deterministic radiation effects based on the gestation age and reasonable estimate of the absorbed radiation dose.[14]

Genetic testing has revolutionized the precision and holistic management of PPGL, but cost and limited accessibility are the common conundrums faced.[15] Thus, immunohistochemical staining of the tumour is slowly paving its way into clinical practice. SDHB immunohistochemistry had a sensitivity of 94.23% and specificity of 86.67%[16] to screen for SDH gene mutation. The immunoreactivity will be lost in a patient with SDH gene mutation.[16] Thus, retained SDHB immunohistochemical stain in our patient's tumour slides is relieving. Despite that, it is recommended that she be screened with a full PPGL-related genetic panel to facilitate long-term prognostication. Defining her genetic predisposition will allow proper pre-pregnancy genetic counseling.

After two unfortunate fetal losses, our patient was co-managed with an obstetrician team for contraception. Multidisciplinary discussion revealed that surgical resection is the key management.[1] Our patient achieved clinical and biochemical resolution following complete resection of the paraaortic lesion. At least ten years of follow-up is recommended, but in higher-risk patients, lifelong follow-up should be considered.[15] Younger age, larger tumours, familial disease and extra-adrenal tumours are predictors of high recurrence risk[17] No specific guideline recommends the optimal time interval between paraganglioma resection and the subsequent pregnancy. Regardless, proper preparation and close monitoring throughout the next pregnancy shall result in favourable pregnancy outcomes.

CONCLUSION

PPGL in pregnancy is a rare neuroendocrine tumour with potentially deleterious pregnancy outcomes. We reported a 28-year-old female who suffered two pregnancy losses due to PPGL in pregnancy. Early detection and multidisciplinary collaboration are essential. Prior to complete resection and biochemical remission, proper contraception should be emphasized.

Ethical Considerations
Patient consent was obtained before the submission of the manuscript.

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

CRediT Author Statement
WMC: Conceptualization, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Funding acquisition; **ZH:** Conceptualization, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Funding acquisition.

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

A Rare Case of Catecholamine-Secreting Adrenal Myelolipoma

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Abstract

Adrenal myelolipoma (AML) is a rare, benign, asymptomatic, nonfunctioning tumor of the adrenal cortex detected incidentally. AML can be accompanied by several other endocrine disorders simultaneously. Here, we report a case of a 36-year-old female with primary hypothyroidism and metabolic syndrome accompanied by severe hypertension and pheochromocytoma. However, the histopathological examination of the excised adrenal gland confirmed myelolipoma. Following surgery, her plasma nor-metanephrine levels decreased to normal values and the patient became normotensive, which suggested that the mass was functioning.

Key words: adrenal myelolipoma, hypertension, normetanephrine

INTRODUCTION

Adrenal myelolipoma (AML) is a rare, benign, asymptomatic, non-functional, incidentally detected tumor of the adrenal cortex, composed of mature adipocytes and hematopoietic tissue. It was first described by Gierke in 1905 and the term 'myelolipoma' was given by Oberling in 1929.[1] It is sporadic with an overall incidence previously reported to be 0.08%–0.4% on autopsy, but is recently reported to have an increased incidence of 10%–15% due to the widespread use of imaging.[2] Men and women are equally affected with its occurrence being more common between the fifth and seventh decades of life.[2] These lesions are usually unilateral and incidentally detected.[2] A certain number of bilateral tumors have been described in the literature. Myelolipomas are often smaller than 4 cm in diameter but can reach wider sizes.[3] Those measuring more than 10 cm in diameter are termed giant adrenal myelolipomas. The largest adrenal myelolipoma reported in the literature weighed 6 kg and measured 31 cm × 24.5 cm × 11.5 cm.[4,5] Surgical intervention is reserved for patients who attain a substantial size, considering the risk of rupture and retroperitoneal hemorrhage. These tumors can rarely be functional, leading to endocrinopathies.[6,7] Primary hypothyroidism is a relatively common condition in the Indian population, with the prevalence being 11%, compared with only 2%-4.6% in the Western population.[8] As such, there is no common pathogenesis between adrenal myelolipoma and thyroid dysfunction. Hence, the co-occurrence of hypothyroidism and the adrenal mass in our case is likely coincidental. However, certain autoimmune conditions can impact both the thyroid gland and adrenal cortex resulting in combined hormone deficiencies as part of autoimmune polyglandular syndrome type 1 (APS-1).

CASE

A 36-year-old Indian female, known case of primary hypothyroidism for the last 11 years, on levothyroxine (100 mcg daily), with anti-TPO levels suggestive of Hashimoto's thyroiditis (496 IU/ml; N.V. <10 IU/ml), presented with complaints of oligomenorrhea, hirsutism, and weight gain over the last 2-3 years without any cushingoid features. Initial weight before hypothyroidism was 65 kg and her current weight is 80 kg with body mass index is 29.4 kg/m^2. The patient was suspected to have polycystic ovarian syndrome, with ovarian ultrasound and fasting insulin levels consistent with PCOS. She satisfied the criteria for metabolic syndrome according to the NCEP ATP-III criteria (Table 1). She was found to have very high blood pressure readings (200/110 mm Hg) on multiple hospital visits with home BP monitoring values also suggestive of severe hypertension. Retrospectively, she also reported a history of intermittent palpitations, headaches, and sweating for the last 3-4 months. Based on her clinical history, she was evaluated for secondary causes of hypertension. There was no history of adrenal gland disease in any of the patient's family members.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: July 28, 2024. Accepted: August 30, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.15

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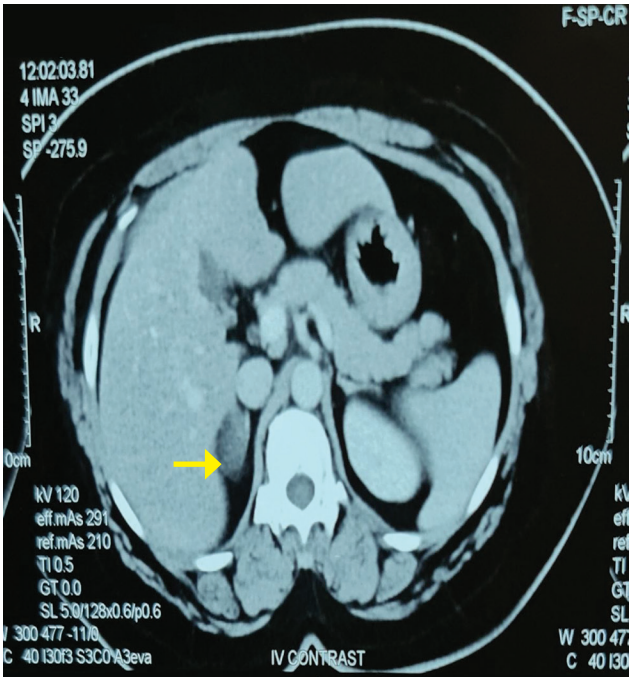

Figure 1. The axial image of computed tomography scan showing a right-sided adrenal mass with fat attenuation value 1 *(yellow arrow)*.

Table 1. NCEP ATP III Criteria for Metabolic Syndrome

Features	Patient's value
Waist Circumference (cm)	96
Fasting Triglyceride Level (mg/dl)	200
Blood Pressure (mm Hg)	200/110
HDL Cholesterol (mg/dl)	40
Fasting Blood Sugar (mg/dl)	95

The patient's serum cortisol after 1 mg overnight dexamethasone suppression test (ONDST) was suppressible (1.0 mcg/dl), and plasma normetanephrine was very high at 836 pg/ml (N.V. <196 pg/ml) with normal metanephrine levels by liquid chromatography with tandem mass spectrometry method (samples were obtained with protocol). The patient was not on any medication or diet which might have raised catecholamine levels. Her potassium level was normal (3.8 meq/L) with normal plasma aldosterone level and normal plasma renin activity (PRA). Her testosterone and dehydroepiandrosterone sulfate (DHEAS) were within normal limits. Contrast-enhanced computed tomography (CECT) of the abdomen showed a right-sided well-defined ovoid hypodense lesion with enhancing soft tissue components arising from the right adrenal gland measuring 3.1 x 1.8 x 1.3 cm with few coarse calcifications and fat attenuation value of 1 with normal left adrenal gland (Figure 1). Therefore, a diagnosis of pheochromocytoma was considered and the patient was shifted to prazosin (alpha-blocker). After achieving adequate alpha blockade, metoprolol (beta blocker) was added for controlling tachycardia.

The patient underwent right adrenalectomy via laparoscopic transperitoneal approach. The descending colon was

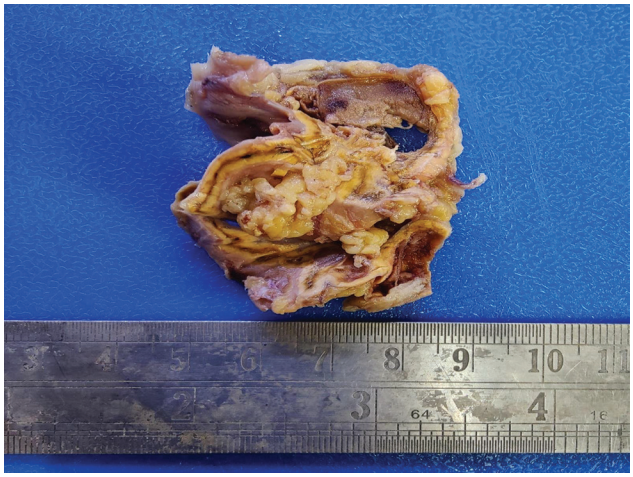

Figure 2. Gross specimen. Compressed adrenal at the periphery with fatty tissue in the center with specks of dark brown area.

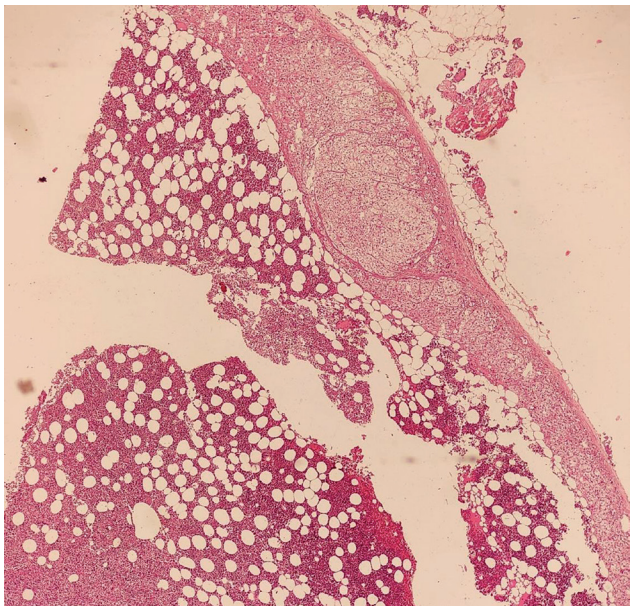

Figure 3. Compressed adrenal parenchyma at periphery, the center of the lesion showing cellular lesion with entrapped adipocyte [Hematoxylin & Eosin (H & E), 4X].

mobilised, and the left renal vein was identified. The adrenal vein was clipped and divided. The mass was separated from the upper pole of the kidney and its lateral attachments using blunt and sharp dissection. There were no significant blood pressure fluctuations intra-operatively.

The patient did not require antihypertensive therapy after surgery, and plasma normetanephrine returned to normal (156 pg/ml) after 10 days of surgery. Gross and histopathological examination revealed myelolipoma (Figures 2–4) with no evidence of pheochromocytoma or medullary hyperplasia with negative chromogranin A staining. These features suggested that the mass was functioning and secreting catecholamine. She remains normotensive without treatment in the follow-up of three months after surgery.

Table 2. Comparison Between Index Case and other Case Reports

Features	Tamidari H et al.	Udupa S et al.	Jakka N et al.	Jindal T et al.	Adapa S et al.	Index Case
Age (Years)	48	58	40	55	40	37
Gender	Female	Male	Male	Female	Male	Female
Side of Tumor	Right	Left	Right	Left	Right	Right
Chief Complaints	Right upper quadrant discomfort, Anxiety attacks with sweating x 45 days	Left Hypochondrium and Left Lumbar pain, BP - 170/110	Hypertension, Adrenal mass	Heaviness in Left Flank	Testicular and Bilateral pedal edema, BP -234/119	Oligomenorrhoea, Hirsutism, Weight gain for 5 years, Episodic paroxysm x 4 months
Past History	Hypertension x 12 years, Controlled on Beta blocker	Diabetes Mellitus, Sustained Hypertension on treatment	Hypertension x 3 years (on treatment)	Hypertension x 2 years controlled on treatment	Hypertension, Chronic Kidney Disease, Morbid obesity, Adrenal mass	Primary hypothyroidism x 8 years
Imaging Findings	11 x 10.5 x 7 cm, well encapsulated, non homogenous, low density (-100 to -200 HFU) suggestive of (s/o) Right Adrenal Mass	18.4 x 10.1 x 9 cm, intermixed area of fat and mildly enhancing soft tissue component s/o left adrenal myelolipoma	9.8 x 8.5 cm, well defined, heterogenous, low density (-80 to -100 HFU) s/o Myelolipoma	10 x 8 x 6 cm, supra renal hypoattenuating mass with macroscopic fat s/o Adrenal Myelolipoma	9.7 x 7.7 x 6.1 cm, hypoattenuating right adrenal mass with attenuation value is 0	3.1 x 1.8 x 1.3 cm, well defined hypodense lesion with enhancing soft tissue component with areas of fat attenuation, Average attenuation value is 1
Investigations	24 hour urine metanephrine increased	24 hour urinary vanillylmandelic acid increased	24 hour urine metanephrine increased	24 hour urinary metanephrine increased	norepinephrine and dopamine increased	Plasma free Normetanephrine increased
Post op value	Normal	Normal	Normal	Normal	Not mentioned	Normal
Post op BP	Normal	Normal	Normal	Normal	Not mentioned	Normal
Biopsy	AML	AML	AML, Chromogranin A +ve	AML	AML	AML, Chromogranin A -ve

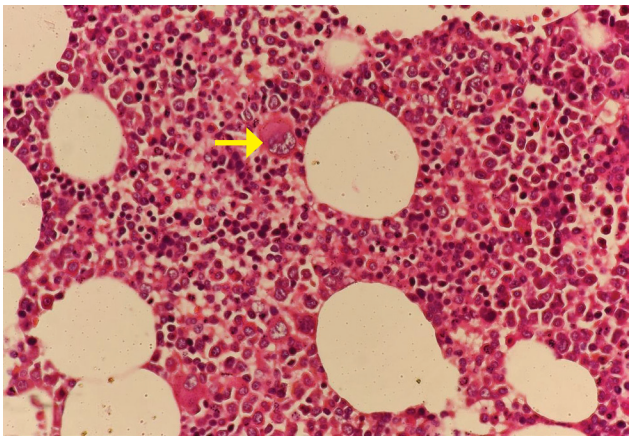

Figure 4. Hematopoietic element comprising megakaryocytes *(yellow arrow)* and erythroid colonies [H & E, 40 X].

DISCUSSION

Adrenal myelolipoma is a nonfunctional benign neoplasm that originates from the adrenal cortex and comprises mature fat and hematopoietic elements. The exact etiology is unknown, but it has been postulated that the lipomatous elements originate from the fat-containing mesenchymal stromal cells of the adrenal cortex, whereas the hematopoietic elements are derived from the reticuloendothelial cells of the blood capillaries. Cross-sectional imaging by computed tomography or magnetic resonance imaging can confirm the diagnosis due to presence of macroscopic and microscopic fat with negative attenuation value with or without calcification. These tumors are considered non secretory, and functional evaluation was not considered mandatory during their work up.[6,7,9] However, this recommendation has been questioned. In a review of the literature, it was observed that nearly 7% of adrenal myelolipomas may be functionally active.[7] The majority of these 'functional myelolipomas' were associated with hypercortisolemia followed by hyperaldosteronism. AML can coexist with other endocrine disorders like Cushing syndrome, congenital adrenal hyperplasia (CAH), primary aldosteronism, and pheochromocytoma. To the best of our knowledge, only seven cases of adrenal myelolipomas have been reported which were associated with catecholamine secretion (Table 2).[7,9-13]

It is interesting to note that all of these patients had giant adrenal masses (>10 cm),[14] but in our case, it is smaller. In our case report, 24-hour urine catecholamine was not measured but we have surrogate evidence that the AML was functional with a >4 times increase in plasma normetanephrine level which was very unlikely to be a false positive result. Also, following surgical excision, the levels decreased to normal. Though the blood pressure normalized after surgery, long-term monitoring by assessing plasma normetanephrine and metanephrine levels annually has been planned. Congenital adrenal hyperplasia has been reported with AML due to chronic adrenocorticotropic hormone (ACTH) stimulation of the adrenal glands.[15] Comorbidities like hypertension, obesity, diabetes mellitus, atherosclerosis, and malignancy have been associated with AML.[16] Few hypotheses have been postulated for the presence of hypertension in a patient with adrenal myelolipoma which include mechanical compression on the renal vessels by the tumor, mechanical irritation of myelolipoma, hemorrhage within the tumor, cortisol or aldosterone hypersecretion

and rarely due to catecholamine hypersecretion, as in the index case. Endocrine workup is beneficial in AML patients with hypertension, in younger patients, in persons with diabetes mellitus or prediabetes, and those with bilateral AML.[7] Thyroid stimulating hormone (TSH) might rise a little in obese patients due to high leptin levels and inflammatory cytokines levels which improve after weight loss.[17] Obesity has been associated with AML but there is no correlation between AML dysfunction and thyroid dysfunction.[16] Genetic studies could not be done due to financial constraints in this index case.

