Philippine Society of Pathologists, Inc.

Vol. 9 No. 2 December 2024
ISSN 2507-8364 (Online)

PHILIPPINE JOURNAL OF PATHOLOGY

The Official Journal of the Philippine Society of Pathologists, Inc.

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Philippine Journal of Pathology
Vol. 9 No. 2 December 2024 | ISSN 2507-8364 (Online)
https://philippinejournalofpathology.org

PHILIPPINE JOURNAL OF PATHOLOGY

The Philippine Journal of Pathology (PJP) is an open-access, peer-reviewed, English language, medical science journal published by the Philippine Society of Pathologists, Inc. Committee on Publications. It shall serve as the official platform for publication of high quality original articles, case reports or series, feature articles, and editorials covering topics on clinical and anatomic pathology, laboratory medicine and medical technology, diagnostics, laboratory biosafety and biosecurity, as well as laboratory quality assurance. The journal's primary audience are Filipino laboratorians, diagnosticians, laboratory managers, pathologists, medical technologists, and all other medical and scientific disciplines interfacing with the laboratory. The PJP follows the **ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, EQUATOR Network Guidelines,** and **COPE Guidelines.** The PJP does not charge any article processing or submission fees from authors. It does not charge any subscription fees or download fees to access content.

Congratulations to the Philippine Journal of Pathology on its 2nd issue for 2024

On behalf of the PSP, Inc., it is my distinct honor to congratulate the Philippine Journal of Pathology (PJP) on the release of its 2nd issue for 2024, marking another milestone in its journey. As we celebrate the journal's 8th year since its revival in 2016, we are reminded of the PJP's steadfast dedication to advancing the field of pathology in the Philippines and beyond.

The PJP has grown to become a vital platform for sharing research, fostering collaboration, and inspiring innovation within the Filipino pathology community. This achievement is a testament to the hard work, commitment, of the editorial team, contributors, and peer reviewers who have contributed to elevate the journal's standards and broaden its reach.

As we look ahead, let us continue to envision a future where the Philippine Journal of Pathology evolves into a world-class scientific publication—a beacon of excellence that reflects the best of Filipino research and expertise. Together, we can propel the PJP to greater heights, ensuring it serves as a key resource not only for local practitioners but also for the global scientific community.

To the entire PJP team, thank you for your unwavering passion and dedication. You are not only chronicling the progress of our field but also paving the way for the next generation of pathologists to thrive.

Congratulations once again on this significant milestone. May the PJP continue to inspire, educate, and lead in the years to come.

Maria Cecilia F. Lim, MD, FPSP
President, Philippine Society of Pathologists, Inc.

Further and Forward

In our previous issue, we asked the question "Quo Vadis:" where are we heading with the Philippine Journal of Pathology? Eight years and fifteen issues since the Philippine Journal of Pathology was revived, I would like to believe that the journal has somehow been able to pull to stand, through the continuing support of the Philippine Society of Pathologists, Inc., akin to a baby that has achieved a developmental milestone of finally standing on both feet: a bit wobbly, but with some stability in balancing its center of gravity.

To ensure its growth and development, continued relevance, and impact, we must craft a comprehensive roadmap for the next six years, 2025-2030. This vision demands a critical assessment of our current status, a clear articulation of our strategic goals, and the formulation of actionable plans to achieve them.

We aim to reinforce the *Philippine Journal of Pathology* as the Society's official platform for the dissemination of high-quality research in pathology. To effectively chart our course from this point forward, we must first understand our current position and come up with strategies that shall enhance academic quality, increase visibility and impact, improve operational efficiency, and strengthen the Filipino pathology scientific community.

To achieve this goal, we will need to reestablish and fully engage the PJP editorial board, implement a robust peer review system with timely reviews and constructive feedback, revisit our author guidelines to ensure high quality submissions, invest in digital infrastructure to streamline operations and further improve accessibility, develop a comprehensive marketing and promotion strategy to increase visibility and readership. This will require forging strategic partnerships, training and mentorship to young pathologists and researchers.

By aligning our strategic direction with global standards in pathology publishing and the evolving needs of the Philippine pathology community, we can position the *Philippine Journal of Pathology* as a leading voice in the field. Let us work together to move further and forward.

Amado O. Tandoc III, MD, FPSP
Editor-in-Chief

https://doi.org/10.21141/PJP.2024.16

Sydney Declaration on Predatory or Pseudo Journals and Publishers

We, the participants in the Joint Meeting of the Asia Pacific Association of Medical Journal Editors (APAME), the Western Pacific Region Index Medicus (WPRIM), and Index Medicus of the South-East Asia Region (IMSEAR), held in Newcastle, New South Wales, Australia from August 28 to 30, 2024:

CONSIDERING

That predatory (or pseudo) journals and publishers offer open access publication in exchange for fees without robust editorial or publishing services; these include "fake" or "scam" journals or publishers who send phishing emails which promise quick review;

That the articles collected by predatory (or pseudo) journals or publishers may never be published, or often are published with poor quality or accessibility, irrespective of any attempts by authors to withdraw them, resulting in such research effectively being lost;

CONFIRM

Our commitment to uphold the quality and integrity of our individual journals and their respective submission, editing and review processes, in opposition to predatory (or pseudo) journal practices;

Our commitment to exercise vigilance and safeguard the quality and integrity of our respective publishers against predatory (or pseudo) publication processes;

Our commitment to ensure that member journals of the Asia Pacific Association of Medical Journal Editors (including those indexed in the Western Pacific Region Index Medicus and Index Medicus of the South-East Asia Region) and their publishers do not engage in predatory (or pseudo) journal or publication practices;

CALL ON

Member States of and governments in the World Health Organization (WHO) Western Pacific and South-East Asia Regions, in collaboration with stakeholders from the nongovernmental and private sectors, to formulate and implement procedures and processes for identifying and dealing with predatory (and pseudo) Sydney Declaration on Predatory or Pseudo Journals and Publishers journals and publishers, and for guiding new and existing journals away from engaging in predatory (and pseudo) journal and publisher practices;

Stakeholders from the public and private sectors, national and international organizations, universities and academic societies to support WPRIM, IMSEAR, the Global Index Medicus of WHO, in ensuring the availability of high quality health information for all that is not marred by predatory (and pseudo) journal and publication practices;

COMMIT

Ourselves and our journals not to engage in predatory (or pseudo) journal practices, by learning about and implementing best journal practices, in accordance with the recommendations and guidelines issued by such bodies as the International Committee of Medical Journal Editors (ICMJE), the Committee on Publication Ethics (COPE), and the World Association of Medical Editors (WAME);

Our organization, APAME, to building collaborative networks, convening meaningful conferences, and organising participative events to educate and empower editors, peer reviewers, authors, librarians, and publishers to recognise and avoid engaging in predatory (or pseudo) journal and publisher practices.

30 August 2024, Newcastle, NSW, Australia

This declaration was launched at the 2024 Convention of the Asia Pacific Association of Medical Journal Editors (APAME) held in New South Wales, Australia from 28 to 30 August 2024. It is concurrently published in Journals linked to APAME and listed in the Index Medicus of the South-East Asia Region (IMSEAR) and the Western Pacific Region (WPRIM).

PSP 75

shining at 75

1950 - 2025

Purpose & Solidarity in Practice

April 10-12, 2025
The Manila Hotel

REGISTRATION MECHANICS

1. Timeline for registration is as follows:
   a. **Early bird registration** begins on **November 15, 2024, 12:00 M.N.** and closes on **December 27, 2024, 11:59 P.M.**
   b. **Regular registration** reopens on **January 2, 2025, 12:00 M.N**. and closes on **March 25, 2025, 11:59 P.M.**
2. Registration should be done only within the abovementioned dates and only through the **PSP Events Page: https://eventsv2.psp.com.ph/login**.
   a. There will be **NO LATE AND ON-SITE REGISTRATION**.
   b. Persons under proxy registration by a company should likewise register within the abovementioned timeline.
   c. Graduates who will take the diplomate exams in 2025 may initially register as graduates. In the event that they pass the exam, the consultant rate shall apply, and they must settle the remaining balance within a certain period. Further details regarding this shall be announced as the results of the diplomate exams are released. The graduate must register within the early bird period to avail of the discounted rates.
   d. For individuals who do not have an account, please visit the PSP Events Page, click **Sign-up**, and follow the on-screen instructions to create your account.
3. Online registration forms must be accomplished first before payment.
   a. There are **limited slots** for **in-person** attendance that will be given on a **first come, first served basis**.
   b. For in-person registrants, please fill out the section of the form on dietary restrictions/food allergies.
4. For payment, please refer to further instructions detailed on the site.
   a. For a single transaction covering multiple individuals (e.g., persons under proxy registration), please indicate the names of the persons covered in the proof of payment/receipt. Then, distribute it to the persons covered, and they may proceed with individual registration using this proof of payment.
   b. Please wait for 2-3 business days for the secretariat to confirm your payment.

REGISTRATION MECHANICS

5. **No reimbursement or refund arrangements shall be entertained by the society.**
6. Online registrants who wish to change their registration to in-person attendance may only do so BEFORE the secretariat confirms the payment.
   a. If payment has not yet been made, please cancel the previous registration attempt and create a new one choosing the preferred method of attendance.
   b. In case that the registrant has already paid for the previous registration, he/she must immediately inform the secretariat and wait for them to confirm the remaining balance, which should be settled as soon as possible.
   c. A single photo/file containing both transaction receipts/proof (original and additional payment) should be used for the new registration.
7. Individuals who registered AND paid for in-person attendance will NOT be able to change their registration to online even if the secretariat has not yet confirmed the payment.
8. Once payment is confirmed, an email notifying the successful registration shall be sent to your registered email address.
9. **Confirmed registrations cannot be changed, cancelled, and refunded.**
10. Consultants who registered for online attendance will be able to join the business meeting. They must be individually logged-in during the business meeting to be considered present.
11. In case of difficulties during registration, kindly contact the PSP secretariat through the following channels:

    Viber: **+63 922 851 7379**

    Email: **pspinc1950@gmail.com**

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Purpose & Solidarity in Practice

April 10-12, 2025
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REGISTRATION RATES

Category	In-person Regular	In-person Early bird	Online
PSP MEMBERS			
Consultants (Including new diplomates)	Php 8,500	Php 7,500	Php 6,500
Residents and Graduates	Php 5,500	Php 5,000	Php 4,500
Regular (60 to 69 yo.)	with 20% discount		
Regular Members (70 above)	FREE but must register before deadline		
NON-MEMBERS			
Locals			
MD: Consultants, non-trainees	Php 9,500	Php 8,500	Php 6,500
MD: Residents and fellows in training/graduates	Same rate as PSP Member Residents and Graduates		
Allied Health	PhP 5,500	PhP 5,000	PhP 4,500
Foreigners	USD 250	-	USD 200

REGISTRATION PERIOD

EARLY BIRD: November 15, 2024 12:00 M.N. to
December 27, 2024 11:59 P.M.

REGULAR: January 02, 2025 12:00 M.N. to
March 25, 2025 11:59 P.M.

SCAN TO REGISTER

PSP 75 1950-2025 Shining at Purpose & Solidarity in Practice

M
THE MANILA HOTEL

ACCOMMODATION RATES

Exclusive for PSP Members

Room	Net Price (Php, per night)*
Deluxe Room Twin	6,500
Deluxe Room King	6,500
Deluxe Room Twin with Extra bed	9,100
Deluxe Room King with Extra bed	9,100
Veranda Suite (King bed only)	10,000
Luneta/Intramuros Suite (King bed only)	11,000
Sunset/Sunrise Suite (King bed only)	14,000

*** Rate is inclusive of local taxes and VAT.**

INCLUSIONS

- Daily buffet breakfast
- Internet connection
- Local mineral water
- Welcome fruits
- Coffee and tea-making facilities (one-time replenishment daily)
- Complimentary use of Health Club facilities
- Complimentary use of outdoor pool

AIRPORT TRANSFERS

to NAIA T1, T2, or T3 (per pick up/drop off)

- **Innova** (**Php 1,975** net) max of **2 adults**
- **Van** (**Php 2,600** net) max of **6 adults**

MODES OF PAYMENT

- Credit Card
- Bank Transfer
- Cash/Credit card upon check-in (applicable to Guest with Credit card guarantee only)
- GCash

TMH x PSP 2025

BOOK HERE

OPEN ACCESS – ORIGINAL ARTICLE

Assessment of RBC Antibody Frequencies and Comparison of Screening and Identification Techniques Used in a Tertiary Hospital in the Philippines

Margarita Rae Rosario, Joaquin Antonio Patag, Rex Michael Santiago

Institute of Pathology, St. Luke's Medical Center, Quezon City, Philippines

ABSTRACT

Background. Pre-transfusion testing is done to avoid transfusion morbidity from unexpected RBC antibodies. Available commercial kits from Western brands may not consider racial differences in antibody frequencies between East/Southeast Asians and Western populations. The limited number of blood banks in the Philippines precludes research on RBC antibody screening and identification in the country.

Objective. This study aimed to compare RBC antibody screening and identification methods in patients at a tertiary hospital in the Philippines, assess the frequency of major blood group antibodies using both techniques, and review clinical histories of discrepant and nonspecific cases.

Methodology. Retrospective review showed 118 cases with both screening and identification tests using both conventional tube-based technique and column agglutination or gel-based technique. Antibody frequencies and discrepant or nonspecific results were recorded. Concordance rates were calculated, and differences between the two methods were analyzed using 95% confidence interval (95% CI). Clinical histories of discrepant and nonspecific cases were also reviewed.