CONCLUSION

Adrenal myelolipoma with hypertension may not be coincidental, it may be due to catecholamine secretion. This case highlights the importance of a detailed workup for adrenal myelolipoma.

Acknowledgments
We would like to acknowledge those who have provided technical help, writing assistance and made sure this case is publishable.

Ethical Consideration
Patient consent forms were obtained before manuscript submission. The potential life-threatening nature of the lesion was explained to the patient and she agreed to surgery.

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

CRediT Author Statement
VJ: Conceptualization; Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **AA:** Conceptualization, Writing – review and editing, Visualization, Project administration; **BK:** Writing – review and editing; **PS:** Writing – review and editing, Supervision; **HG:** Writing – review and editing, Supervision

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

Bilateral Pheochromocytoma with a Novel Pathogenic Variant in the MAX gene: A Case Report

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Abstract

Pheochromocytomas and paragangliomas syndrome are grouped into three specific disease clusters based on their underlying genetic alterations. Pathogenic variants affecting the myelocytomatosis-associated factor X (MAX) gene predispose pheochromocytomas and paragangliomas syndrome to occur at younger ages, with more than half having bilateral pheochromocytomas. We report a case of bilateral pheochromocytomas with a novel pathogenic variant identified in the MAX gene (c.234_235dup). This young male was found to have a huge left suprarenal mass after he presented with severe hypertension and myocardial infarction. His endocrine workup confirmed a diagnosis of pheochromocytoma as evidenced by elevated levels of normetanephrine, metanephrine, and 3-methoxytyramine in the urine. CT of the adrenal glands revealed bilateral adrenal masses; the widest diameter for the left adrenal mass was almost 8 cm whereas for the right one was 2 cm. ^{68}Gallium-DOTATATE functional imaging showed significant uptake in the left adrenal mass, but indeterminate on the right, and no significant uptake was seen elsewhere to suggest metastatic lesions. He did not have syndromic features associated with multiple endocrine neoplasia, neurofibromatosis or von Hippel Lindau disease. The collective findings raised the clinical dilemma of whether unilateral or bilateral adrenalectomy should be pursued. The detection of pathogenic MAX gene was therefore crucial in guiding personalized treatment strategy. Following the bilateral adrenalectomy, his hypertension was cured. Annual biochemical screening and 2-yearly MRI imaging to look for recurrence of pheochromocytomas were planned according to international consensus.

Key words: hypertension, pheochromocytoma, genetic predisposition to disease, adrenalectomy

INTRODUCTION

The understanding of the genetic pathophysiology of pheochromocytomas and paragangliomas (PPGLs) syndromes has advanced significantly over the last two decades. More than 20 driver genes have been discovered in either the disease's hereditary or sporadic form.[1] The eponym "ten percent tumour" derived from the belief that 10 % of PPGLs are familial has since become obsolete. In fact, forty percent of PPGLs cases are hereditary in origin and they are typically present at a young age. The Cancer Genome Atlas (TCGA) has classified PPGLs into three distinct molecular clusters namely pseudohypoxic PPGLs (cluster 1), kinase-signaling PPGLs (cluster 2), and Wnt-signaling PPGLs (cluster 3).[2,3] Hereditary proportions of Cluster 2 PPGLs are approximately 20% and the driver genes classified under this group include RET, NF1, MAX, and TMEM127.[3] Each cluster has a unique molecular-clinical-biochemical-imaging phenotype, which can be used to facilitate personalized treatment strategy for individuals with PPGLs.[2,3]

CASE

A 28-year-old Malay male was found to have severe hypertension during dental scaling. Unfortunately, he did not continue treatment for hypertension. Four months later, he was hospitalized for non-ST elevation myocardial infarction with supraventricular tachycardia. The echocardiogram showed a good left ventricular ejection fraction with some septal wall hypokinesis, otherwise, there were no features of cardiomyopathy. Coronary angiography findings were normal. Renal Doppler scan was negative for renal artery stenosis; however, a large left suprarenal mass was discovered. He was then referred to the endocrine team for further management.

This patient did not recall significant hyperadrenergic spells to suggest PPGLs. He reported no family history of multiple endocrine neoplasia (MEN) or von Hippel Lindau (VHL) syndrome among his parents and siblings. Endocrine workup revealed significantly elevated urine fractionated metanephrines with the presence of dysglycemia (Table 1). His thyroid ultrasonography and retinal examination were normal. Contrast-enhanced computed tomography (CT) of the adrenal glands reported a huge left suprarenal mass

eISSN 2308-118x (Online)
Printed in the Philippines

Received: September 25, 2024. Accepted: October 19, 2024.
Published online first: April 29, 2025.
https://doi.org/10.15605/jafes.040.01.16

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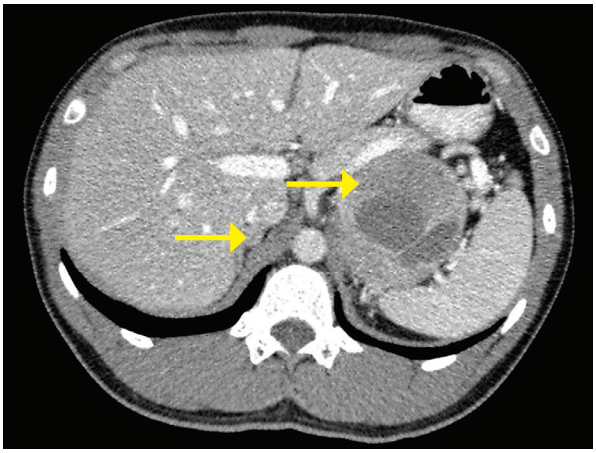

Figure 1. Axial view of the contrasted adrenal-directed CT during the venous phase showed bilateral adrenal masses of lipid-poor content, measuring in size [left: 7.1 x 7.5 x 7.4 cm; right: 2.0 x 1.1 x 1.8 cm] *(yellow arrows)*.

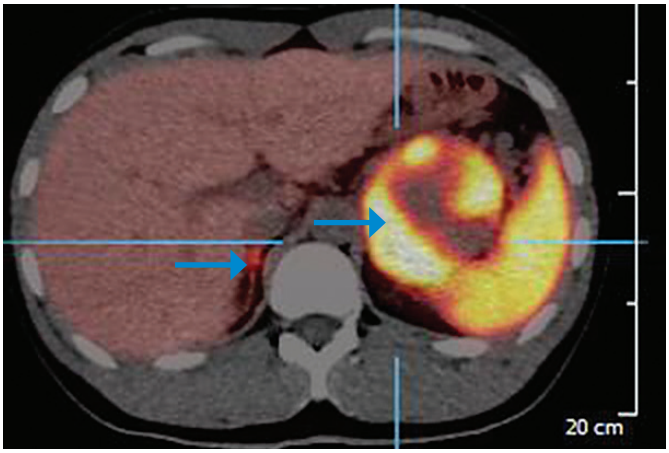

Figure 2. Axial view of the ^{68}Gallium-DOTATATE PET-CT showed an avid left adrenal mass (SUVmax 45.0) with necrotic centre whereas the right adrenal nodule was still within the physiological uptake (SUVmax 19.6) *(blue arrows)*.

Table 1. Biochemical results

Investigations	Initial diagnosis	6 months after surgery	Reference range
24-hour urine metanephrine			
Normetanephrine (µmol/day)	30.8	1.8	0 – 2.13
Metanephrine (µmol/day)	38.8	0.1	0 – 1.62
3-methoxytyramine (µmol/day)	6.5	0.9	0.1 – 1.79
Serum cortisol after overnight dexamethasone suppression test (nmol/L)	21.0	Not Relevant	<50
Fasting plasma glucose (mmol/L)	7.6	4.6	3.9 – 6.0
Glycated hemoglobin (%)	6.4	4.7	≤5.6

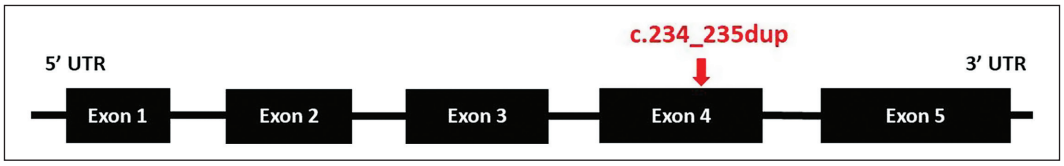

Figure 3. Schematic diagram of MAX gene mutation in the patient. UTR, untranslated region.

with mixed areas of central haemorrhage, necrosis, and cystic components measuring 7.1 x 7.5 x 7.4 cm (anterior-posterior x width x cranio-caudal)]. There was another smaller lipid-poor adenoma found in the right adrenal gland (Figure 1). Next, ^{68}Gallium-DOTATATE positron emission with computed tomography (PET-CT) showed significant uptake in the left adrenal mass, but indeterminate on the right (Figure 2). There was no evidence of nodal involvement or distant metastasis.

Our clinical dilemma was whether both adrenal lesions were pheochromocytomas (PCCs). We explained to the patient the role of genetic screening for hereditary PPGLs syndrome in facilitating the decision-making process during the multidisciplinary team meeting. He agreed and consented to genetic testing in an overseas genetic laboratory. Saliva sample was collected and exported to Invitae Laboratory, an accredited genetic laboratory based in the United States. Next-generation sequencing-based technique was used, targeting 14 genes susceptible to hereditary PPGLs. In this panel genes, EGLN1, FH, KIF1B, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, and VHL were covered. His genetic study identified a variant c.234_235dup (p.His79Profs*92), a sequence change that resulted in a frameshift mutation in the MAX gene (Figure 3). The genetic report explained that the variant would disrupt the last 82 amino acids of the MAX protein and extend the protein by 9 additional amino acid residues. Furthermore, this variant interrupts a region of the MAX protein in which other variants (p.Gln97*) have been determined to be pathogenic, further supporting this is a clinically significant region of the protein, for which the disruption caused by the variant would generate a pathogenic process. This is also a variant that was not previously registered in the population databases. Invitae Laboratory submitted this novel finding to the ClinVar registry, the public archive of the reports of the relationships among human variations and phenotypes curated by the National Center for Biotechnology Information (NCBI).

Following the multidisciplinary team discussion, bilateral adrenalectomy was proposed to the patient. Before the

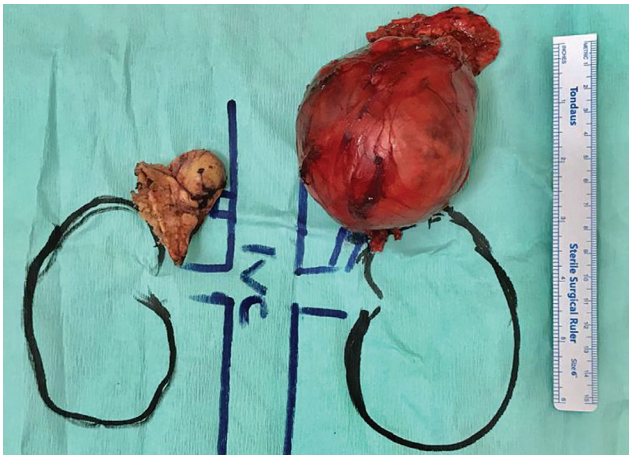

Figure 4. The gross specimen showed a huge, well-encapsulated left adrenal mass and a smaller right adrenal nodule.

surgery, he received combined alpha- and beta-adrenergic blockade using phenoxybenzamine and metoprolol. The right adrenal gland with the smaller nodule was first removed laparoscopically via a retroperitoneal approach. Then, the left adrenal gland and tumour were resected by open laparotomy (Figure 4). Pathology examination confirmed both adrenal masses were PCCs with benign histological characteristics. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) for the left PCC was 2/20, and for the right PCC was 0/20.

He was discharged home a week after the surgery, with hydrocortisone and fludrocortisone replacement. Six months later, repeated CT scan did not show any evidence of recurrence, and 24-hour urine for catecholamines was within normal limits (Table 1). He was advised for lifelong follow-up and an MRI from the base of the skull to the pelvis was scheduled in two years. Among the immediate family members, only his elder brother consented to do genetic testing, and he tested negative for MAX gene mutation.

DISCUSSION

PPGLs are a rare secondary cause of hypertension, accounting for only about 0.3 % of cases.[4] Untreated disease often leads to cardiovascular morbidity, as seen in our case. According to the 2014 Endocrine Society guideline, clinical scenarios that prompt evaluation for PPGLs include patients presenting with hyperadrenergic symptoms, symptoms provoked after using medications associated with adverse effects, incidental lipid-poor adrenal adenomas, hereditary predisposition or syndromic features suggesting hereditary PPGLs.[5]

Bilateral PCCs are uncommon, comprising 7–10 % of PPGLs.[6] Between 60 – 90% of bilateral PCCs harbor a germline mutation.[6] They are particularly associated with MEN type 2A and type 2B, in families with neurofibromatosis type 1 and VHL disease or in patients with MAX and TMEM127 gene mutation.[6] Additionally, bilateral PCCs can manifest either as synchronous or metachronous lesions, creating further clinical challenges for surgical technique planning and future tumour surveillance.

There is scarce data depicting the genetic landscape of PPGLs in our country due to limited access to genetic screening. As one of the major referral centers for PPGLs, findings from our research conducted in the year 2013 revealed two of twenty-four patients with non-syndromic features of PPGLs had bilateral PCCs and both carried a pathogenic mutation in the VHL gene.[7] Other gene mutations identified in this cohort were RET, SDHB, SDHA, and KIF1B. More recently, Burciulescu et al., reported that 14 out of 112 PPGLs patients in their series were bilateral PCCs, and most carried RET and VHL mutations.[6] It is therefore noteworthy to highlight the rarity of bilateral PCCs associated with MAX gene variants in the current literature.

Germline mutation affecting the MAX gene (five exons, located on chromosome 14q23) was first identified in 2011 as one of the causes of hereditary PPGLs.[4] MAX encodes a component of the MYC/MAX/MXD protein signaling pathway which are essential for regulating cell proliferation, differentiation, and apoptosis.[4] It exhibits an autosomal dominant inheritance with preferential paternal transmission of the disease.[4] Thus far, 58 cases have been described with 29 different germline mutations.[8] Mutations include missense in 38 %, nonsense mutations in 46 %, and splice site or frameshift mutations in 16 % of patients.[8]

Although the mean age at diagnosis is 32 years, 21 % of patients are diagnosed at pediatric age.[1] Considering the enormous size of the left PCC, our patient most likely developed the tumour at a much younger age as well. Mutations in MAX gene are associated with a distinctive biochemical profile with elevated levels of normetanephrines and normal or slightly increased levels of metanephrines.[9] This is, however, different from what was observed in our patient, which demonstrated hypersecretion of normetanephrines, metanephrines and 3-methoxytyramines. Interestingly, Daly et al., also reported a young male without apparent family history had markedly elevation for plasma epinephrine and norepinephrine; and urinary norepinephrine, normetanephrine and vanillyl mandelic acid levels.[10] Suffice it to say, further research would be needed to clarify the secretory phenotypes of PCCs associated with MAX gene mutations.

Fifty percent of PCCs related to germline MAX mutation manifest as bilateral disease.[4] The rate of metastatic disease is difficult to define given the low incidence of MAX mutation (<2 % of PPGLs).[1] Nonetheless, the case series reported by Burnichon et al., found two of twenty-three cases (8.7 %) having metastases.[10] Apart from bilateral PCCs, pituitary neuroendocrine tumours (NETs), pancreatic NET, erythrocytosis, and renal oncocytomas have also been described.[1,8]

A recent meta-analysis involving 1444 patients with bilateral PCCs concluded that partial adrenalectomy offers a chance of preserving adrenal hormone function but is associated

with a higher risk of local tumour recurrence.[11] There was no difference in the risk of metastasis and overall mortality among the group with bilateral PCCs undergoing total or partial adrenalectomy.[11] These findings will facilitate the shared decision-making process between the patient and the multidisciplinary team. Our patient underwent bilateral total adrenalectomy after considering the tumor size, the risk of recurrence, and metastasis.

Expert consensus suggested patients with any of the following criteria should undergo lifelong follow-up: germline mutation, age less than 20 years at initial diagnosis, tumour size of at least five centimeters, multiple or recurrent PPGLs, history of PGL, or noradrenergic/dopaminergic phenotype.[12] Screening with annual biochemical testing and full-body MRI imaging from the skull base to the pelvis every two years are therefore recommended for our patient. MRI is superior to CT imaging for identifying extra-adrenal tumours and minimizing radiation exposure for patients who require lifelong follow-up.[12]

The main limitation of this case report would be the lack of genetic screening for all immediate family members, which will further establish the germline status of his MAX gene variant. On the contrary, Burnichon et al., analysed 245 PCCs tumours in their case series and found 4 cases (1.65 %) carrying a mutation that was confirmed as somatic, which was supported by an absence of mutation in the germline DNA.[10] Greater public awareness is needed to promote the inferred benefit of genetic screening for this intriguingly rare, yet highly heritable endocrine tumour.

CONCLUSION

In the era of precision medicine, genetic screening of PPGLs is fundamental to ensure optimal outcomes for the patient and their immediate family members. Our case has also highlighted the importance of managing PPGLs in a specialized center dedicated to the diagnosis, treatment, and surveillance of this rare syndrome. Lastly, all patients with a history of PPGLs require a lifetime, individualized follow-up schedule according to their mutation status and disease characteristics.