Results. The most frequent major blood group was Rh (41 cases or 34.7%), followed by MNS (34 cases or 28.8%) and Kidd (15 cases or 12.7%). The most common antibody was Anti-E (24 cases or 20.3%), followed by Anti-Mi^a (19 cases or 16.1%), and Anti-M and Anti-c (12 cases each, or 10.2% each). The concordance rate for screening was statistically significant at 72%. Concordance rate for identification was 59.3%, with significant difference in identifying Anti-Mi^a. Clinical histories for discrepant or nonspecific cases showed previous transfusions, pregnancy, lymphoproliferative conditions, and certain medications.

Conclusion. Statistically significant differences between the two methods were found, with the gel-based technique identifying more Anti-Mi^a cases. Negative results from the tube-based method do not fully exclude Anti-Mia. These discrepancies highlight the benefit of using both methods for comprehensive RBC antibody screening and identification, done as a complement to the other.

Key words: blood bank, blood transfusions, blood grouping, antibody

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 16 October 2024.
Accepted: 19 November 2024.
Published online first: 28 November 2024.
https://doi.org/10.21141/PJP.2024.13

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INTRODUCTION

A common cause of transfusion morbidity is unexpected RBC antibodies.[1,2] To avoid this, pre-transfusion testing through screening and identification of major blood group antibodies is done. Different test kits implore the use of reagent RBCs or screening cells, where their reaction to patient serum leads to agglutination or hemolysis.

Two methods used for the detection and identification of RBC antibodies include the tube-based method and the gel-based method, each with its own advantages and disadvantages. The conventional tube technique is based on the visible macroscopic aggregates of hemagglutination seen. It offers flexibility to test at different phases, as well as an option to use additive solutions. While it has been considered the reference method,[3,4] it has unstable endpoint and interobserver variability.[5] On the other hand, the column agglutination technique or gel-based method is based on differential migration of RBC agglutinates through a small microcolumn containing a dextran

acrylamide size exclusion gel column. Compared to the previous technique, it allows for a more standardized and reproducible approach. However, it has a higher incidence of false positives and has been shown to enhance serologic reactivity that may not be clinically significant.[5,6]

Available commercial kits utilizing these two techniques are often manufactured in Western countries, and are often based on American or European demographics.[7] Issues may arise, as there have been recorded racial differences in the frequencies of RBC antibodies in East and Southeast Asians compared to Western populations.[7-9] Literature on Asian countries show that the frequently seen antibodies are: E, D, M, and Mi^a in Chinese; Lea, E, Mi^a and Le^b in Southeast Asians; and Mi^a and E antibodies in Eastern Taiwanese.[9] Antibodies against MNS blood group were also the most common in Malaysia and Taiwan.[7] This is in contrast to frequencies seen in Western populations, where the most frequent antibodies identified in Americans are E, Le^a, K, D, Le^b, M, P_1, Fy^a, C, and c.[9] With existing commercial kits being often based on Western data where the kit was manufactured, this may be disadvantageous for Asian countries that rely on such kits for routine use.[7] It cannot be dismissed that some antibodies may not be represented in the panels that are utilized in these kits.[10] For example, while antibodies to MNS antigens are common in South and East Asian populations, these are often missed in standard screening cells.[11] Unfortunately, due to the limited number of blood banks that offer such services in the country, there is yet to be a study exploring RBC antibody frequencies, as well as screening and identification techniques used in the Philippines.

This study aimed to compare the two (2) antibody screening and identification methods for the major blood group antibodies in patients who underwent antibody screening and identification in the blood bank of a tertiary hospital in the Philippines. Additionally, it aimed to assess the frequency of major blood group antibodies, and to review clinical histories of discrepant and nonspecific cases.

METHODOLOGY

This is a retrospective, descriptive-analytical, and cross-sectional study approved by the Institutional Ethics Review Committee (IERC) of St. Luke's Medical Center – Quezon City (SLMC-QC), which abided by the Principles of the Declaration of Helsinki (2013) and conducted along the Guidelines of the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) on privacy and confidentiality. The two kits used for antibody screening were the Panoscreen I, II and III 3-vial set by Immucor, Inc. (tube-based method) and the ID-Diacell I-II-III Asia by Bio-Rad (gel-based method). On the other hand, the two kits used for antibody identification were the Panocell-10 12-vial set by Immucor, Inc. (tube-based method) and the ID-DiaPanel by Bio-Rad (gel-based method).

Patient selection

Of 1703 cases reviewed from the Blood Bank and Transfusion Medicine Section of the Institute of Pathology laboratory information systems and manual records, from January 2012 to October 2023, only those included in this study were patients who had complete data on both their RBC antibody screening and identification results using both methods for each test, leaving a total of 118 cases. Cases with incomplete records were excluded in this study.

Data analysis

Data gathered from medical records included the following: age, sex, antibody screening result with corresponding type of kit used, antibody identification result with corresponding type of kit used, and clinical history. Frequency by percentage was used for the descriptive analysis of the study. The concordance rate in percentage was calculated between the two screening and two identification methods. Analysis of the significance of the difference was done using 95% CI.

RESULTS

This study included 118 patients out of 1703 cases reviewed, of which 79 were female and 39 were male. The mean age of our sample population was 57.42 (SD 20.9 years). In terms of major blood groups, the most frequent were antibodies to variants of Rh (41 samples or 34.7%), followed by MNS (34 samples or 28.8%), and Kidd (15 samples or 12.7%). The less frequent blood groups were Lewis (5 samples or 4.2%), Lutheran (2 samples or 1.7%), Kell and Duffy (1 sample each, or 0.8%) (Figure 1). Regarding specific RBC antibody, the most common was Anti-E (24 samples or 20.3%) followed by Anti-Mi^a (19 samples or 16.1%), Anti-M and Anti-c (12 samples or 10.2% each), and Anti-Le^a (11 samples or 9.3%). The less common antibodies in the sample population were Anti-Jk^b (8 samples or 6.8%), Anti-Jk^a (7 samples or 5.9%), Anti-P_1 (5 samples or 4.2%), Anti-Le^b (3 samples or 2.5%), Anti-Lu^a, Anti-e and Anti-C (2 samples or 1.7% each), and Anti-s, Anti-S, Anti-N, Anti-Fy^a, Anti-K, and Anti-C^w (1 sample or 0.8% each) (Table 1, Figure 2).