Ethical Consideration
Patient consent forms were obtained before manuscript submission.

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

CRediT Author Statement
CKL: Conceptualization, Writing – original draft preparation, Visualization; **KK:** Writing – original draft preparation, Visualization; **ABN:** Conceptualization, Writing – review and editing; **ZH:** Conceptualization, 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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Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

A Tumultuous Journey of Metastatic Pancreatic Neuroendocrine Tumor with Carcinoid Syndrome

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Abstract

A 25-year-old woman presented with metastatic pancreatic neuroendocrine tumor with carcinoid syndrome. She was refractory to octreotide and did not respond well to chemotherapy. Although surgical debulking remains the primary approach for managing these tumours, it entails inherent risks, including potentially exacerbating carcinoid syndrome. We strategically delivered the one Peptide Receptor Radionuclide Therapy cycle before tumor debulking, a decision that yielded a remarkable response, stabilizing her condition.

Key words: pancreatic neuroendocrine tumor, metastatic, octreotide refractory, peptide receptor radionuclide therapy, norepinephrine

INTRODUCTION

Pancreatic neuroendocrine tumors (pan-NETs) present a formidable challenge in clinical practice, particularly when metastatic. We present the case of a patient with metastatic pan-NET, whose clinical course and management were determined after thorough deliberation and discussion within the framework of a multidisciplinary team.

CASE

A 25-year-old woman was doing well until 2019 when she noticed facial flushing followed by dry cough, vomiting and diarrhea that lasted for 4-5 hours, suggestive of carcinoid syndrome. These episodes happened 3-5 days a week. A computed tomography (CT) scan of the abdomen was done, which showed a well-defined heterogenous arterial enhancing mass of 7.2 x 5.3 cm in the body and tail of pancreas suspicious of NET with metastasis to the liver, periportal lymph nodes and T10 vertebra, as shown in Figure 1. Laparoscopy guided biopsy of pancreatic mass revealed a well-differentiated Grade 2 NET with MIB-1 index of 12%. She was started on a monthly injection of octreotide LAR 30 mg. However, her symptoms recurred 18 days after treatment. After medical oncology consultation, everolimus was added to octreotide. Her symptoms were well controlled for almost a year, however, she began experiencing carcinoid syndrome episodes again. Everolimus was discontinued, based on its waning efficacy. Repeat liver biopsy showed a MIB-1 index of 30%, suggestive of tumour progression to Grade 3, and O6-Methylguanine-DNA Methyltransferase (MGMT) staining was positive.

She underwent a successful transarterial embolization (TAE) of the liver via the right hepatic artery, which precipitated a carcinoid crisis. Considering the higher grade of the tumour and MGMT methylation status, she was given sunitinib, temozolomide and capecitabine. However, these were discontinued after four cycles as her quality of life did not improve.

At this point, she transferred to our institution and had ^{18}Fluro deoxyglucose positron emission tomography (^{18}FDG-PET/CT) and ^{68}Ga DOTATATE PET/CT done (Figure 2). Following the scan, she developed a carcinoid crisis that progressed to acute kidney injury (Figure 3). She was put on octreotide infusion, which was gradually increased to 200 mcg/hour, and she recovered over 3 days. However, she suffered two more crises within a week despite being on daily short-acting octreotide. A multi-disciplinary team (MDT) comprising experts in Surgical-gastroenterology, Medical-Oncology, Endocrinology and Nuclear Medicine was constituted to develop a comprehensive management protocol. It was decided that one cycle of peptide receptor radionuclide therapy (PRRT) would be given, followed

eISSN 2308-118x (Online)
Printed in the Philippines

Received: May 28, 2024. Accepted: July 7, 2024.
Published online first: April 20, 2025.
https://doi.org/10.15605/jafes.040.01.04

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by surgical debulking and three more cycles of PRRT. Lu^{177} DOTATATE 150 mCi was given. She responded well after the first PRRT and successfully underwent a repeat TAE of the right hepatic artery two weeks later. The following week, she was taken for surgery with short-acting octreotide infusion started 24 hours prior to the procedure. Despite that, several carcinoid spells occurred during tumour manipulation. During resection of liver metastasis, she developed profound hypotension (70/40 mm Hg). She was stabilized with noradrenalin infusion, and pancreatic masses were removed (Figure 4). After ligating the pancreatic vessels, her blood pressure improved significantly, indicating no release of hormonal mediators further into the circulation. At the end of surgery, both octreotide and noradrenalin were stopped. She has not developed any further episodes of carcinoid crisis following surgery, and she has subsequently received three cycles of PRRT. A follow-up DOTATATE scan showed evidence of metastasis only in the T10 vertebra and periportal lymph nodes, as depicted in Figure 5. She remains stable and

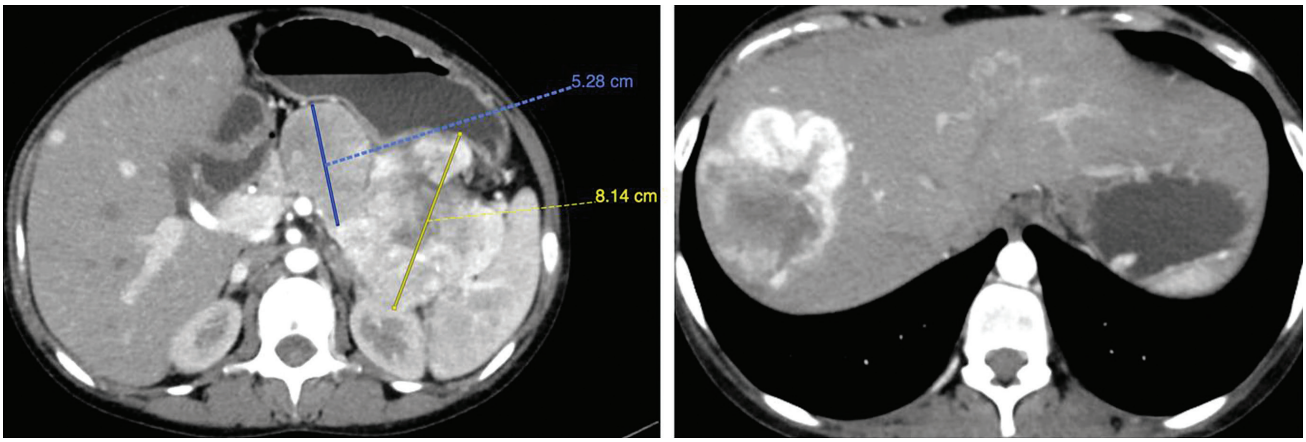

Figure 1. Triphasic CT shows lobulated, heterogenous, hyperenhancing partly exophytic focal lesion with central hypodense area with necrosis without calcification involving distal body and tail of pancreas. An irregular hyperenhancing focal lesion with central necrosis noted in segment 7/8 of liver. Few tiny well defined hyperattenuating lesions also noted in segments 6 and 4.

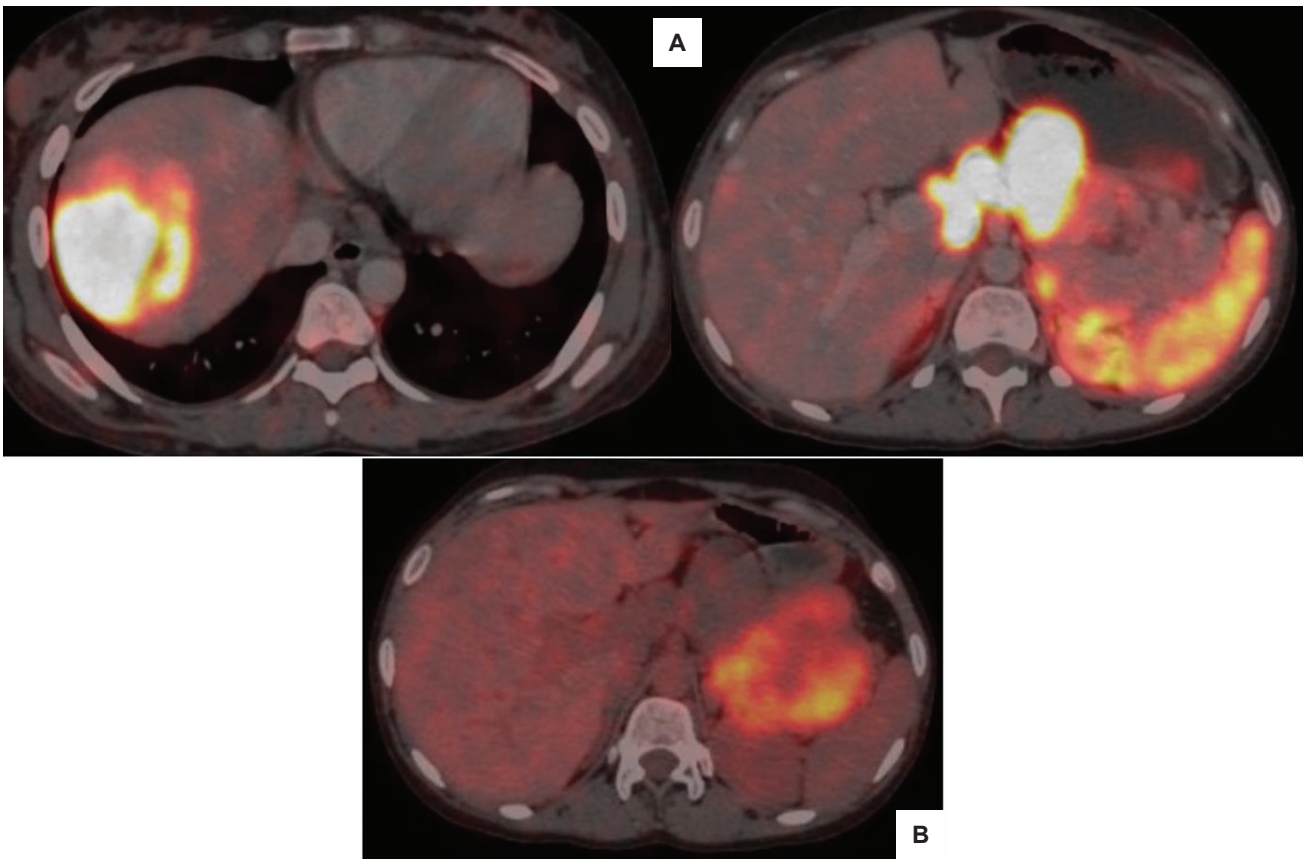

Figure 2. (A) ^{68}Ga DOTATATE PET/CT image before surgery shows avid uptake seen in segment 8 of liver and pancreatic head and body; **(B)** ^{18}FDG-PET/CT image before surgery shows uptake is present in mass in tail of pancreas.

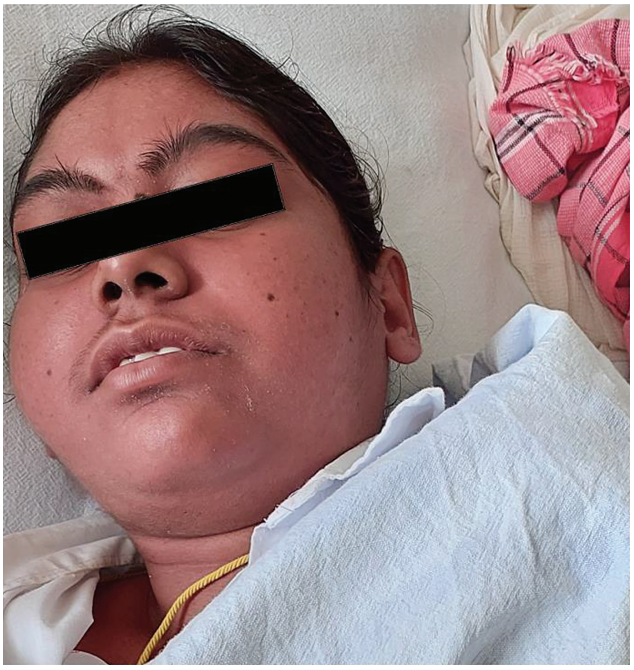

Figure 3. Clinical picture of carcinoid syndrome showing with facial flushing and erythema.

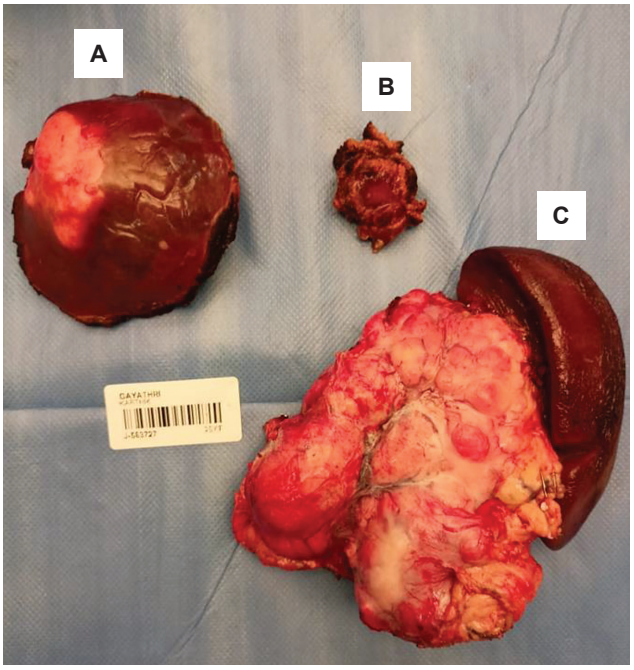

Figure 4. She underwent non anatomical resection of liver. **(A)** Liver segment 8; **(B)** Liver segment 2; **(C)** Distal pancreatico-splenectomy specimen.

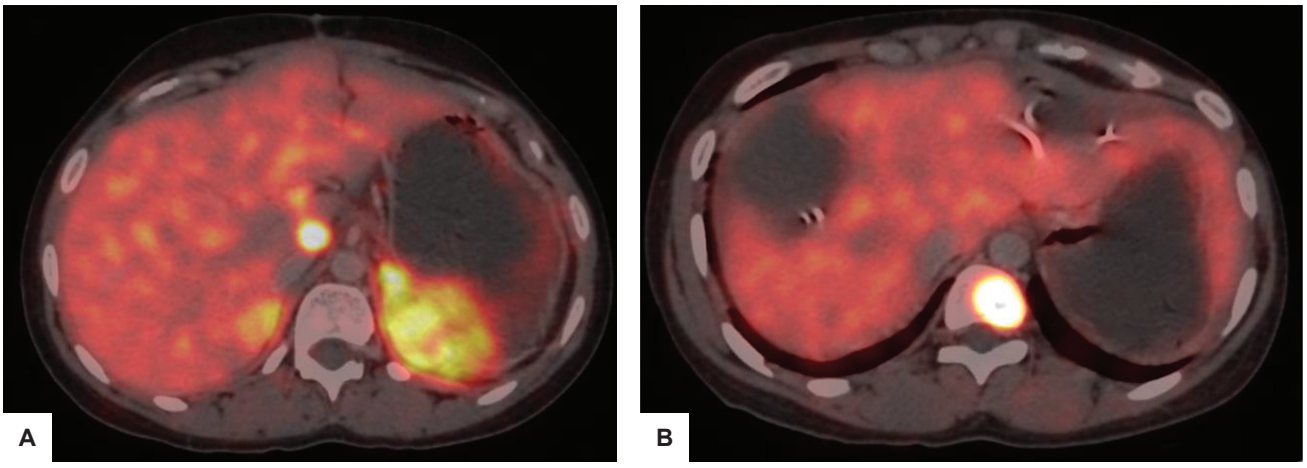

Figure 5. Follow up ^{68}Ga DOTATATE PET/CT scan after surgery. **(A)** Scan shows avid uptake in Periportal lymph node; **(B)** Avid uptake in D10 vertebra.

asymptomatic. The timeline of treatment is shown in Figure 6.