Table 1. Frequency of RBC antibodies

Antibody	n (%)
Anti-D	0 (0)
Anti-C	2 (1.7)
Anti-c	12 (10.2)
Anti-E	24 (20.3)
Anti-e	2 (1.7)
Anti-C^w	1 (0.8)
Anti-K	1 (0.8)
Anti-k	0 (0)
Anti-Fy^a	1 (0.8)
Anti-Fy^b	0 (0)
Anti-Jk^a	7 (5.9)
Anti-Jk^b	8 (6.8)
Anti-Le^a	11 (9.3)
Anti-Le^b	3 (2.5)
Anti-M	12 (10.2)
Anti-N	1 (0.8)
Anti-S	1 (0.8)
Anti-s	1 (0.8)
Anti-Mi^a	19 (16.1)
Anti-H	0 (0)
Anti-P_1	5 (4.2)
Anti-Lu^a	2 (1.7)
Anti-Lu^b	0 (0)
Autoantibodies present	36 (30.5)
Nonspecific antibody/ies	15 (12.7)

Based on our findings, the gel-based screening method was able to detect more cases with RBC antibodies (117 samples or 99.2%) compared to the tube-based screening method (86 samples or 72.9%). Concordant positive results were 72% (85 samples). The difference between the two methods was statistically significant based on their non-overlapping computed 95% CI, with the gel-based method having a 95% CI of 96.1 – 99.9, and the tube-based method having a 95% CI of 64.4 – 80.3 (Table 2). In the discrepant screening results, the majority of cases were positive in the gel-based method and negative in the tube-based method (32 samples or 97%), with only one case being positive in the tube-based method and negative in the gel-based method. Among these, Anti-Mi^a was the most identified antibody (16 samples or 48.5%) (Table 3, Figure 3). On the other hand, comparing the tube-based versus the gel-based methods in antibody identification, concordance was 59.3% (70 samples) (Table 4). The difference in identifying Anti-Mi^a antibody was notably statistically significant between the two methods based on their non-overlapping 95% CI, with the gel-based having a 95% CI of 9.6 – 22.5, and the tube-based having a 95% CI of 1.2 – 7.9. There was no statistical difference seen in the other antibodies (Table 5, Figure 4).

Of the 48 discrepant identification results, clinical review showed history of transfusion (30 cases or 62.5%), past pregnancy (22 cases or 45.8%), malignancy (16 cases or 33.3%), history of a volume expander (11 cases or 22.9%), infection (4 cases or 8.3%), and autoimmune disease (2 cases or 4.2%) (Table 6, Figure 5). The clinical history of the 15 cases who were deemed to have antibodies with no specificity were also reviewed, which showed history of transfusion (10 cases or 66.7%), past pregnancy (10 cases or 45.8%), malignancy (8 cases or 53.3%), history of a volume expander (7 cases or 46.7%), infection (5 cases or 33.3%),

Table 2. Concordance between gel-based and tube-based methods

Screening kit, n=118	n (%)	95% CI
Gel-based*		
Positive	117 (99.2)	96.1 - 99.9
Negative	1 (0.8)	0.1 - 3.9
Tube-based*		
Positive	86 (72.9)	64.4 - 80.3
Negative	32 (27.1)	19.7 - 35.6
Concordance	85 (72.0)	

* ID-Diacell I-II-III Asia (Bio-Rad)
** Panoscreen I, II and III 3-vial set (Immucor, Inc.)

Table 3. Frequency of identified antibodies from the discrepant cases

Antibody identified	n (%)
Anti-E	2 (6)
Anti-Jk^a	1 (3)
Anti-Le^a	1 (3)
Anti-Le^b	1 (3)
Anti-M	2 (6)
Anti-N	1 (3)
Anti-Mi^a	16 (48.5)
Anti-Lu^a	1 (3)
Autoantibodies present	9 (27.3)
Nonspecific antibody/ies	6 (18.2)

Table 4. Concordance between the gel-based and tube-based identification kits

Identification kit, n=118		n (%)
Concordance	Yes	70 (59.3)
	No	48 (40.7)

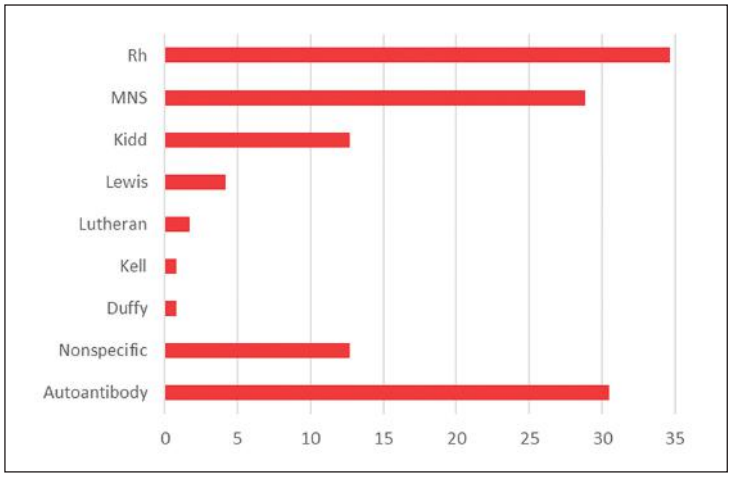

Figure 1. Frequency of RBC major blood group identified.

Table 5. Frequency of identified antibodies per method

Antibody identified	Gel-based, n (%)	95% CI	Tube-based, n (%)	95% CI
Anti-D	0 (0)	-	0 (0)	-
Anti-C	2 (1.7)	0.4 - 5.3	1 (0.8)	0.1 - 3.9
Anti-c	9 (7.6)	3.8 - 13.5	6 (5.1)	2.1 - 10.2
Anti-E	18 (15.3)	0.6 - 22.5	17 (14.4)	9 - 21.6
Anti-e	1 (0.8)	0.1 - 3.9	2 (1.7)	0.4 - 5.3
Anti-C^w	2 (1.7)	0.4 - 5.3	1 (0.8)	0.1 - 3.9
Anti-K	1 (0.8)	0.1 - 3.9	1 (0.8)	0.1 - 3.9
Anti-k	0 (0)	-	0 (0)	-
Anti-Fy^a	0 (0)	-	0 (0)	-
Anti-Fy^b	0 (0)	-	0 (0)	-
Anti-Jk^a	2 (1.7)	0.4 - 5.3	2 (1.7)	0.4 - 5.3
Anti-Jk^b	5 (4.2)	1.6 - 9	5 (4.2)	1.6 - 9
Anti-Le^a	9 (7.6)	3.8 - 13.5	7 (5.9)	2.7 - 11.3
Anti-Le^b	1 (0.8)	0.1 - 3.9	1 (0.8)	0.1 - 3.9
Anti-M	15 (12.7)	7.6 - 19.6	13 (11)	6.3 - 17.6
Anti-N	0 (0)	-	0 (0)	-
Anti-S	2 (1.7)	0.4 - 5.3	0 (0)	-
Anti-s	0 (0)	-	1 (0.8)	0.1 - 3.9
Anti-Mi^a	18 (15.3)	9.6 - 22.5	4 (3.4)	1.2 - 7.9
Anti-H	0 (0)	-	0 (0)	-
Anti-P$_1$	2 (1.7)	0.4 - 5.3	4 (3.4)	1.2 - 7.9
Anti-Lu^a	1 (0.8)	0.1 - 3.9	0 (0)	-
Anti-Lu^b	0 (0)	-	0 (0)	-
Pan-agglutination	20 (16.9)	11 - 24.5	20 (16.9)	11 - 24.5
Non-specific	19 (16.1)	10.3 - 23.5	24 (20.3)	13.8 - 28.3

and Daratumumab medication (1 case or 6.7%) (Table 7, Figure 6). It can also be noted that many cases in the sample population showed the presence of autoantibodies (36 samples or 30.5%) (Table 1), as well as in cases with discrepant results (6 or 18.2%) (Table 3).

DISCUSSION

Our findings show similarities with other Asian countries in terms of frequency of each RBC antibody. Anti-E had a frequency of 20.3% in our sample, which is comparable to Southeast Asians (17.3%) and Taiwanese (15.6%); it is more prevalent among Chinese (53.1%). Our sample's Anti-E antibody frequency is also similar to Americans (20.3% versus 20.8%). Next, the frequency of Anti-Mi^a antibody in our sample (16.1%) is also comparable with the frequencies in Chinese (10.9%) and Southeast Asians (12.5%); it is more prevalent among Taiwanese population (44.4%).[9] The Anti-Mi^a antibody belong to the Miltenberger (Mi) subsystem associated with the MNS blood group. It is rarely reported in the Western population and is rare

Table 6. Clinical history of cases with discrepant results

	n (%)
Autoimmune Disease	2 (4.2)
Infection	4 (8.3)
Volume Expander*	11 (22.9)
Malignancy	16 (33.3)
Past Pregnancy	22 (45.8)
Previous Transfusion	30 (62.5)

*Volume expander including (dextran, gelatin derivatives, hydroxyethyl starch, and human albumin solutions)

Table 7. Clinical history of cases signed out as "antibody of no specificity"

	n (%)
Autoimmune disease	0 (0)
Infection	5 (33.3)
Volume expander*	7 (46.7)
Malignancy	8 (53.3)
Past pregnancy	10 (66.7)
Previous transfusion	10 (66.7)
Daratumumab	1 (6.7)

*Volume expander including (dextran, gelatin derivatives, hydroxyethyl starch, and human albumin solutions)

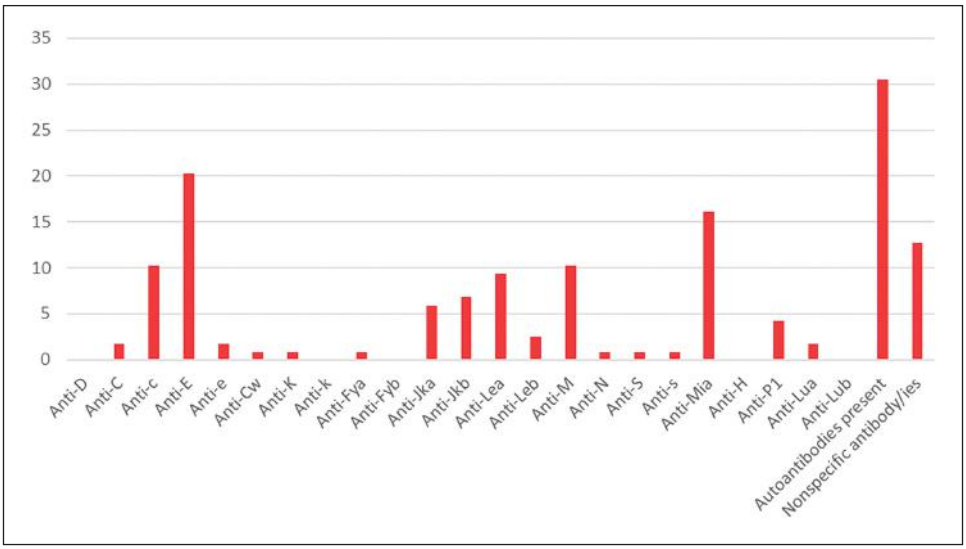

Figure 2. Frequency of RBC antibodies.

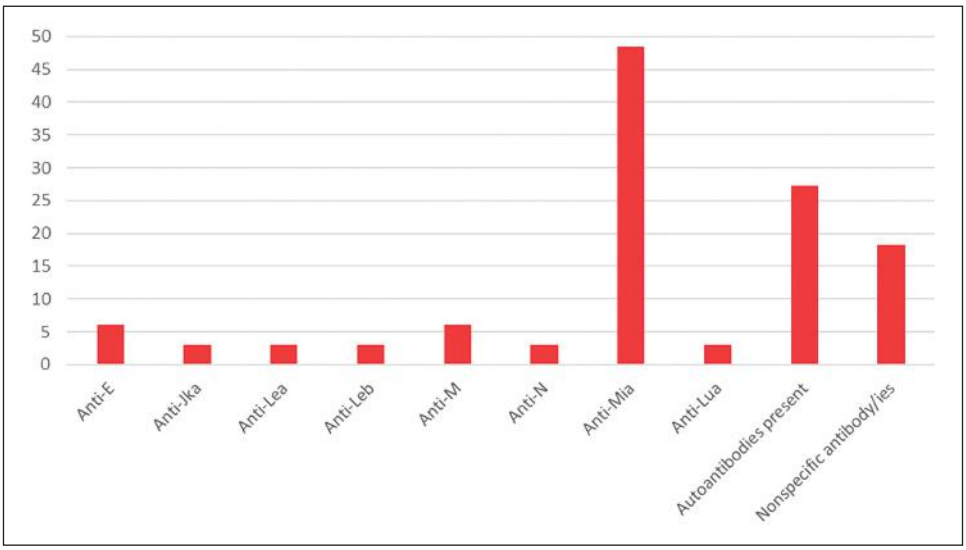

Figure 3. Frequency of antibodies in discrepant cases.

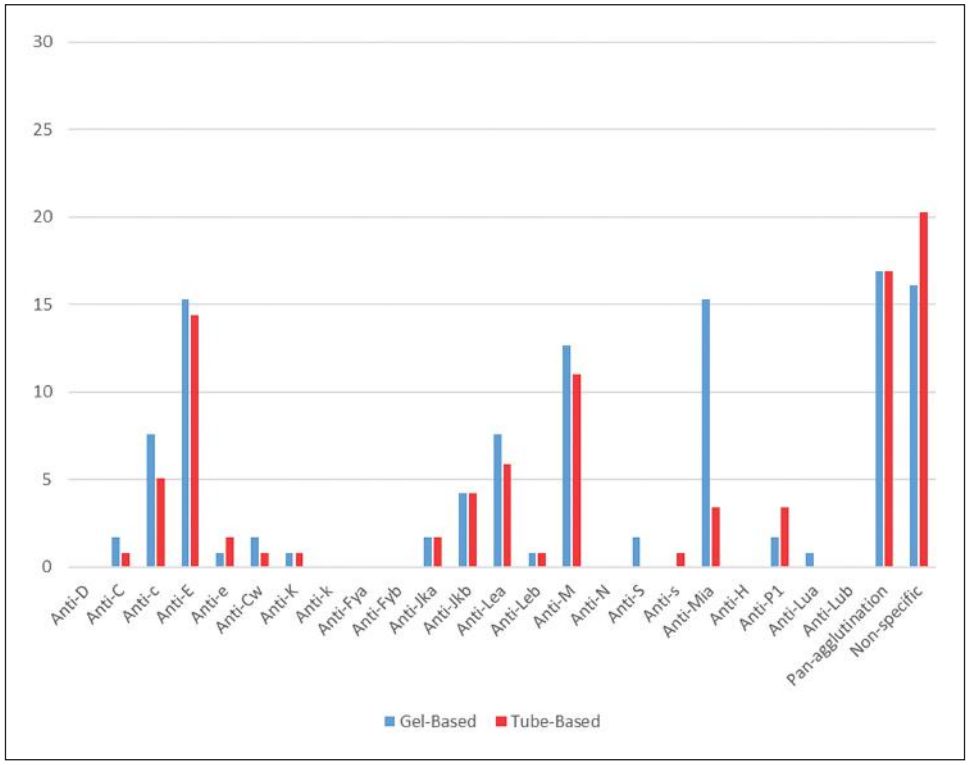

Figure 4. Frequency of identified antibodies per method.