DISCUSSION

Pancreatic NETs present formidable obstacles to curative surgical interventions because they are often diagnosed in advanced stage with widespread metastases. Somatostatin analogues (SSAs) emerge as invaluable palliative agents, mitigating hormonal hypersecretion and reducing tumor burden. Therefore, the European Neuroendocrine Tumor Society advocates its use as initial therapy. However, our patient gradually deteriorated despite being on octreotide. PRRT and targeted molecular therapies are typically reserved for these SSA refractory cases.[1] At the molecular level mTOR pathway stimulates cell growth and it is aberrantly activated in NETs. Everolimus exerts antineoplastic effect by inhibiting the mTOR pathway. The latest European Society for Medical Oncology guidelines endorse the use of everolimus in Pan-NETs considering its synergistic benefit with SSAs.[2] Although she initially responded to this combination for almost a year, recurrence happened due to exhaustion of the antineoplastic effect of everolimus, which is a known fact. Long-term disease control seems achievable by integration of surgery and targeted molecular therapies. Surgery and PRRT can be combined in various clinical situations, such as in neoadjuvant settings for initially unresectable NETs or adjuvant settings to reduce recurrence risk following major surgery. PRRT is a targeted radiation therapy that

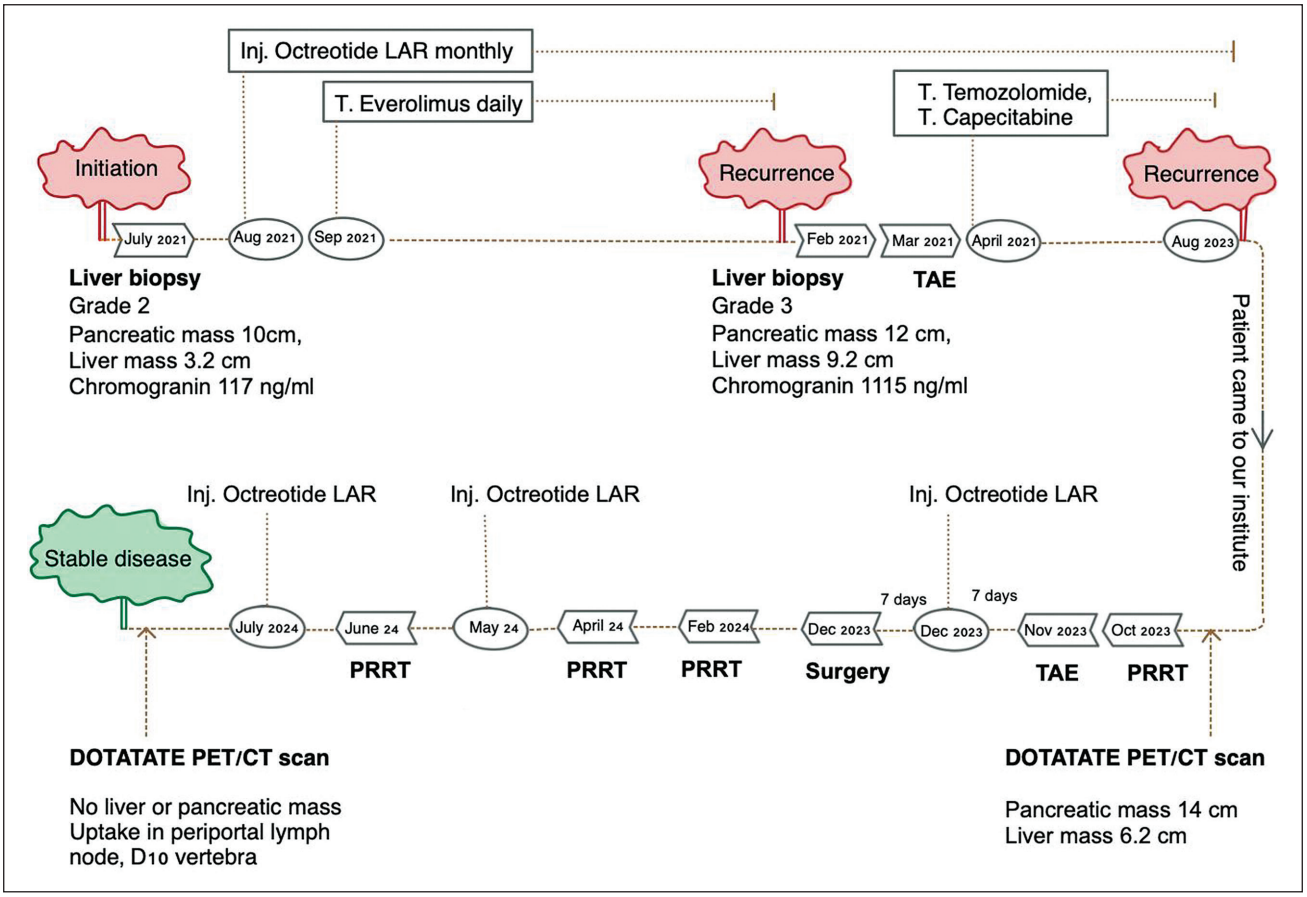

Figure 6. Timeline of events.

delivers radiation to the tumor precisely by delivering a radionuclide chelated to a peptide that targets Somatostatin receptor (SSTR), which is overexpressed on the surface of NET cells. She had a high disease burden when she came to our institute. Although the size of liver metastasis decreased from 9.2 cm to 6.6 cm following TAE, she was symptomatic with recurrent carcinoid spells. Our MDT found that the tumors exhibited a low NET-PET score of P2 (Figure 2) which could explain the failure of chemotherapy that she received outside. Despite the high grade (Grade 3) of the tumors, significant DOTATATE uptake was observed, favouring PRRT over chemotherapy. According to Bertani et al., patients who had surgery as first line treatment had a better median overall survival (112 vs 65 months) compared to patients who just received PRRT.[3] So, tumor debulking was identified as crucial to maximise the effectiveness of PRRT. Moreover, debulking liver metastasis by 70% is helpful for palliation of carcinoid symptoms.[4] However, surgical debulking entails inherent risks, including potentially exacerbating carcinoid syndrome. Two of the six patients in a Polish series with incurable NET had excision following PRRT-induced tumor size reduction.[5] Similarly, an Italian series revealed that the neoadjuvant PRRT group had a much lower incidence of nodal metastases and significantly longer progression-free survival than the group who underwent surgery as first line therapy.[6] PRRT also causes fibrosis, which lowers the chance of a pancreatic fistula formation following surgery. Hence, we strategically gave her one PRRT cycle before tumor debulking which stabilized her condition significantly. She was able to undergo surgery without major complications. The other three cycles of PRRT were given after surgery to improve outcomes. This kind of combination surgery and PRRT technique has been described in few specialized centers with small cohorts with encouraging results; nonetheless, to definitively evaluate this intriguing treatment approach, a randomized controlled study comparing neoadjuvant PRRT with adjuvant PRRT is essential.[7]

One more interesting observation was her hemodynamic improvement with norepinephrine. Since sympathomimetic drugs may paradoxically worsen hypotension by triggering further release of peptides from tumors, vasopressin or selective α1 agonist phenylephrine are the preferred vasopressors in this context. She showed no response to these treatments; but responded well through the administration of norepinephrine.

CONCLUSION

Metastatic pan-NET is a rare entity that has no clear treatment algorithm. Surgical debulking remains the mainstay in managing pan-NET, even in the presence of liver metastases. To mitigate the risk of carcinoid crisis during tumor manipulation the option of pre-surgery single-cycle PRRT can be considered, followed by three

subsequent cycles of PRRT to address any residual or micro-metastases. SSAs play a role in preventing crises, yet their efficacy in treating hemodynamic crises is limited. In such cases, norepinephrine serves as a primary treatment modality. This case illustrates successful individualized therapeutic paradigm in managing a challenging metastatic pan-NET.

Acknowledgment
Dr. Nikhila who is junior resident of Anesthesia managed the patient intraoperatively and provided details of treatment during surgery.

Ethical Consideration
Patient consent form was obtained before manuscript submission.

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

CRediT Author Statement
SG: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data Curation, Visualization**; SK:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – review and editing, Visualization, Supervision, Project administration; **KR:** Methodology, Validation, Investigation, Resources, Writing – review and editing; **NP:** Methodology, Validation, Investigation, Resources, Writing – review and editing, Project administration; **DN:** Validation, Formal analysis, Resources, Writing - review and editing, Project administration; **JS:** Supervision, Project Administration.

Authors Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Oscillation between Hyperthyroidism and Hypothyroidism in an Adolescent Female with Graves' Disease

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Abstract

Graves' disease (GD) presenting as fluctuations between hyperthyroidism and hypothyroidism is a rare phenomenon and poses a diagnostic challenge. A 14-year-old female with GD, initially thought to have Hashimoto's thyroiditis presented with a goiter and oscillating thyroid function over the course of 4 years. This case depicts a case of GD with oscillating thyroid function and stresses the importance of TSH receptor antibodies (TRAb) in the evaluation of patients with hyperthyroidism without Graves' ophthalmopathy.

Key words: Graves' disease, hyperthyroidism, hypothyroidism

INTRODUCTION

Autoimmune thyroid disease is the most common autoimmune disorder and has a prevalence of 2% in the female population.[1] It occurs more commonly in adults, but it is also the most common cause of thyroid dysfunction in children and adolescents, with a peak age prevalence in the early to mid-puberty.[2] Autoimmune thyroid disease encompasses autoimmune thyroiditis and Graves' disease (GD), which are two thyroid disorders at different ends of the clinical spectrum. In autoimmune thyroiditis, there is T lymphocytic infiltration of the thyroid gland with formation of antithyroid peroxidase (anti TPO Ab) and antithyroglobulin antibodies (anti TG Ab) leading to antibody-dependent cell-mediated lysis of thyroid cells and subsequent hypothyroidism.[3] This entity includes atrophic thyroiditis (non-goitrous form) and Hashimoto's thyroiditis (goitrous form).[3] In contrast, in GD, lymphocytic infiltration of the thyroid gland results in activation of TSH receptor antibody (TRAb) producing B cells leading to hyperthyroidism.[3]

Patients with GD present with hyperthyroidism but may become euthyroid or even hypothyroid in later years.[4] Those with Hashimoto's thyroiditis can also have a transient phase of hyperthyroidism that is usually mild termed 'Hashitoxicosis,' before they progress into hypothyroidism.[3] Graves' disease with alternating thyroid status has been reported albeit rare.[4-8] We present a case of GD in an adolescent female with fluctuating thyroid status, initially presenting with transient hyperthyroidism, followed by a 2-year duration of hypothyroidism before evolving back to a state of hyperthyroidism.

CASE

A 14-year-old female initially presented at our clinic for evaluation of thyroid swelling that had been present since 8 years of age but gradually increasing in size for the past 2 years. She had symptoms of palpitations, emotional lability and heat intolerance. Clinically, she had a diffuse smooth goiter, more prominent on the right side, with an appreciable bruit. There was a family history of thyroid disease in her paternal grandmother and uncle, but the exact nature of the thyroid disease was not known. She was slightly tachycardic (pulse rate 104 beats/min) but was normotensive. Fine tremor was noted. Weight and height were on the 50th-75th percentile. No proptosis or lid lag was seen. Initial thyroid function test showed suppressed thyroid stimulating hormone (TSH) <0.01 mIU/L (0.47-4) and slightly raised free thyroxine (FT4) 19.38 pmol/L (10-17.6) and free triiodothyronine (FT3) 7.81 pmol/L (2.63-5.7). The patient's anti TPO Ab and anti TG Ab were both positive, 600 IU/ml (0-34) and 4000 IU/ml (0-115) respectively. Thyroid ultrasound showed a diffusely heterogenous and enlarged thyroid gland with markedly raised Doppler signal. There were no thyroid nodules.

She was started on low dose carbimazole of 5 mg daily and propranolol due to persistent symptoms of palpitations. However, she became biochemically hypothyroid three months after commencement of carbimazole. A provisional diagnosis of Hashimoto's thyroiditis with Hashitoxicosis was made due to the findings of mild hyperthyroidism before progression to hypothyroidism, supported by positive anti TPO Ab and anti TG Ab and absence of ophthalmopathy. She remained hypothyroid despite

eISSN 2308-118x (Online)
Printed in the Philippines

Received: July 24, 2024. Accepted: August 26, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.07

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stopping carbimazole and required daily replacement of thyroxine 100 mcg. Subsequently, she became clinically and biochemically euthyroid for one year while on thyroxine replacement therapy. However, she was detected to be hyperthyroid again at 17 years of age during serial thyroid function monitoring and her hyperthyroid status persisted despite withholding thyroxine. She also had significant weight loss, heat intolerance and palpitations. An increase in goiter size with bruit, fine tremors and tachycardia were observed. The patient's diagnosis was revisited, and further work-up for hyperthyroidism was done, yielding a positive TRAb at 30.45 IU/L (normal <1.75). Anti TPO Ab and anti TG Ab remained positive; >600 IU/ml (normal <35); 966 IU/ml (normal <64) respectively.

Repeat thyroid ultrasound showed similar findings of enlarged bilateral thyroid lobes with heterogenous echogenicity and increased thyroid vascularity (Figure 1). In view of the unusual clinical picture of oscillating thyroid status, a radionuclide Tc-99m pertechnetate thyroid scintigraphy was also performed. It revealed bilateral diffuse homogenous tracer uptake of the thyroid gland with no hot or cold nodule seen, suggestive of a hyperfunctioning thyroid gland consistent with GD (Figure 2). Carbimazole 10 mg daily and propranolol were restarted. Serial FT4 and TSH trends are shown in Figure 3.

DISCUSSION

Graves' disease presenting as oscillating hyperthyroidism and hypothyroidism is a rare phenomenon and poses a diagnostic challenge. There are several case reports on the conversion of hyperthyroidism to hypothyroidism and vice versa, but only a few reported in children.[5-9] The alternating thyroid status in an individual with GD can be explained by the concurrent presence of two different types of TRAb i.e., TSAb and TBAb.[10] The hyperthyroid state is caused by TSAb whereas hypothyroidism is caused by TBAb.[10]

Previous studies of oscillating thyroid status in patients with GD have reported the co-existence of both TSAb and TBAb, whereby the clinical status is determined by the predominance of one antibody over the other.[5-10] The switch between TSAb and TBAb is more commonly

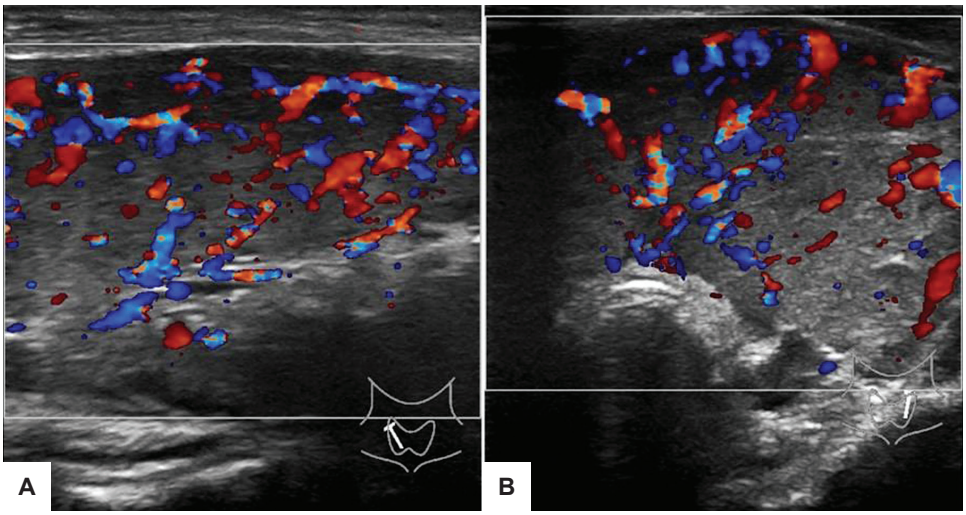

Figure 1. Ultrasound color Doppler thyroid gland showing heterogenous echogenicity and increased thyroid vascularity of right **(A)** and left **(B)** lobes.

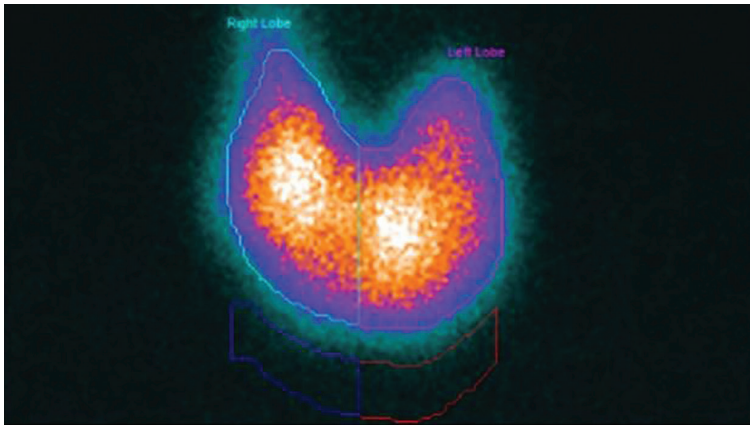

Figure 2. Radionuclide Tc99m thyroid scintigraphy showing bilateral diffuse homogenous tracer uptake 20.4%, (normal 5-15%), suggesting hyperfunctioning thyroid gland in Graves' disease.

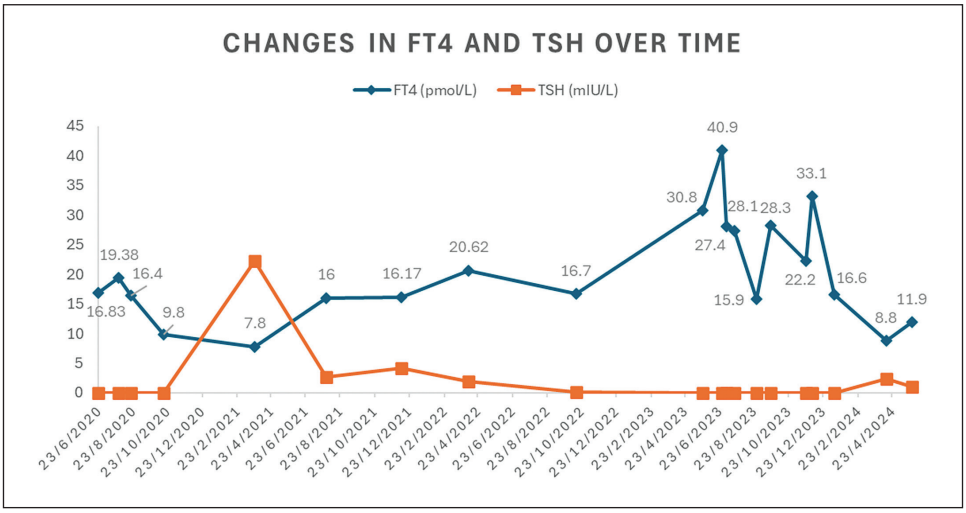

Figure 3. Serial FT4 and TSH trends

found in females.[7] It has been postulated that the use of levothyroxine could inhibit the T regulatory cells and enhance the expression of costimulatory molecules by dendritic cells, causing an increase in the TSAb and conversion to the hyperthyroid state.[5,8,11,12] Conversely, the use of antithyroid drugs reduces thyroid autoimmunity and TSAb synthesis, causing a switch to the hypothyroid state.[5,8,11,12] This may explain the underlying mechanism contributing to the change in thyroid status in our patient as she had reverted from hyperthyroidism to hypothyroidism shortly after initiation of carbimazole. Subsequently two years later, she switched back to hyperthyroidism while on thyroxine replacement.