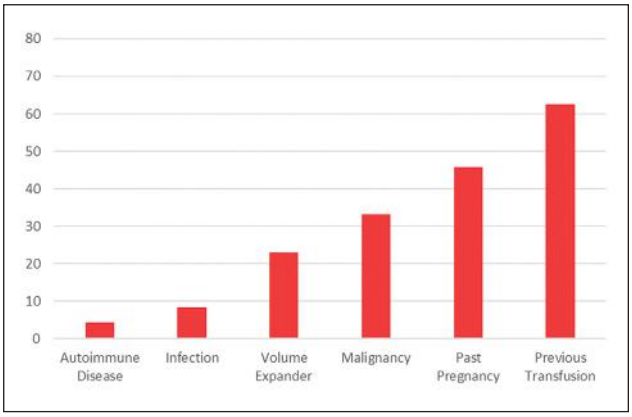

Figure 5. Clinical history of cases with discrepant results.

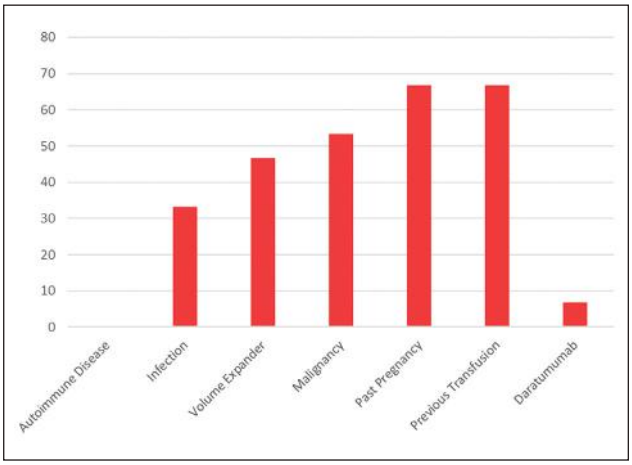

Figure 6. Clinical history of cases signed out as antibody of no specificity.

in Europeans and Africans, but is commonly found in Chinese and Southeast Asians, particularly Taiwanese, Hong Kongese, Thai, and Malaysians.[10] Lastly, the Anti-K antibody is noted to be low in our sample population, which coincides with its lower frequency in Southeast Asian populations compared to European or Caucasian counterparts.[8]

Concordance rates between the two methods from English literature were as low as 73% and as high as 98.68%.[12] It can be noted however that these studies mostly compared similar gel-based kits to one another, in contrast to our study. From our data, it is evident that the gel-based method was able to detect and identify Anti-Mi^a antibody more frequently. The gel-based kit contains at least one red cell reagent that is positive for Anti-Mi^a, which is lacking based on the standard RBC reagents used in the tube-based kit. As the antibodies identified using red cells in the gel-based kit are naturally occurring IgM antibodies, Syed Azim et al., theorized that some of the Anti-Mi^a antibodies identified by the said kit could well be IgM only antibodies.[7] As IgM antibodies tend to react at cold or room temperature compared to the IgG antibodies that react at body temperature, they rarely cause hemolysis in vivo and are therefore considered less significant. It can be argued that kits that detect only the clinically significant antibodies are preferred, since they preserve scarce personnel resources and minimize delay in the provision of compatible blood components.[13] Nevertheless, proper detection of Anti-Mi^a antibodies is still important during pre-transfusion testing especially among Asian populations, as there are some studies that show that Anti-Mi^a antibodies are IgG reactive to 37°C and have been implicated in causing hemolytic disease of newborn and hemolytic transfusion reactions.[10,14,15]

Nonspecificity in antibody identification during pre-transfusion testing is uncommon, where a positive antibody screen leads to inconclusive antibody identification. Exposure to new red cell antigens, as in past blood transfusions or past pregnancies, can lead to alloimmunization and the development of additional alloantibodies. The presence of circulating donor red cells for patients with recent transfusions may also affect testing. It is possible that lymphoproliferative syndromes, including malignancy, infection, or rheumatologic or autoimmune diseases, can lead to autoantibody formation, as seen in systemic lupus erythematosus, multiple myeloma, chronic lymphocytic leukemia, or lymphoma. However, one cannot dismiss the fact that patients with chronic illnesses tend to require frequent transfusions that increase the risk for alloimmunization. Lastly, treatment using Daratumumab, intravenous immunoglobulins (IVIG), or volume expanders may manifest pan-agglutination in kits. Daratumumab can bind to CD38 on the surface of reagents red cells, while IVIG can contain unexpected antibodies.[16] To resolve this, autocontrol cells and direct Coombs testing (DAT) can facilitate the differentiation of autoantibodies.[16] Kandasamy et.al. (2018) also suggested washing the reagent cells.[17] Additional steps can also be done through phenotyping, using enzyme treatment such as papain and ficin which can inhibit MNS/Duffy antibodies, additive solutions like poly-ethylene glycol, or adsorption/elution methods.[16]

CONCLUSION

In comparing the methods, namely conventional tube-based technique versus the column agglutination or gel-based method, the resulting antibody screening and identification results showed statistical significance, with the latter being able to detect and identify more cases of Anti-Mi^a antibody. While the conventional tube method is considered the gold standard in the identification of antibodies, one cannot totally exclude the presence of Anti-Mi^a antibodies in patients who screened negative using this type of method. The high number of discrepant cases between the two methods highlights the advantage of using both in the screening and identification of RBC antibodies, done as a complement to the other.

ACKNOWLEDGMENTS

The authors thank Dr. Regine G. Bustonera, Ma. Rizalina F. Chua, Dr. Macario F. Reandelar Jr., and Mr. Jayson L. Guihama for their valuable contribution to the conduct of this study.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declare no conflict of interest.

FUNDING SOURCE

None.

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OPEN ACCESS – CASE REPORT

Conjunctival Melanoma with Rhabdomyosarcomatous Differentiation: A Case Report

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ABSTRACT

This is a case of malignant melanoma with rhabdomyosarcomatous differentiation presenting as a conjunctival mass in a 50-year-old male. Melanoma cells were seen to react with desmin, myogenin and vimentin, indicating rhabdomyosarcomatous differentiation. This condition is very rare, with less than twenty cases reported in the literature, which contributes to the limitations in molecular characterization and standard treatment protocols for this entity. This condition has an aggressive course with a poor prognosis.