Oscillating thyroid status has been more commonly reported in adults and its presentation is similar to that of children and adolescents.[5-10] In a study by Takasu et al conducted amongst adult men and women, 34 patients with hypothyroidism who were TBAb-positive and 98 patients with Graves' hyperthyroidism who were TSAb-positive were evaluated over a 10- year period.[10] Out of the 34 TBAb-positive patients, 17 had persistence of the TBAb and remained hypothyroid. Fifteen out of the 34 TBAb-positive patients had disappearance of the TBAb and resolution of hypothyroidism. Two out of the 34 TBAb- positive patients developed TSAb and Graves' hyperthyroidism. Amongst the 98 patients with Graves' disease who were TSAb positive, TSAb persisted in 10 patients who continued to have Graves' hyperthyroidism. Thyroid stimulating antibodies (TSAb) disappeared in 73 patients with 60 having remission of GD. Two of the 98 patients developed TBAb and reverted to hypothyroidism. Case reports describing such changes in TSAb and TBAb levels resulting in alternating thyroid status between hyperthyroidism and hypothyroidism have also been reported in adults.[13,14]

A second hypothesis to explain the oscillating thyroid status in this patient is the fact that both Graves' disease and Hashimoto's thyroiditis are manifestations of the same disease spectrum whereby thyroid-reactive T lymphocytes are formed and infiltrate the thyroid gland with an overlap of anti TPO Ab, anti TG Ab and TRAb in both conditions. Graves' disease with hyperthyroidism may occur in patients whose thyroid glands histologically show either Hashimoto's thyroiditis alone or a mixture of both parenchymatous hypertrophy of Graves' disease and extensive lymphocytic infiltrations.[15] Therefore, these patients present with hyperthyroidism and evolve into a hypothyroid state over a few months' time, resembling "Hashitoxicosis."[15] The hyperthyroid status may be due to the presence of TSAb associated with GD co-existing with the destruction of thyroid follicles. The spontaneous disappearance of the TSAb, with the underlying thyroid inflammation allows the Hashimoto's thyroiditis phenotype to predominate. Recurrent hyperthyroidism may be due to reemergence of the TSAb. In a review of 69 children with Hashimoto's thyroiditis, 11.69% were diagnosed with Hashitoxicosis with the duration of hyperthyroidism ranging from one to four months before evolving into hypothyroidism or euthyroidism.[16]

In this patient, the enlarged thyroid gland and marked increase in Doppler signal in her thyroid ultrasound pointed more to GD.[17] In Hashimoto's thyroiditis, the chronic inflammation leads to a reduction in thyroid gland volume with a normal or reduced vascularization on ultrasound Doppler.[17] An important discerning feature between Hashimoto's thyroiditis and GD is the presence of TRAb predominantly in the latter. In a review by Saravanan and Dayan, TRAb was positive in 70-100% of patients with GD but it was only positive in 2-6% of patients with Hashimoto's thyroiditis.[1] Anti TG Ab and anti TPO Ab are present in both Hashimoto's thyroiditis and GD and cannot be used to differentiate both conditions (anti TG Ab 35-60% and anti TPO Ab 80-99% in Hashimoto's thyroiditis versus anti TG Ab 12-30% and anti TPO Ab 45-80% in GD).[1] The diagnosis of GD in this patient was further supported by the demonstration of homogenous increase in radiotracer uptake in thyroid scintigraphy as it would be expected to be normal or reduced in Hashimoto's thyroiditis.[17]

Management of GD with fluctuating thyroid function is challenging. The management options proposed are radioactive iodine ablation, thyroidectomy and pharmacological therapy.[5-7,9] Pharmacological treatment may involve the combined use of thyroxine and antithyroid therapy in cases of rapidly changing thyroid function to achieve euthyroid status.[4] The thyroid status of our patient is currently still manageable with a single agent. However, she requires more frequent thyroid function monitoring to detect possible switching of thyroid status. Due to the unpredictability of the clinical course, a reasonable definitive management option to consider in her case is radioactive iodine ablation during hyperthyroid phase or thyroidectomy.

CONCLUSION

Graves' disease with oscillating hyperthyroidism and hypothyroidism is a rare phenomenon that can be explained by co-existence of both TSAb and TBAb. It may be confused with Hashimoto's thyroiditis in patients who present with only transient mild hyperthyroidism before switching to hypothyroidism. Thyroid stimulating hormone receptor antibody is an important diagnostic tool to differentiate between Hashimoto's thyroiditis and GD in patients with hyperthyroidism without Graves' ophthalmopathy. Thyroid scintigraphy is also invaluable in cases of diagnostic uncertainty. Management of GD with oscillating thyroid status includes close monitoring of thyroid function with consideration of radioactive iodine ablation or thyroidectomy.

Ethical Consideration
Patient consent form was obtained from the parents of the patient before manuscript submission.

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

CRediT Author Statement
YLL: Conceptualization, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration.

Author Disclosure
The author declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Lymphocytic Hypophysitis Presenting as Acute-onset Arginine Vasopressin Deficiency and Pituitary Stalk Thickening: A Case Report

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Abstract

Lymphocytic hypophysitis (LHy) is a rare autoimmune inflammatory process that selectively affects the neurohypophysis and infundibulum, typically presenting with arginine vasopressin deficiency (AVP-D). On magnetic resonance imaging (MRI) with contrast, there is a thickening of the pituitary stalk, enlargement of the neurohypophysis or both with homogeneous enhancement. LHy can be self-limiting and regression can be seen radiologically during follow-up.

A 22-year-old male presented with clinical findings consistent with AVP-D in 2016. MRI brain demonstrated enlargement of the pituitary stalk and absence of a posterior pituitary bright spot. He was given a trial of glucocorticoid treatment. His serial MRI brain showed a reduction of the pituitary stalk, but the AVP-D persisted. He was diagnosed with LHy.

LHy is characterized by lymphocytic infiltration, leading to eventual destruction of the pituitary tissue accompanied by varying degrees of pituitary dysfunction. Definite diagnosis can only be established via pituitary stalk biopsy. Due to the wide range of possible aetiologies, close monitoring is strongly recommended for the treatment of presumed cases lacking histopathologic confirmation. The response rate to glucocorticoids has been variable. Periodic monitoring of anterior pituitary function and pituitary MRI are essential in the management of this condition.

Key words: lymphocytic hypophysitis, arginine vasopressin deficiency, pituitary stalk, infundibulum

INTRODUCTION

Hypophysitis is a rare inflammatory disorder that affects the pituitary gland and infundibulum and aetiologies include autoimmune, infectious, neoplastic, infiltrative, immunoglobulin G4 IgG4, immunotherapy-induced or sometimes idiopathic.[1,2] LHy, one of the causes of primary hypophysitis, is a rare autoimmune inflammatory process that selectively affects the infundibulum and neurohypophysis, typically presenting with arginine vasopressin deficiency (AVP-D).[3] Magnetic resonance imaging (MRI) with contrast demonstrates thickening of the pituitary stalk, enlargement of the neurohypophysis, or both with homogeneous enhancement.[3,4] The inflammatory process in LHy can be self-limited and regression can be seen radiologically during follow-up.[4] This case report will illustrate the clinical and radiological course of a rare case of LHy who received glucocorticoid treatment and was closely monitored under our follow-up.

CASE

A 22-year-old male presented with a sudden onset of polyuria and polydipsia for 2 months in 2016. He developed a predilection for cold drinks with concomitant nocturia which occurred hourly incurring a total urine volume excreted in a day of approximately 9 litres. Symptoms such as headache, visual disturbances, fever, cough or weight loss were absent. He denied exposure to individuals infected with tuberculosis (TB). He had no remarkable past medical history or family history and was not taking any medications. On examination, he had normal secondary male characteristics, with a height of 1.78 m and a body mass index (BMI) of 25.2 kg/m^2. Clinically, he had an unremarkable respiratory, abdominal and neurological examination. There were no skin lesions, lymphadenopathy, bone pain or joint swelling. Renal profile was significant for hypernatremia (serum sodium 150 mmol/l) in the presence of dilute urine (urine specific gravity 1.005); the

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 5, 2024. Accepted: September 13, 2024.
Published online first: April 20, 2025.
https://doi.org/10.15605/jafes.040.01.08

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corresponding serum and urine osmolality were 321 mOsm/kg and 105 mOsm/kg, respectively. Water deprivation test was deferred due to the presence of marked hypernatremia. A trial of available oral desmopressin was given resulting in a significant reduction of polyuria. Overall, the clinical and laboratory findings were consistent with AVP-D.

Cranial MRI (Figure 1) demonstrated enlargement of the pituitary stalk (6 mm) and homogenous enhancement of both pituitary gland and stalk post-gadolinium contrast. The pituitary gland appeared normal and the posterior pituitary bright spot was absent. The patient refused the planned possible pituitary biopsy.

Other anterior pituitary hormones were within normal limits, except for mildly raised prolactin levels 1440 (86-324 mIU/L), equivalent to 67.7 ng/ml. Besides that, the anti-TPO level was elevated at 491 (<35 IU/ml). Investigations for secondary aetiologies including anti-neutrophil cytoplasmic antibodies (ANCA), alpha-fetoprotein (AFP), Beta-hCG (B-HCG), Immunoglobulin G4 (IgG4), Antinuclear antibody (ANA), Rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), urine analysis, angiotensin converting enzyme (ACE) and imaging including skeletal survey, computed tomography (CT) thorax and serial chest radiographs were not significant. He was commenced on a trial of glucocorticoid treatment with oral prednisolone starting at 50 mg daily. This was tapered by 10 mg monthly until dose reached prednisolone 30 mg daily. This was followed by a 5 mg reduction monthly until oral prednisolone was 10 mg daily. This was tapered further to 7.5 mg daily for a month, then reduced further to another month of oral prednisolone at 5 mg daily before steroid treatment discontinuation. Despite high doses of glucocorticoid treatment, the AVP-D persisted and required regular doses of desmopressin. His serial pituitary MRI in 2017 (9 months after the initial MRI) and 2021 (5 years and 4 months from the initial MRI) showed a gradual reduction in the diameter of the pituitary stalk which measured 5 mm and 4.5 mm, respectively.

His other hormones were monitored during follow-up and remained unremarkable (Table 1). The short synacthen test performed in 2017 showed adequate cortisol response: 264 nmol/l (0 min), 476 nmol/l (30 min), 519 nmol/l (60 min). The previously mildly elevated serum prolactin normalised during subsequent visits. Signs and symptoms suggestive of secondary causes of LHy did not manifest during follow-up and his weight remained stable throughout

Table 1. Serial hormone assessments on the patient's follow-up

Hormones tested	2016	2021	2022
Free T4 (thyroxine) (Normal range: 12-22 pmol/L)	18.6 pmol/L	14 pmol/l	14 pmol/l
Cortisol nmol/l (Normal range: 133-537 nmol/L)	219 nmol/l	303 nmol/l	309 nmol/l
Testosterone (Normal range 8.64-29 nmol/L)	9.75 nmol/L	11.0 nmol/L	12.0 nmol/L
Insulin-like growth factor 1 (IGF-1) (Normal range: 115-340 ug/l)	203 ug/l		

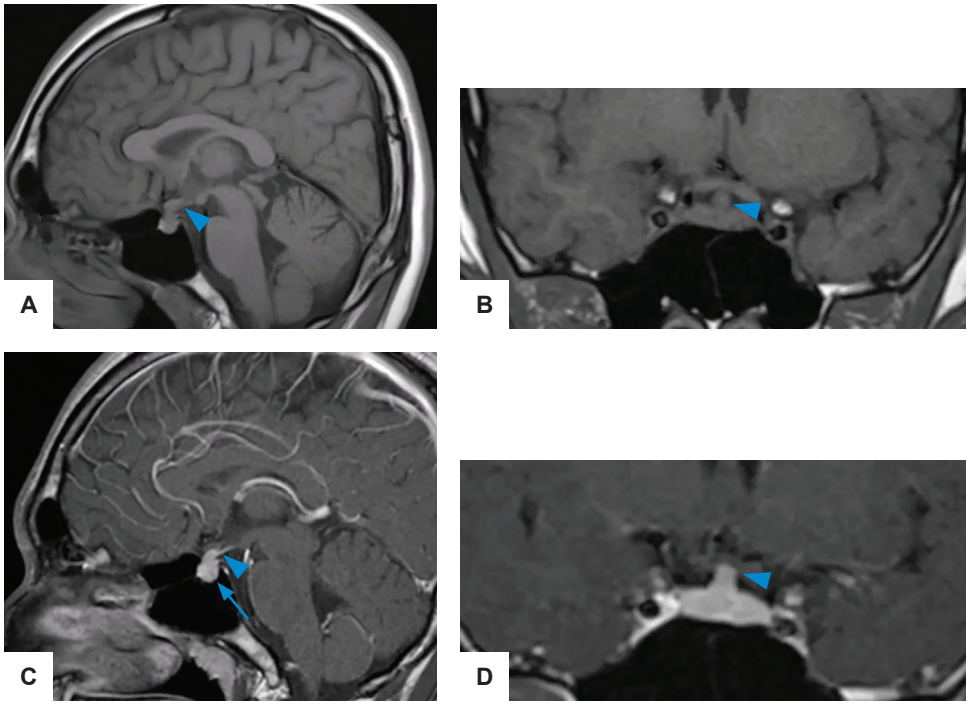

Figure 1. Magnetic resonance imaging of hypothalamic-pituitary regions in 2016 **(A-D)**. Thickening of pituitary stalk measuring 6 mm *(arrowheads)* and absence of posterior pituitary bright spot *(arrow)* at initial presentation **(A, B)** non-contrast T1-weighted; **(C, D)** contrast-enhanced.

this period. He got married and fathered a child naturally the next year. However, anti-TPO was still elevated (215 IU/ml), suggesting an associated autoimmune disorder. Ultimately, a diagnosis of LHy was made and the patient continued to be monitored closely. He was switched from oral to sublingual desmopressin when it became available in our center. His condition remains stable on sublingual desmopressin 180 mcg, 120 mcg, 180 mcg thrice a day, with development of polyuria with delayed or missed doses and serum sodium ranging from 139 to 140 mmol/l during follow-up.

DISCUSSION

Hypophysitis is a rare inflammatory disorder that affects the infundibulum and pituitary gland. Diagnosis is usually made based on clinical presentation, dedicated magnetic resonance imaging, laboratory findings and, in some cases, biopsy. Hypophysitis can be further categorised according to its anatomical involvement, whereby inflammation can affect the anterior pituitary (adenohypophysitis), entire pituitary (panhypophysitis), infundibulum and posterior pituitary (infundibulo-neurohypophysitis).