Key words: malignant melanoma, eye, rhabdomyosarcomatous differentiation, conjunctival melanoma

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 2 August 2024.
Accepted: 20 August 2024.
Published online first: 30 September 2024.
https://doi.org/10.21141/PJP.2024.12

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INTRODUCTION

Malignant melanoma is known to show a wide heterogeneity in its appearance, exhibiting non-melanocytic neoplastic components in its histology. This is termed divergent differentiation, showing elements such as skeletal muscle, smooth muscle, fibroblasts, nerves, cartilage and neuroendocrine components.[1] Melanoma with rhabdomyosarcomatous differentiation is a very rare entity, with less than twenty pathologically confirmed cases reported.[2] This is associated with a poor prognosis, with distant metastases seen in most documented cases.[3] This report describes a case of melanoma with rhabdomyosarcomatous differentiation in a 50-year-old male, presenting as a right conjunctival mass.

CASE

This is a case of a 50-year-old male who presented with a right conjunctival mass. Two months prior to admission, the patient noticed the development of a small, pigmented mass in his right eye following the accidental scratching of a pre-existing mole. The patient reported that this mole had been present since childhood and had remained unchanged in size and color over the years. However, in the intervening months, the lesion began to increase in size, prompting the patient to seek initial consultation at a local hospital, followed by referral to our institution for further evaluation. The patient was a farmer and had an unremarkable family history and past medical history.

Physical examination revealed complete ptosis of the right eye with reduced visual acuity (OD: 20/100, OS: 20/50), and a visible pigmented mass located at the superior fornix (Figure 1). There was no mass, ptosis, or restricted range of motion in the extraocular muscles of the left eye. The skin showed no pallor or suspicious lesions. Additionally, no cervical lymphadenopathy was present. The rest of the physical findings were unremarkable. The patient was then admitted to our institution with the diagnosis of "consider conjunctival melanoma."

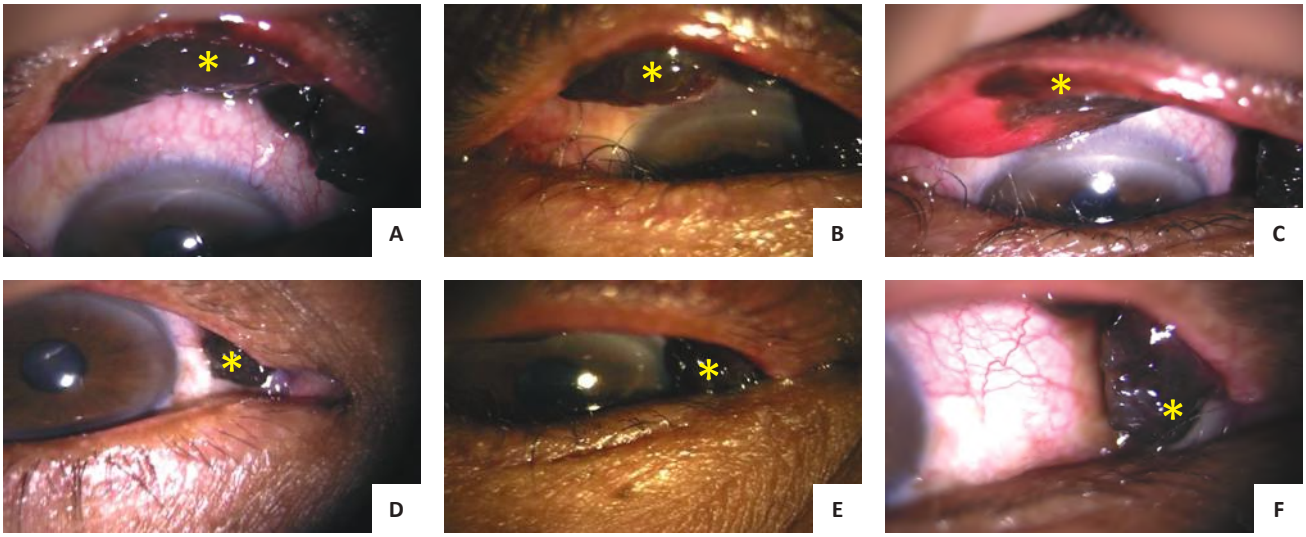

Figure 1. Examination of the patient's right eye reveals **(A)** a brown, fleshy, mass arising from the superior conjunctival fornix. **(B)** The mass spreads along the superior palpebral conjunctiva, and **(C)** extends toward the posterior lid margin. It further protrudes outward, reaching **(D)** the plica semilunaris and **(E, F)** the caruncle. *(Yellow asterisks indicate the relative location of the mass.)*

CT scan of the patient's eye mass revealed an irregular, ill-defined soft tissue lesion located at the right supraorbital region anterior to the globe approximately measuring 0.95 x 1.1 x 1.4 cm. The patient then underwent exenteration of the right eye, with an uneventful postoperative course.

The specimen submitted for pathology consists of the entire right eye with attached periorbital cuff, muscle and fascia that entirely measures 4.5 x 4 x 3 cm (Figure 2). The optic nerve measures 0.2 x 0.3 cm. The cut section of the eye reveals a tan, ill-defined mass (2 x 1.3 x 1.2 cm) at the palpebral conjunctival area (Figure 3). The mass is 2.2 cm from the optic nerve, 0.6 cm from the superior margin, 2 cm from the inferior margin, and 0.2 cm from the anterior margin.

Histologic examination of the eye mass shows nests of atypical cells consisting of pleomorphic polygonal cells with eccentric, hyperchromatic, vesicular nuclei and large, prominent nucleoli. The cytoplasm is abundant and eosinophilic with varying degrees of pigmentation visible. Tumor cells are seen invading the stroma, and 10 mitotic figures were seen per 10 high-power fields. Lymphovascular invasion was not identified (Figure 4).

The biopsy was signed out as "consistent with malignant round cell neoplasm, consider (1) melanoma, (2) rhabdomyosarcoma" with suggestions for immunohistochemistry with myogenin, desmin, vimentin, S100, HMB-45, and MART-1 for additional evaluation. No definitive post-surgical plan was made pending final identification of the malignancy, and the patient was lost to follow-up after discharge.

Immunohistochemical examination of the specimen was done, and the neoplastic cells showed diffuse positivity for melanocytic markers S-100, and Melan A (Figure 5). The neoplastic cells were also focally positive for skeletal muscle markers myogenin, desmin and vimentin (Figure 6), indicating rhabdomyosarcomatous differentiation.