Hypophysitis can also be categorised according to its aetiology as primary or secondary. Primary hypophysitis is characterised by autoimmune and other infiltrative or inflammatory forms of isolated pituitary involvement of unknown aetiology. Secondary hypophysitis is characterised by a reaction due to a local process, infection, drug, systemic disease or malignancy. Alternatively, hypophysitis can be categorised using its histological features including lymphocytic, granulomatous, IgG4-related, xanthomatous, necrotizing and mixed forms. The most common form is lymphocytic hypophysitis.[1]

Hypophysitis usually presents with symptoms related to the deficiency of pituitary hormones with or without mass effect symptoms, such as headaches and vision disturbances. AVP-D is common.[2] Various imaging characteristics can be seen. The most common MRI finding is a thickened, non-deviated pituitary stalk or associated symmetric pituitary gland enlargement.[1] The evaluation of a patient with thickening of the pituitary stalk involves assessing the function of both the anterior and posterior pituitary gland and identifying the underlying cause. Other possible aetiologies include neoplastic lesions and metastases, inflammatory conditions such as Langerhans cell histiocytosis, neurosarcoidosis and infections such as tuberculosis.[1,5] Biopsy may be the only modality for definitive diagnosis and is useful in establishing the histopathological type and in excluding other secondary aetiologies.[1] However, aside from being invasive, biopsy carries risks such as hypopituitarism, bleeding and infection. Currently, there are no established criteria for pituitary biopsy. Because the differential diagnosis is broad,

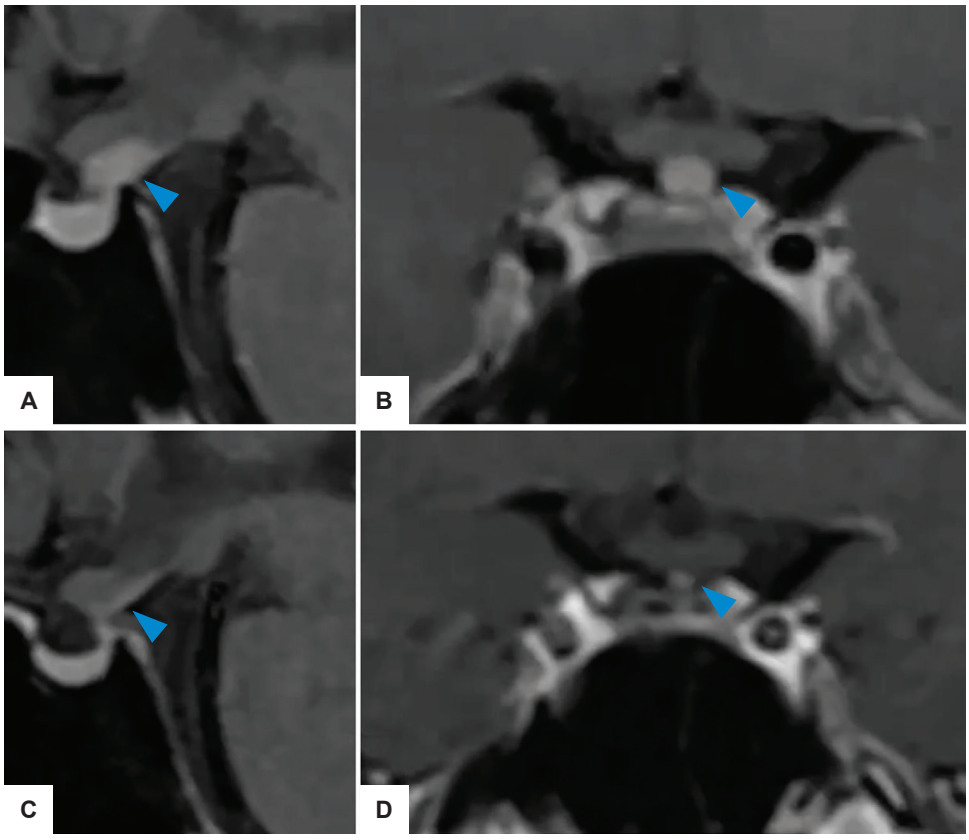

Figure 2. Magnetic resonance imaging of hypothalamic-pituitary regions (contrast-enhanced T1-weighted) during follow-up **(A-D)**. Pituitary stalk *(arrowheads)* was less thickened in 2017, measuring 5 mm **(A, B)** and the pituitary stalk diameter was further reduced in 2021, measuring 4.5 mm **(C, D)**.

it is crucial to establish a presumptive diagnosis based on non-invasive investigations given that histopathology is not always available for confirmation.[2]

Specific investigations such as IgG4, ANCA, ACE, ANA, B-HCG, AFP and tuberculin skin test can be performed to exclude other causes. Occasionally, whole-body computed tomography or fluorodeoxyglucose-positron emission tomography (FDG- PET) can be useful to delineate the underlying aetiology.[1] Rabphilin-3A is reported to be a predominant auto-antigen in LHy. There are recent studies that demonstrated the utility of anti-rabphilin-3A antibodies as sensitive markers of LHy in patients with AVP-D. Testing for anti-rabphilin-3A antibodies could be useful in distinguishing LHy from other pituitary disorders, potentially eliminating the need for invasive pituitary biopsy in the future.[6,7] A trial of empiric high-dose glucocorticoid treatment could be considered if all investigations are negative, as most inflammatory and infiltrative lesions will respond to glucocorticoid treatment. While the mass effects will likely improve with administration of glucocorticoid, the pituitary function is unlikely to return to normal.[1]

Approximately two-thirds of cases of primary hypophysitis are found to be lymphocytic hypophysitis. It is frequently associated with autoimmune diseases such as autoimmune thyroid disease, primary biliary cirrhosis, lupus and celiac disease. LHy is characterized by lymphocytic infiltration, leading to eventual destruction of the pituitary tissue accompanied by varying degrees of pituitary dysfunction. In LHy, AVP-D is the main and most pronounced symptom due to lymphocytic infiltration of the neurohypophysis and infundibulum.[4,8] Mass effect symptoms such as headache can occur. The anterior pituitary function is frequently intact, with occasional mild and transient involvement of the anterior pituitary function. Radiologically, LHy is characterised by diffuse thickening of the infundibulum and marked gadolinium enhancement of the stalk, with a diameter exceeding 3.5 mm at the level of the median eminence of the hypothalamus. The usual neurohypophyseal "bright spot" is also lost.[4] This case is likely a case of lymphocytic hypophysitis based on its clinical course, imaging features and absence of clinical features suggestive of secondary causes during follow-up. Although tuberculosis (TB) was considered due to its endemic presence in the region, the absence of related clinical signs, symptoms and radiological features at diagnosis and during follow-up suggested that TB was unlikely to be the cause.

While glucocorticoid treatment is efficacious, its dose, duration and benefits are still of much contention. There are reports of mixed outcomes such as cured cases of LHy with glucocorticoids and cases with spontaneous regression without glucocorticoids.[8,9] This case showed that despite early initiation of steroids at high doses, the AVP-D persisted even when imaging features improved. Since no randomised controlled trials have been conducted due to the rarity of this condition, it is uncertain whether glucocorticoids can lead to better pituitary function recovery compared to observation alone in the treatment of hypophysitis.[1,2] It is reported that the response rate to glucocorticoids in primary hypophysitis varies widely, ranging from 20% to over 95% for partial or complete improvement in radiological and hormonal response.[1] Hypophysitis is regarded as severe if mass effects, such as headache, cranial nerve palsy or visual field defects, occur. This requires administration of glucocorticoids and consideration of pituitary biopsy.[1,2] However, it is important to evaluate the benefits and risks of glucocorticoid treatment in treating mild cases of primary hypophysitis given the wide range of potential glucocorticoid side effects.[1] A recent meta-analysis observed a more marked improvement with very high dose intravenous glucocorticoid and for a longer treatment duration (>6.5 weeks). It is also suggested that those who did not respond to glucocorticoids had longer symptom duration and irreversible fibrosis may have occurred.[10] Nevertheless, periodic clinical assessment for the recovery of pituitary function is required and pituitary MRI surveillance can be performed at 3 to 6 months, initially.[1,5] Some suggest repeating MRI surveillance annually for 5 years and at the same time evaluating for anterior pituitary function yearly. Due to the wide range of possible aetiologies, caution and close monitoring are strongly recommended for the treatment of presumed cases lacking histopathologic confirmation.[1,2]

CONCLUSION

This case shows that a diagnosis of LHy can be made with close monitoring with hormonal and radiological assessment and long-term follow-up in the absence of a highly invasive pituitary biopsy. There are no evidence-based guidelines on the management of LHy due to its rarity. Glucocorticoid response rate has been variable. An individualised approach is warranted. A conservative medical approach is often used as LHy is often self-limiting, especially when symptoms of mass effect are absent.

Ethical Considerations
Patient consent was obtained before the submission of the manuscript.

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

CRediT Author Statement
LZY: Conceptualization, Investigation, Resources, Writing - original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **SV:** Investigation, Resources, Writing – review and editing, Supervision.

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

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CASE SERIES

ROHHAD-NET Syndrome: A Case Series

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Abstract

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and neural crest tumor (ROHHAD-NET) though a rare disease, is potentially fatal. It is of utmost importance to be understood and urgently diagnosed. We hereby report a series of three cases, the first of its kind from India. Children older than 18 months old usually exhibit rapid weight growth as a presenting symptom. Hypothalamic dysfunction could lead to endocrine issues, respiratory dysfunction and autonomic dysregulation. Over the years, with variable timing, one or more signs of hypothalamic dysfunction appear: hyperprolactinemia, growth hormone deficiency, central hypothyroidism, central adrenal insufficiency or Cushing syndrome, early or delayed puberty, water-electrolyte balance disorders. The diagnosis is difficult because there is no reliable test, and the treatment is mainly supportive. All the three children who were thriving well, presented with rapid weight gain and then developed symptoms of hypothalamic dysfunction. While in one a neural crest tumor was incidentally detected, the second had persistent hypernatremia and the third child presented with intestinal obstruction. The varied presentation and vague symptom spectrum exhibit a diagnostic challenge to the clinician and underscores the importance of creating awareness. An individualized strategic approach is needed as it is clinically difficult to distinguish ROHHAD syndrome from other obesity syndromes of genetic origin.

Key words: ROHHAD, obesity, central hypoventilation, neural crest tumor

INTRODUCTION

Rapid onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation and neuroendocrine tumor (ROHHAD-NET) is an uncommon polymorphic disorder involving the autonomic, respiratory and multiple other systems during childhood and carries a significant mortality risk. In 1965, the first case report was published[1] and and since then over the span of five decades only a couple of hundred cases have been reported world-wide.[2] Recognizing this syndrome continues to pose a significant challenge to the clinicians. At present, the criteria used to identify ROHHAD syndrome are clinical in nature and they include: 1) dramatic weight gain; 2) central hypoventilation appearing between age 1.5 and 7 years in a previously healthy child; 3) signs of hypothalamic dysfunction such as such as hyperprolactinemia, central hypothyroidism, erratic water balance, aberrant response to growth hormone (GH), adrenal insufficiency, or puberty disorders; 4) autonomic dysfunction.[3] The common tumors associated with ROHHAD NET are ganglioma, ganglioneuroblastoma, and rarely even neuroblastomas.[4]

Although their causes are still unknown, ROHHAD or ROHHADNET may exhibit hypothalamic-pituitary dysfunctions and mimic genetic obesity or syndromes such as Prader Willi Syndrome. Children experience a progressive loss of central respiratory control, which is frequently fatal.[5] In order to limit morbidity and death and to offer timely respiratory assistance, prompt diagnosis based on early identification is crucial. We report three children with a probable diagnosis of ROHHAD NET who presented at our tertiary care centre.

Early onset obesity is commonly encountered and it is important to keep this rare diagnosis in mind and appropriately investigate a child with rapid weight gain. Early diagnosis improves the clinical management and prognosis in ROHHAD syndrome, and it has a strong association with neural crest tumors.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 21, 2024. Accepted: September 23, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.10

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CASE 1

A 6.5 year old female student presented with recent weight gain. Her mother reported that the child consumed a high caloric diet, but she did not report diet high in calories and she did not report snoring, sleep disturbances or constipation. Her exposure to screen time was not significant and the mother reported that she did not play as she did previously. She was born at term with a birth weight of 3.25 kg, with an uneventful neonatal period and had normal developmental milestones. Her weight was 35 kg (z score +2.4 SD), height 125 cm (z score +1.4 SD) and Body Mass Index (BMI) 22.5 kg/m^2 (+3 SD). She had acanthosis nigricans over the neck, axilla and groin, she did not appear cushingoid and no striae were noted. Investigations revealed her fasting blood sugar to be 5.7 mmol/L, fasting lipid profile showed elevated triglycerides 5.4 mmol/L and LDL 3.7 mmol/L and normal thyroid function test (Free T4 15.4 pmol/L [NR: 10.9-22.5 pmol/L], TSH 3 mIU/ml [NR: 0.6-5.5 mIU/ml]). Her bone age was 7 years. She was considered to be a child with exogenous obesity and was advised lifestyle modifications. Two months later, she was admitted to the pediatric intensive care unit with complaints of difficulty in breathing and features of intestinal obstruction. She was found to have hypertension (BP 150/92 mm Hg) and low potassium (2.2 mEq/L). Computed Tomography (CT) scan abdomen revealed an adrenal mass; her 24-hour urine vanillylmandelic acid and metanephrines were normal. She was started on amlodipine and alpha blockers; her BP was controlled however the hypokalemia persisted. Her midnight serum cortisol was 206 nmol/L, overnight dexamethasone suppression test showed a cortisol level of 524 nmol/L. The possibility of Cushing's syndrome was considered. The pediatric surgeon advised removal of the tumor. A large mass was removed; however, she went into shock post-operatively and expired. Histopathology revealed an adrenal ganglioneuroma. On retrospection, we consider the possibility of ROHHAD-NET in her case. Another possibility we considered was Ectopic ACTH secretion from ganglioneuroma but the postoperative severe hypotension and hypoventilation which did not respond to steroid treatment makes the diagnosis of ROHHAD syndrome more likely. The cause of death could be respiratory depression which could be a part of ROHHAD syndrome in retrospect.

CASE 2

A 4 year and 9 month-old-female presented with acute onset of rapid weight gain for the last 3 months. She had gained almost 10 kg in 3 months. The mother reported an increased appetite, she ate a lot of fried food and simple sugars. Her dietary intake of fruits and vegetables were negligible. She was apparently very active previously and was now less interested in play. She was not interacting well with others and spent a lot of time lying in the bed. Her exposure to screen time was only 15-30 minutes per day. Mother had also noticed that she had started snoring recently, but did not report day time sleepiness or breathing difficulty. She did not complain of headache, vomiting, frequent urination or excessive thirst. She had no history of prolonged intake of corticosteroids or any other medications. On probing further regarding the diet, she was taking double the quantity of food that she was consuming previously. She was a second born child of a non-consanguineous marriage with an uneventful antenatal period. Her birth weight was 3.2 kg with and the postnatal period was uneventful; she was exclusively breastfed for 6 months. Family history was unremarkable except for maternal grandfather who had type 2 Diabetes Mellitus. On examination, she appeared alert, blood pressure was 126/72 mm Hg, at the 95th centile. She appeared to have moon facies, a buffalo hump and acanthosis nigricans over the neck. Her weight was 23.5 kg (z score +1.85 SD), height 97 cm (z score -2.33 SD) and BMI 24.9 kg/m^2 (+4.45 SD). She was short, obese and prepubertal, with no signs of virilization (Figure 1). Her systemic examination was unremarkable.

A complete hemogram done was normal. Renal and liver function tests were normal. Free T4 was 21.8 pmol/L [NR: 10.9-22.5 pmol/L], TSH- 6.2 mIU/ml [NR: 0.6-5.5mIU/ml]. Random blood sugar, glycated hemoglobin and serum electrolytes were normal. Initial 8 am serum cortisol was 262 nmol/L [NR: 110-606 nmol/L] and ultrasonography of the abdomen done in another health centre was reported as normal. Her bone age corresponded to chronological age. A repeat 8 am serum cortisol was 634 nmol/L [NR: 110-606 nmol/L], and ACTH 36.7 pg/ml [NR: 6-48 pg/ml]. An overnight dexamethasone suppression test was done,

Figure 1. Child described in Case 2. She was short, obese and was prepubertal, with no signs of virilization.

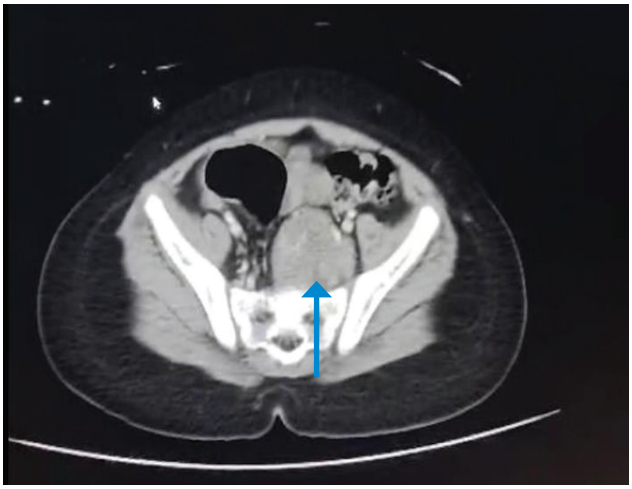

Figure 2. Heterogeneously enhancing lesion with defined soft tissue density lesion in the pelvis with sacral foraminal extension with a possibility of a neurogenic neoplasm.

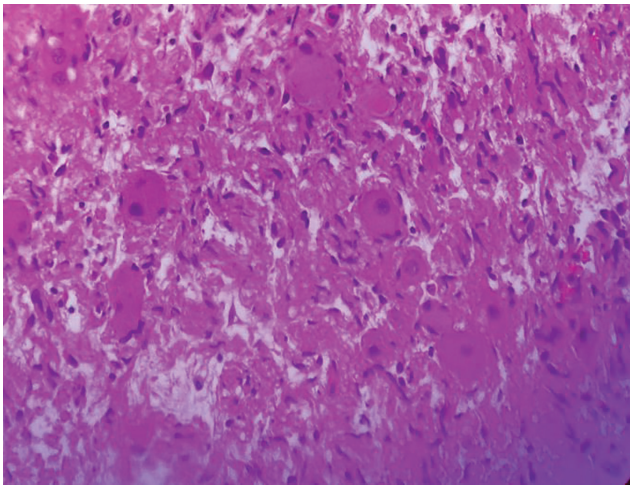

Figure 3. Histopathology revealed an admixture of ganglion cells and Schwann cells with no blastemal component which was suggestive of ganglioneuroma.

serum cortisol was 44 nmol/L [NR <50 nmol/l]. In view of further suspicion, a CT scan of the abdomen was done which showed a heterogeneously enhancing lesion with fairly defined soft tissue density lesion in the pelvis with sacral foraminal extension with a possibility of a neurogenic neoplasm (Figure 2). She was tested for tumor markers which were negative. Urinary vanillylmandelic acid was 26.4 µmol/day [NR:0-38.5 µmol/day], serum AFP 1.62 ng/ml [NR: 5-10ng/ml], β HCG <0.1 IU/L [NR:0.02-0.8 IU/L], carcinoembryonic antigen 3 mcg/L [NR: <3 mcg/L], serum testosterone 0.21 nmol/L [NR: 0.08-0.34 nmol/L] and dehydroepiandrosterone sulphate (DHEAS) 0.14 µmol/L [NR: 0.5-3.8 µmol/L]. Tumor excision was done. Post laparotomy, histopathology revealed an admixture of ganglion cells and Schwann cells with no blastemal component which was suggestive of ganglioneuroma (Figure 3). She was discharged post recovery. We considered the possibility of ROHHAD-NET, weight gain as a part of paraneoplastic syndrome with ectopic ACTH production or simple exogenous obesity with incidentally detected tumor. Genetic testing was not done due to financial reasons. We plan to monitor her closely for symptoms of hypoventilation.

CASE 3

A 3-year and 8 month-old female was referred to our tertiary care centre with prolonged fever, seizure and hypernatremia. She had already been on ventilatory support for 15 days at the time of presentation (Figure 4). On admission to the Pediatric Intensive Care Unit (PICU), her Glasgow Coma Scale score was 3 requiring high ventilatory support (SpO_2 87-90%, with FiO_2 100%), febrile, high-volume pulse and normal blood pressure. Arterial blood gas showed metabolic alkalosis and chest X ray ruled out pneumothorax. Bedside echocardiogram showed good contractility and was normal. Hemogram showed hemoglobin of 8.5 g/dl, total leucocyte count of 19,400 cells/µL (neutrophils 69% and lymphocytes 26%), Erythrocyte

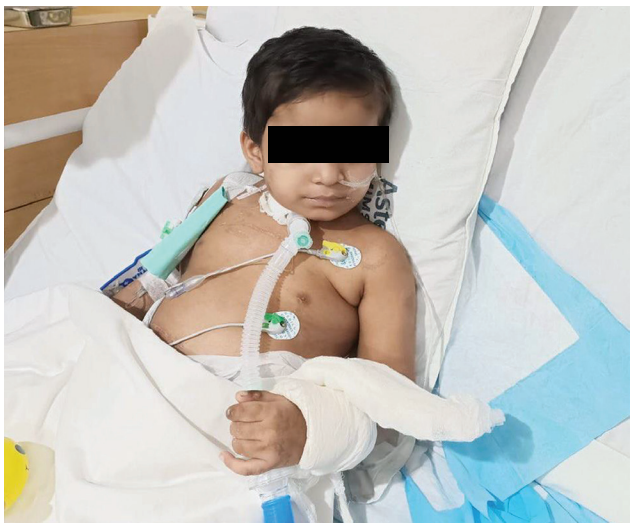

Figure 4. Case 3. Three-year-8-month-old referred with prolonged fever, seizure and hypernatremia. She had already been on ventilatory support for 15 days at the time of presentation to our center.

Sedimentation Rate 73 mm/hour, C-reactive protein – 15 mg/L, serum electrolytes showed hypernatremia (158 mmol/L and hypokalemia (3.2 mmol/L). Liver and renal function tests were normal. Chest X ray showed bilateral infiltrates. She was started on hypernatremia correction and broad-spectrum antibiotics after sending blood and urine cultures. She had hypotension and mild ventricular dysfunction which was stabilized with multiple inotropes, also required high ventilatory support and hence lung protective measures were initiated; inotropes were tapered and stopped by day 4 of admission. MRI brain was done considering the possibility of meningoencephalitis. It showed leptomeningeal enhancement in bilateral occipital and frontal region, hemorrhagic changes in the right pons and cerebellar hemisphere. Cerebrospinal fluid (CSF) examination was normal and Electroencephalogram (EEG) showed mild cerebral dysfunction. She continued

to have serially increased sodium levels up to 176 mmol/L with borderline low potassium levels (3.1-3.7 mmol/L), low urine sodium (<10 mmol/L), normal renal function and normal urine output. The paired serum osmolarity was 290 mosm/kg and urine osmolarity was 200 mosm/kg. We suspected a dysfunction in the renin angiotensin aldosterone pathway; however, PRA and aldosterone were normal. In view of persisting hypernatremia, an adrenal pathology was suspected and CT scan abdomen was done which showed right adrenal mass and thrombus involving bilateral external and common iliac veins. She was started on desmopressin, spironolactone and hemodialysis was done in view of persisting hypernatremia and failure of conventional methods; serum sodium levels dropped to 159 mmol/L, free water correction was continued according to sodium levels. Pediatric endocrinology consultation was sought, the possibilities of adrenocortical carcinoma, aldosterone secreting adenoma and pheochromocytoma were entertained, but evaluation showed normal DHEAS level- 0.005 µmol/L [NR: 0.5-3.8 µmol/L], normal cortisol level-468 nmol/L [NR: 110-606 nmol/L], normal ACTH-18 pg/ml [NR: 6-48 pg/ml], testosterone-0.08 nmol/L[NR: 0.08-0.34 nmol/L] and urine vanillylmandelic acid and plasma metanephrine levels. IVC filter placement was done in view of an iliac thrombus to avoid a catastrophe of pulmonary thromboembolism in a patient who had just recovered from shock. She was started on prazosin for pre-operative stabilization. Laparotomy and right adrenalectomy was done (Figure 5), biopsy showed a ganglioneuroblastoma, bone marrow biopsy was negative for N-myc and Positron Emission Tomography (PET)- CT scan was normal.

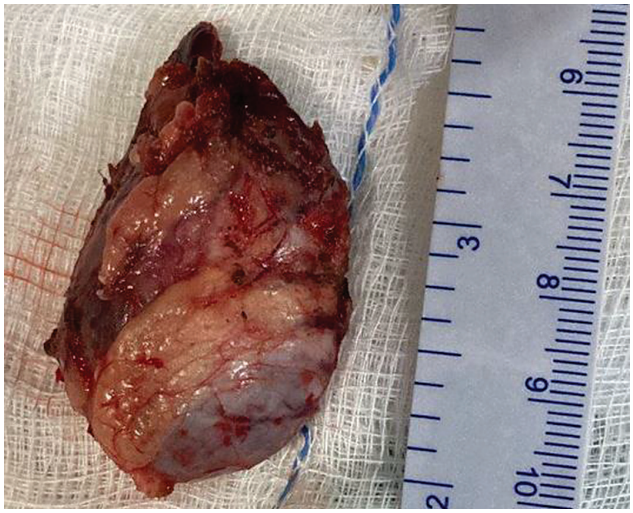

Figure 5. Case 3. Laparotomy and right adrenalectomy were done. Biopsy showed ganglioneuroblastoma.

Post surgery she continued to have hypernatremia and hypertension which responded to vasopressin and clonidine. A final diagnosis of ROHHAD-NET was considered, in view of rapid weight gain, persistent sodium disturbance, the hypoventilation, autonomic instability and the presence of a ganglioneuroma. She needed a tracheostomy and weaned off to a portable Bilevel Positive Airway Pressure (BIPAP). Table 1 summarizes the investigations done in the three cases discussed. Table 2 compares the three cases with respect to clinical symptoms, investigations, management and outcome.

Table 1. Summarizing the blood and urine investigations in our 3 cases

	Case 1	Case 2	Case 3
Hemoglobin (g/dl)	11	11.2	8.5
Total leucocyte count (cells/µL)	6600	8,000	19,400
Platelet count (lakh/mm^3)	4	3.8	3.5
ALT (IU/L) [NR: 7-45]	45	43	55
AST (IU/L) [NR: 8-33]	32	32	60
Serum sodium (mmol/L) [NR: 135-145]	4.1	138	158-176
Serum potassium (mmol/L) [NR: 3.5-5.5]	2.2	4.7	3.2
Serum osmolarity			290
Urine osmolarity			200
Urine sodium			<10
Fasting blood sugar (mmol/L) [NR: 3.9-11.1]	5.7	5	6
Fasting lipid profile (mmol/L)	TG – 5.4 mmol/L LDL – 3.7 mmol/L		
Free T4 (pmol/L) [NR: 10.9-22.5 pmol/L]	15.4	21.8	16
TSH (mIU/ml) [NR: 0.6-5.5mIU/ml]	3	6.2	5
Serum prolactin (µg/L) [NR: <25 µg/L]	150	138	Not done
8 am serum cortisol [NR: 110-606 nmol/L]	206 (midnight)	262-634	468
ACTH	Not done	36.7	18
Dexamethasone suppression test [NR <50 nmol/L]	524	44	
DHEAS (µmol/L) [NR: 0.5-3.8]		0.14	0.005
Serum testosterone (nmol/L) [NR:0.08-0.34)		0.21	0.08
Urine metanephrines mcg/day [57-210 mcg/day]	90	120	100
Urine VMA µmol/day [NR:0-38.5 µmol/day]	6	26.4	20
Serum Alpha fetoprotein [NR: 5-10 ng/ml]		1.62	
Humam chorionic gonadotropin (IU/L) [NR: 0.02-0.8]		0.1	
Carcinoembryonic antigen 3 (mcg/L) [NR <3 mcg/L]		3	

DISCUSSION

We describe 3 cases characterized by rapid onset obesity and investigations confirmed the presence of an adrenal neuroendocrine tumor. The diagnosis was delayed in the first two cases and by the time the third child presented, we were more aware and equipped to diagnose ROHHAD.

Dramatic weight gain between the ages of 2 and 4 accompanied by excessive eating is usually the presentation of ROHHAD.[3] Prior to the onset of the above symptoms these children were reportedly healthy. In the months and years that follow, hypothalamic and autonomic dysfunction can manifest.[6] Endocrine disorders such as hypothyroidism or precocious puberty may be early signs for recognition. However, a study done by Desse et.al, have reported four cases who presented with autonomic dysfunction at first, followed by hypothalamic dysfunction and these subset patients developed ROHHAD without obesity.[7] The intensity and timing of these patients' clinical presentations vary. Some individuals show clear behavioral abnormalities, while others show clear endocrine involvement. Electrolyte imbalance, especially dysnatremia, was present in a majority of the patients, requiring attention. Polydipsia or diabetes insipidus leads to water imbalance and dysnatremia secondary to hypothalamic dysfunction. ROHHAD is now also called ROHHAD-NET as 40% of the cases are accompanied by ganglioneuroma in the abdomen and lungs and neuroendocrine tumors such as ganglioneurobalstoma.[8] Most children recorded a short period of around two years between the onset of obesity and the diagnosis of neural crest origin tumor.[4]

The prognosis is poor as alveolar hypoventilation often results in a cardiac arrest in these children. All the three children had a normal chest X ray and 2D echocardiography, metabolic and neurological disorders were also ruled out, hence, central hypoventilation was considered.[5] Three main etiopathogenetic hypothesis have been postulated: genetic, epigenetic, and autoimmune. Extensive screening and chromosomal analysis have failed to uncover any genetic alteration, despite the fact that an underlying genetic component has been hypothesized for the pathophysiology of ROHHAD due to its similarities with Congenital Central Hypoventilation Syndrome (CCHS). However, in order to rule out a *PHOX2B*, genetic testing is advised for all suspected cases of ROHHAD. We could not carry out genetic testing in our cases due to financial constraints.[4] *PHOX2B* mutations are absent, as is the case for other candidate genes, like *ASCL1*, *BDNF* and *HCRT*. *ASCL1* gene is required for the generation of ventral neuroendocrine neurons which acts as a modifier gene for *PHOX2B* and

Table 2. Summarizing the clinical manifestations, investigations, management and outcome of the 3 cases

	Case 1	Case 2	Case 3
History			
1. Age of presentation	6.5 years old girl	4-year-9-month-old girl	3-year-8-month-old girl
2. Presenting symptom	Recent onset weight gain, within two months developed difficulty in breathing, abdominal distension and vomiting.	Rapid onset weight gain 3 months, snoring	Prolonged fever, seizures, hypernatremia, prolonged ventilation
Examination	Body Mass Index (BMI) 22.5 kg/m^2 (+3 SD). Acanthosis nigricans + Hypertension +	BMI 24.9 kg/m^2. (+4.45 SD). She appeared to have moon facies, a buffalo hump and acanthosis nigricans over the neck. Blood pressure at the 95th centile	Prolonged fever, seizures, Hypotension Prolonged ventilation
Investigations			
1. serum electrolytes	Hypokalemia(2.2 mmol/L)	Normal	Hypernatremia (176 mmol/L), low potassium levels (3.1 mmol/L)
2. Serum cortisol	206 nmol/L	593 nmol/L	468 nmol/L
3. Dexamethasone suppression test	serum cortisol 524 nmol/L	serum cortisol was 44 nmol/L	Not done
4. Serum prolactin	150 µg/L	138 µg/L	Not done
5. CT abdomen findings	An adrenal mass	A heterogeneously enhancing lesion with fairly defined soft tissue density lesion in the pelvis with a possibility of a neurogenic neoplasm.	Right adrenal mass and thrombus involving bilateral external and common iliac veins.
Management			
1. Surgery	Laparotomy done and a large mass was removed.	Tumor excision was done.	She was started on desmopressin, spironolactone and hemodialysis. Laparotomy and right adrenalectomy was done.
2. Histopathology	Adrenal ganglioneuroma.	Ganglioneuroma	Ganglioneuroblastoma
Outcome			
1. Immediate post-operative	Succumbed	Discharged	Post surgery continued to have hypernatremia and hypertension. She needed tracheostomy.
2. Long term		She had gained 5 kg on follow up after 2 months.	Gaining weight

Table 3. Key differentiating features between ROHHAD syndrome, PWS and CCHS

	ROHHAD syndrome	PWS	CCHS
Rapid onset obesity	Yes	Yes	No
Hypoventilation	Yes	Sometimes	Yes
Growth Hormone deficiency, Hypothyroidism, Adrenal dysfunction, precocious puberty, hypogonadism	Sometimes	Sometimes	No
Hyperprolactinemia	Yes	No	No
Disturbance in water balance	Yes	No	No
Bradycardia	Sometimes	No	Sometimes
Gastrointestinal dysmotility	Yes	No	Yes
Thermal dysregulation	Yes	Yes	Yes
Cold extremities, increased sweating	Yes	No	Yes
Altered pain perception	Yes	Yes	Yes
Behavioural disorders	Sometimes	Yes	Sometimes
Sleep abnormalities	No	Yes	Sometimes
Neural crest tumors	Yes	No	Yes
Neonatal hypotonia	No	Yes	No
Delayed motor and cognitive skills	No	Yes	Yes
Dysmorphic facial features	Sometimes	Yes	Sometimes
Genetic testing	No candidate genes	Parent specific DNA methylation	PHOX2B mutation

BDNF gene has a role in neuronal development. Epigenetic hypothesis is supported by report of discordant presentation of ROHHAD syndrome in monozygotic twins.[6] Numerous authors who have described patients with clinical presentations consistent with ROHHAD and whose CSF fluid analysis revealed intrathecal secretion of oligoclonal bands as well as the detection of anti-hypothalamic and ant pituitary antibodies have proposed the immune-mediated etiology.[9] The possibility of a genetic etiology is slowly losing value and newer possibilities like the epigenetic theory, paraneoplastic syndrome, an autoimmune syndrome or the need for a trigger seems more promising.[10] Table 3 highlights the key differentiating features between ROHHAD, Prader Willi Syndrome (PWS) and Congenital Central Hypoventilation Syndrome (CCHS).

Due to phenotypic similarities, patients with ROHHAD syndrome are usually missed for Prader-Willi syndrome, a disorder characterized by early childhood obesity. In the absence of low birth weight, infantile hypotonia and feeding difficulties during early infancy, this differential was excluded.[11] A potential overlap between ROHHAD and Smith–Magenis syndrome (SMS) has also been suggested.[12] CCHS secondary to PHOXB2 mutation can be a differential for central hypoventilation, however as our cases presented with other clinical features of ROHHAD, this diagnosis was ruled out.

Sixteen individuals of ROHHAD syndrome have been recorded to have died from respiratory or cardiac issues, or from an underlying NET such as neuroblastomas or ganglioneuromas.[2] It is believed that paraneoplastic involvement of the hypothalamus may result from these malignancies.[1] Dysautonomia is an additional prevalent ROHHAD syndrome presentation that can result in arrhythmias, sudden cardiac arrest, sleep apnea, and/or narcolepsy, among other potentially fatal occurrences.[13]

CONCLUSION

ROHHAD/NET is an uncommon illness that primarily affects females and manifests in childhood. The early indicators that can be identified are rapid obesity and hypothalamic dysfunction. Early detection and prompt respiratory support administration may avoid serious complications that could result in untimely death.

LESSONS LEARNED

1. ROHHAD syndrome is a rare cause of hypothalamic obesity accompanied by pituitary hormone abnormalities and autonomic dysfunction that should be kept in mind in the differential diagnosis of monogenic early-onset obesity.
2. All patients with ROHHAD syndrome should be screened for neuroendocrine tumors by imaging and biomarkers.
3. ROHHAD syndrome is a potentially fatal disease that requires timely diagnosis and management by a multidisciplinary team.

Ethical Consideration

Patients' consents were obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfilment of ICMJE authorship criteria.

CRediT Author Statement

DS: Conceptualization, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing; **MSI:** Investigation, Resources, Writing – draft preparation; **JG:** Investigation, Resources, Writing – review and editing; **VMV:** Writing – review and editing, Supervision; **PR:** Writing – review and editing, Supervision; **KMR:** Investigations, Resources; **BA:** Investigation, Resources, Writing – review and editing; **AM:** Supervision

Author Disclosure
The authors have no conflict of interest.

Funding Source
None.

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LETTER TO THE EDITOR

In response to the article, *'Severity and Factors Associated with Depressive Symptoms Among Type 2 Diabetic Patients in Vietnam,'* by Nguyen, et al., published in JAFES Vol. 38 No. 2.

Before Explaining Depression Solely Caused by Diabetes, All Other Causes Must Have Been Ruled Out

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Key words: depression, PHQ-9, type 2 diabetes

We were interested to read the article by Nguyen et al. on a cross-sectional study on the prevalence of depression assessed with the Patient Health Questionnaire-9 (PHQ-9) in 419 patients with type 2 diabetes (T2D).[1] It was found that 45% of the included patients had depression of varying severity.[1] Mild, moderate, moderately severe and severe depressive symptoms were found in 36.0%, 7.6%, 1.4% and 0.2%, respectively.[1] Patients who had been treated for T2D for a longer period of time were more likely to have depressive symptoms.[1] Depression was positively correlated with current alcohol consumption, comorbidities and irregular physical activity.[1] Patients with major depression (high PHQ-9 score) were more likely to have not taken their antidiabetic medication in the last month.[1] The study is excellent, but some points should be discussed.

The first point is that causes of depression other than T2D were not sufficiently ruled out. Alternative causes of depression that were not considered were loss of close relatives, burnout, insomnia, pressure from superiors, poor social status, job loss, drugs, medications, mental comorbidities, relationship breakdown, pregnancy, menopause, physical or sexual abuse, major life changes, chronic pain, loneliness, financial problems and genetic predisposition. Unless alternative causes of depression have been adequately ruled out, depression cannot be solely attributed to T2D.

The second point is that the included patients were not systematically subjected to cerebral imaging.[1] A study analyzing the frequency of depression in T2D patients should also correlate the frequency of depression with organic abnormalities of the central system (CNS). Therefore, we should know how many patients had diabetic encephalopathy, previous stroke or hemorrhage, history of infectious or immunological encephalitis or meningitis, demyelinating disease, cognitive impairment or dementia, neurodegenerative disease, or a primary or secondary brain tumor.

The third point is that there was no mention of how many of the included patients were already diagnosed with depression before the onset of T2D. Knowing if they had depression before the onset of T2D is crucial, as these patients should have been excluded from a study analyzing the association between depression and T2D.

The fourth point is that the patients were not examined for the presence of anxiety. Since depression can be associated with generalized anxiety disorder, social anxiety disorder, panic attacks, phobias, obsessive-compulsive disorder or post-traumatic stress disorder,[2] it would have been imperative to ask the included patients about this aspect of depression as well.

The fifth point is that the increase in PHQ-9 score with duration of diabetes may also be due to the fact that as the duration of T2D increases, more complications and comorbidities develop, thus the individual patient may require more medication. These comorbidities can trigger depression or exacerbate existing depressive symptoms.

The sixth point is that HbA1c levels were not included in the analysis and correlated with the depression score. Poor diabetes control could be another risk factor for depression in T2D.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 19, 2024. Accepted: August 19, 2024.
Published online first: April 19, 2025.
https://doi.org/10.15605/jafes.040.01.12

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In summary, this interesting study has limitations that influence the results and their interpretation. Addressing these limitations could strengthen the conclusions and reinforce the message of the study. Before attributing depression to persons with diabetes, solely to T2D alternative causes of depression need to be considered and thoroughly ruled out.

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IMAGES IN ENDOCRINOLOGY

Aplasia Cutis Congenita on the Scalp

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Key words: ectodermal dysplasia, fetal diseases, Graves' disease, methimazole, pregnancy, teratogenesis

INTRODUCTION

Aplasia cutis congenita is a rare condition characterized by localized absent skin at birth, often affecting the scalp. The exact pathogenesis is unclear, but it is likely related to disrupted prenatal skin development. Potential etiologies include genetic factors, trauma, intrauterine infections, teratogens, incomplete neural tube closure, and vascular compromise. We present a case of aplasia cutis congenita on the scalp potentially associated with maternal methimazole use.

A term male newborn was delivered by a 34-year-old female with a history of Graves' disease. The newborn had three well-demarcated, round lesions of absent skin on the scalp, measuring up to 1 centimeter in diameter. (Figure 1) The mother had been treated with methimazole 5 mg/day for mild Graves' hyperthyroidism. After 78 days of treatment, she tested positive for pregnancy. Methimazole was switched to propylthiouracil 50 mg/day at 9 weeks of gestation. She remained euthyroid, and propylthiouracil was discontinued at 23 weeks of gestation until delivery. The diagnosis of aplasia cutis congenita was made, potentially

Figure 1. Three well-demarcated, round scalp lesions characterized by full-thickness skin loss without involvement of the calvarium or signs of inflammation, each measuring up to 1 cm in diameter, consistent with aplasia cutis congenita on the scalp.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 21, 2024. Accepted: September 13, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.11

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related to methimazole exposure, known as methimazole embryopathy. Treatment involves simple wound care, leading to healing within a few months and often leaving an atrophic scar. Large lesions or those involving the skull may require surgical reconstruction.

In this patient, with deep scalp lesions located at the midline vertex, imaging studies are indicated to assess for underlying bone defects, vascular anomalies, or brain malformations such as meningomyelocele or porencephaly. Fortunately, the ultrasound revealed no abnormalities. Diagnosis is generally based on clinical assessment; a skin biopsy is not necessary in our case unless other lesions are suspected, and it should not be performed without prior imaging. The differential diagnosis includes conditions such as obstetric trauma from forceps, vacuum extraction, or fetal scalp monitor electrodes; infections like herpes simplex or varicella zoster; and epidermolysis bullosa. However, there is no evidence of these conditions in this case.

Current evidence does not establish a direct causal relationship between aplasia cutis congenita and methimazole use. However, antithyroid drugs should be avoided in the first trimester of pregnancy to prevent teratogenic effects, as both methimazole and propylthiouracil cross the placenta.[1] The 2017 American Thyroid Association Guidelines recommend using propylthiouracil in the first trimester and switching to methimazole in the second trimester. This approach helps mitigate the risk of hepatotoxicity associated with propylthiouracil while effectively managing hyperthyroidism, and reduces the teratogenic risks of methimazole, which can cause more severe birth defects than propylthiouracil, as major organs and systems are formed by the end of the first trimester.[2,3] For patients with mild hyperthyroidism, propylthiouracil may be considered before conception, and antithyroid drugs can be discontinued upon confirming pregnancy if thyroid function remains normal.[2,3]

Acknowledgments
The authors would like to express their sincere gratitude to Dr. Sidtinon Julawukkananon for the photograph.

Ethical Consideration
The patient consent form was obtained before manuscript submission.

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

CRediT Author Statement
SW: Conceptualization, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization; **CS:** Conceptualization, Investigation, Resources, Data Curation, Writing – review and editing, Visualization, Supervision, Project Administration.

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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Disclosure of Editorial Conflict of Interest

As part of good publication practices, all editors of the JAFES (Editor-in-Chief, Vice Editor-in-Chief, Associate Editors, Editorial Board and Advisers) are required to disclose on an annual basis, any potential conflict of interest, including current or recent financial relationships with any commercial entity whose products or services may be contained in the journal content. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. This policy follows the recommendations of the International Committee of Medical Journal Editors (ICMJE) and the Committee on Publication Ethics (COPE).

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Prof. Jimeno receives honoraria for lectures on lipid lowering drugs (Atorvastatin, Rosuvastatin, Ezetimibe, Insulin Glargine) from Organon, AstraZeneca, Merck, Menarini, Sanofi). She also receives support for attending meetings on various antidiabetic medications from GX Pharmaceuticals, LG Chem, Corbridge. She is the Treasurer/ Member of the Board of Directors of the Philippine Lipid and Atherosclerosis Society (PLAS). She is a stockholder of the Metro Pasay Medical Center.

GABRIEL V. JASUL JR. | Associate Editor
Prof. Jasul received honoraria for lectures from Sanofi Aventis, Novo Nordisk, MSD, Boehringer Ingelheim, Abbott Nutrition, AstraZeneca, LRI- Therapharma, UMed and Woerwag.

MADE RATNA SARASWATI | Associate Editor
Prof. Saraswati receives honoraria for lectures from Merck, Zuellig Pharma Therapeutics, Kalventis Sinergi Farma and Novo Nordisk.

NORLAILA MUSTAFA | Associate Editor
Prof. Mustafa receives grants for lectures from Novo Nordisk, Astra Zeneca, Zuellig Pharma, Servier and Eli Lilly.

THAN THAN AYE | Associate Editor
Prof. Aye has nothing to disclose.

CHAICHARN DEEROCHANAWONG | Associate Editor
Prof. Deerochanawong has nothing to disclose.

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Assoc. Prof. Khue receives consulting fees from Merck. She receives honoraria for lectures from Servier, Boehringer Ingelheim and Novo Nordisk. She is an Advisory Board of Merck Serono.

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Prof. Abacan receives grants as principal investigator of the Registry of Lysosomal Storage Disorders from Sanofi Genzyme (2014 to present) and as co-investigator of the SHP-ELA-401 - A Long-Term, Open-Label, Multicenter, Phase IV Study to Assess Longitudinal Changes on Height and Weight in Patients with MPS II who are receiving Elaprase and started Treatment with Elaprase at <6 Years of Age - Shire (2015-present). She is a Consultant Medical Specialist at the Institute of Human Genetics at the University of the Philippines-National Institutes of Health. She received honoraria as a lecturer of the Acute and Chronic Management of Organic and Amino Acidurias Training by Nutricia and Workshop for Dietitians (April 26, 2025). She is a co-chair of the National Transplant Ethics Committee of the Department of Health and of the Metabolic Experts Panel at the Newborn Screening Reference Center of the National Institutes of Health.

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Prof. Abad has nothing to disclose.

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Prof. Alejandria received research grants from the Department of Science and Technology – Philippine Council for Health Research and Development and from CRDF Global.

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Prof. Bagamasbad received grant funding from the Department of Science and Technology-Philippine Council for Health Research Development (DOST-PCHRD) to conduct research on prostate cancer and SARS-CoV-2 and the DOST-National Academy of Science and Technology (NAST) to conduct research on prostate cancer. She received honoraria as a plenary speaker of the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM) and the Philippine Society of Medical Oncology (PSMO). She is a member of the Endocrine (ENDO) Society (no financial involvement).

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Prof. Nattapol has nothing to disclose.

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Dr. Chng has nothing to disclose.

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Dr. Silao receives research grants from the Newborn Screening Reference Center, National Institutes of Health, Department of Science and Technology-Philippine Council for Health Research Development (DOST-PCHRD). She receives honoraria for lectures and manuscript writing from Nestle Nutrition Institute. She receives support for attending meetings at the Asia Pacific Society of Human Genetics, Medical Genetics and Genomics Association in Thailand and Universitas Yarsi in Indonesia. She is part of the research group for the Methods and Means for Prognosticating the Occurrence of Pulmonary Complications in Leptospirosis and Early Diagnosis and Prognosis of Complicated Leptospirosis using Molecular Markers. She is the Secretary/Board of Director of the Asia Pacific Society of Human Genetics (no financial involvement) and member of the Human Genome Education Committee (no financial involvement). She is a stockholder of the Clinical Genetics and Genomic Counseling Care Services (CGGCCS) Inc.

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Dr. Tangco has nothing to disclose.

NGUYEN VAN TUAN | Editorial Board Member
Prof. Van Tuan received financial support from the Australian National Health and Medical Research Council for his research. He also received a grant from Amgen to conduct research in osteoporosis. He is a member of Healthy Bone Australia (no financial involvement).

MYO WIN | Editorial Board Member
Prof. Win has nothing to disclose.

MARITA V.T. REYES | Ethics Adviser
Dr. Reyes received a research grant to the Women's Health Care Foundation from the Philippine Council for Health Research and Development. She receives honoraria as Department of Science and Technology-Philippine Council (DOST-PCHRD) Philippine Health Research Ethics Board. She is the President and Chair of the Board of Trustees of the Women's Health Care Foundation (WHCF), Inc. She is a stockholder of Makati Medical Center, Manila Doctors Hospital, The Medical City.

AMADO O. TANDOC III | Editorial Coordinator
Dr. Tandoc receives fees as a Consultant Editor of the Scientific Proceedings of the Lung Center of the Philippines, Philippine Journal of Orthopaedics and the Philippine Journal of Allergy, Asthma and Immunology. He is also the Editor-in-Chief of the Philippine Journal of Pathology. He is a speaker and Treasurer of the Philippine Association of Medical Journal Editors (PAMJE).

Journal of the
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Instructions to Authors

The **Journal of the ASEAN Federation of Endocrine Societies (JAFES)** is an open-access, peer-reviewed, English language, medical and health science journal that is published two times a year by the ASEAN Federation of Endocrine Societies (AFES). **Authors may include members and non-members of the AFES.**

Manuscripts, correspondences and other editorial matters should be sent via electronic mail to JAFES@asia.com or JAFES.editor@gmail.com.

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ARTICLE TYPES

JAFES welcomes manuscripts on all aspects of endocrinology and metabolism in the form of original articles, review articles, case reports, feature articles (clinical practice guidelines, clinical case seminars, book reviews, et cetera), editorials, letters to the Editor, brief communications, images in endocrinology and special announcements. See Inset Box for descriptions and specific requirements per article type.

COVER LETTER

A cover letter must accompany each manuscript which should cite the title of the manuscript, the list of authors (complete names and affiliations and their specific role/s in writing the manuscript), with one (1) author clearly designated as correspondent, providing his/her complete postal/mailing address, telephone number, e-mail and fax number. The **JAFES cover letter template** must be used.

*All authors are required to obtain an ORCID iD. To register, kindly follow this link: https://orcid.org/register.

AUTHOR FORM

For submissions to the JAFES to be accepted, all authors must read and accomplish the **JAFES Author Forms** consisting of: (1) the Authorship Certification, (2) the Author Declarations, (3) the Author Contribution Disclosure, (4) the Author Publishing Agreement and (5) the Conversion to Visual Abstract (optional for original articles only) to improve dissemination to practitioners and lay readers. The completely accomplished JAFES Author Forms shall be scanned and submitted along with the manuscript. No manuscript shall be received without the completely accomplished JAFES Author Forms.

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To improve and standardize reporting of findings depending on the study type, authors should ensure compliance with and submit the appropriate accomplished EQUATOR (Enhancing the QUAlity and Transparency of Research) Network Guidelines. These guidelines are freely available at: http://equator-network.org.

1. CONSORT (2010) Checklist for Reporting Clinical Trials
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3. COREQ (2007) Checklist for Reporting Qualitative Research
4. PRISMA (2009) Checklist for Reporting Systematic Reviews and Meta-Analyses
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7. CHEERS (2013) Checklist for Reporting Economic Evaluation of Health Interventions
8. SQUIRE (2015) Checklist for Quality Improvement Reporting in Healthcare
9. ARRIVE (2013) Guidelines for Reporting Animal Research

ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

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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:

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2. The manuscript should be arranged in sequence as follows: (1) Title Page, (2) Abstract, (3) Text, (4) References, (5) Tables, and (6) Figures & Illustrations.
3. References should pertain directly to the work being reported.
4. All the sheets of the manuscript should be labelled with the family name of the main author (all in capital letters) and page number (in Arabic Numerals) printed on the upper right corner.
5. All manuscripts not complying with the above shall be promptly returned for correction and resubmission.

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Keywords
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Text
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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.

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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.
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5. A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
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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.

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2. Create tables, preferably using Microsoft Excel, with one table per worksheet.
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5. Font should be Arial Narrow size 8.
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5. Up to a maximum of five (5) tables are allowed.

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5. All identifying data of the subject/s or patient/s under study such as name or case numbers should be removed.
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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.
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4. Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal.

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ARTICLE TYPES

Original Articles
The abstract should contain no more than 200 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.

Reviews
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. The abstract should be from 50 to 75 words and should not be structured. A manuscript for reviews should not exceed 15 typewritten pages (including tables, figures, illustrations and references) or 4000 words.

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The abstract should be from 50 to 75 words and should not be structured. A manuscript for case reports or case series should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words.

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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. The abstract should be from 50 to 75 words and should not be structured. A manuscript for feature articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Endocrine Perspectives
JAFES may invite topic experts to publish viewpoints, opinions, and commentaries on relevant topics. A manuscript for endocrine perspectives should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words. *Not peer reviewed.

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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. The abstract should be from 50 to 75 words and should not be structured. A manuscript for brief communications should not exceed 5 typewritten pages (including tables, figures, illustrations and references) or 1500 words.

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.

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JAFES welcomes feedback and comments on previously published articles in the form of Letters to the Editor. No abstract or keywords necessary. A Letter to the Editor must not exceed 2 typewritten pages or 500 words.

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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.

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Authors may submit interesting, unique, rare, highly educational images from actual cases with an accompanying brief history and discussion. No abstract or keywords are necessary. The image should be at least 600 dpi. The write up should not exceed 500 words with a maximum of 10 references.

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Instructions to Authors	☐ Review manuscript submission guidelines
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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
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Cover Letter

(Date)

To: **The Editor-in-Chief**
Journal of the ASEAN Federation of Endocrine Societies (JAFES)

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.

Attached herewith are the following: the completely accomplished **Author Form with author contribution disclosure** and **author publishing agreement**, in which all the authors certified authorship criteria was satisfactorily met and the specific contributions of the authors are listed and the author copyright is retained granting publishing and distribution rights to the JAFES; the **Author Declaration** that the work is original and is not under simultaneous consideration in other journals and the **ICMJE Disclosure forms** of ALL the authors (*where all conflicts of interest have been declared/there are no conflicts of interest*).

For original articles, we submit a scanned copy of our Ethics Review Approval/registration in trial registries (as appropriate) and the appropriate EQUATOR Network checklist used in writing the manuscript.

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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☐ (3) that we are all responsible for the final approval of the version to be published; AND
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