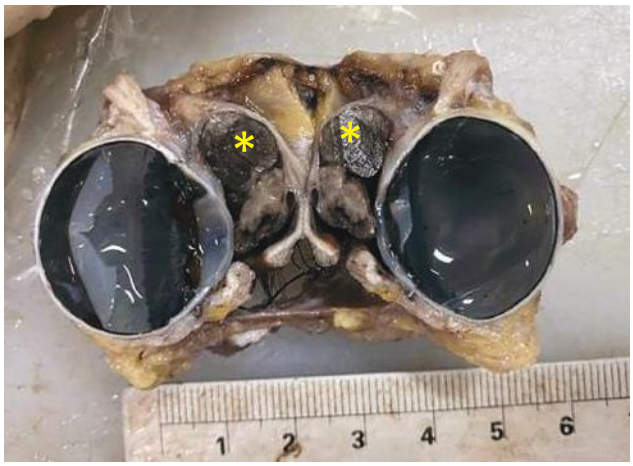

Figure 2. Cut section of the patient's exenteration specimen. The mass is seen occupying the superior palpebral conjunctiva *(yellow asterisks)*.

Figure 3. A mass is seen at the palpebral conjunctival area of the eye *(yellow asterisk)*.

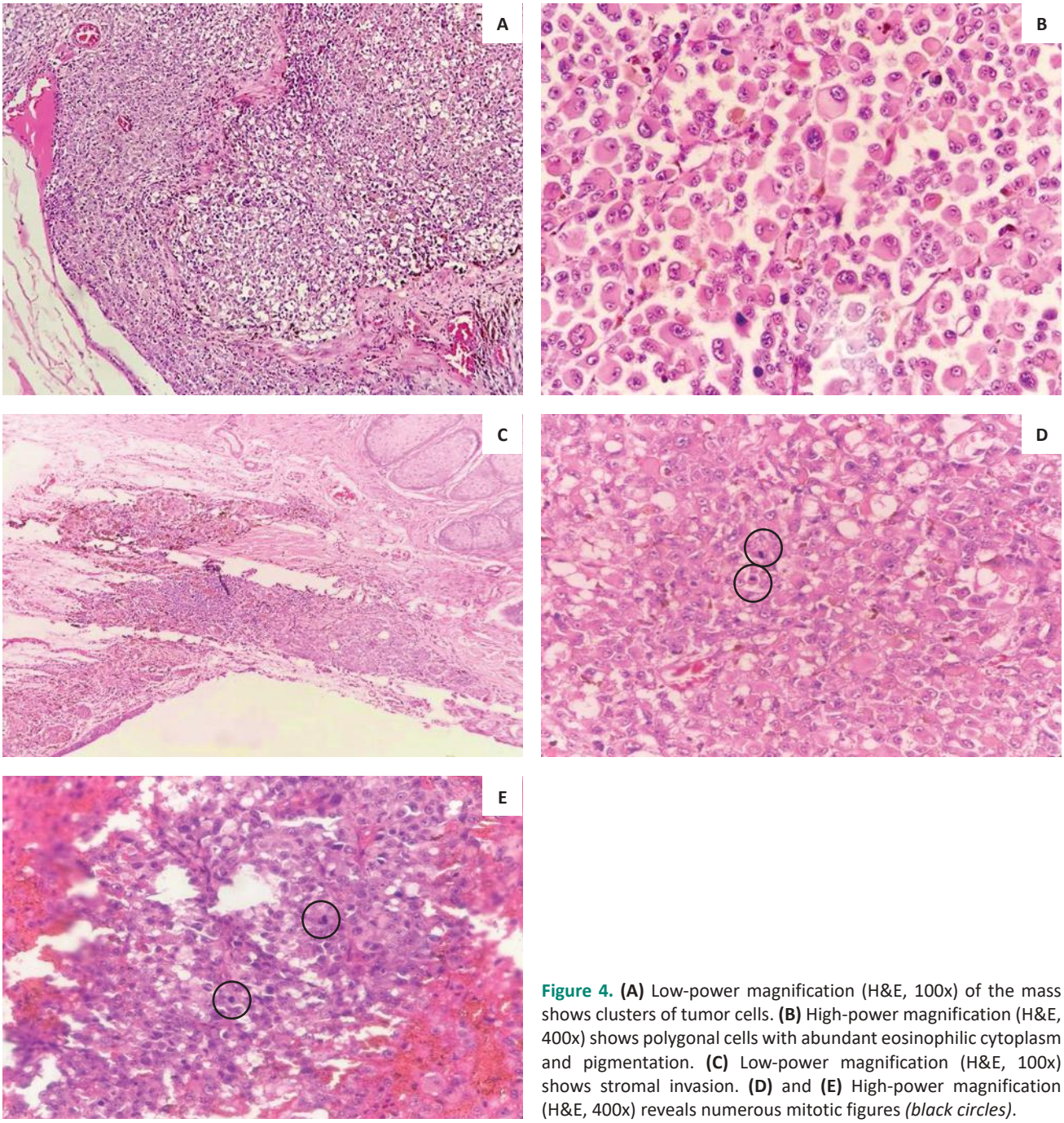

Figure 4. **(A)** Low-power magnification (H&E, 100x) of the mass shows clusters of tumor cells. **(B)** High-power magnification (H&E, 400x) shows polygonal cells with abundant eosinophilic cytoplasm and pigmentation. **(C)** Low-power magnification (H&E, 100x) shows stromal invasion. **(D)** and **(E)** High-power magnification (H&E, 400x) reveals numerous mitotic figures *(black circles)*.

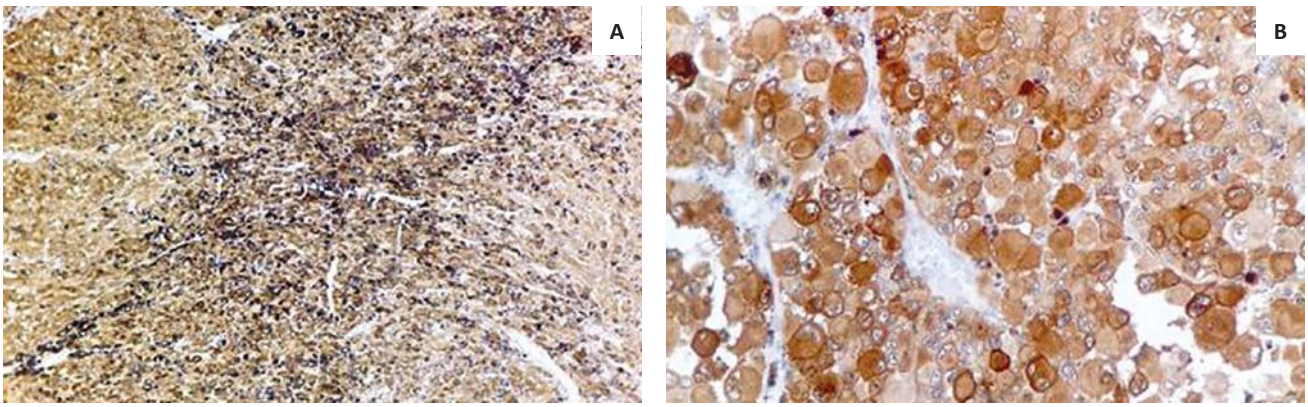

Figure 5. Immunohistochemistry was diffusely positive for **(A)** S100 and **(B)** Melan-A.

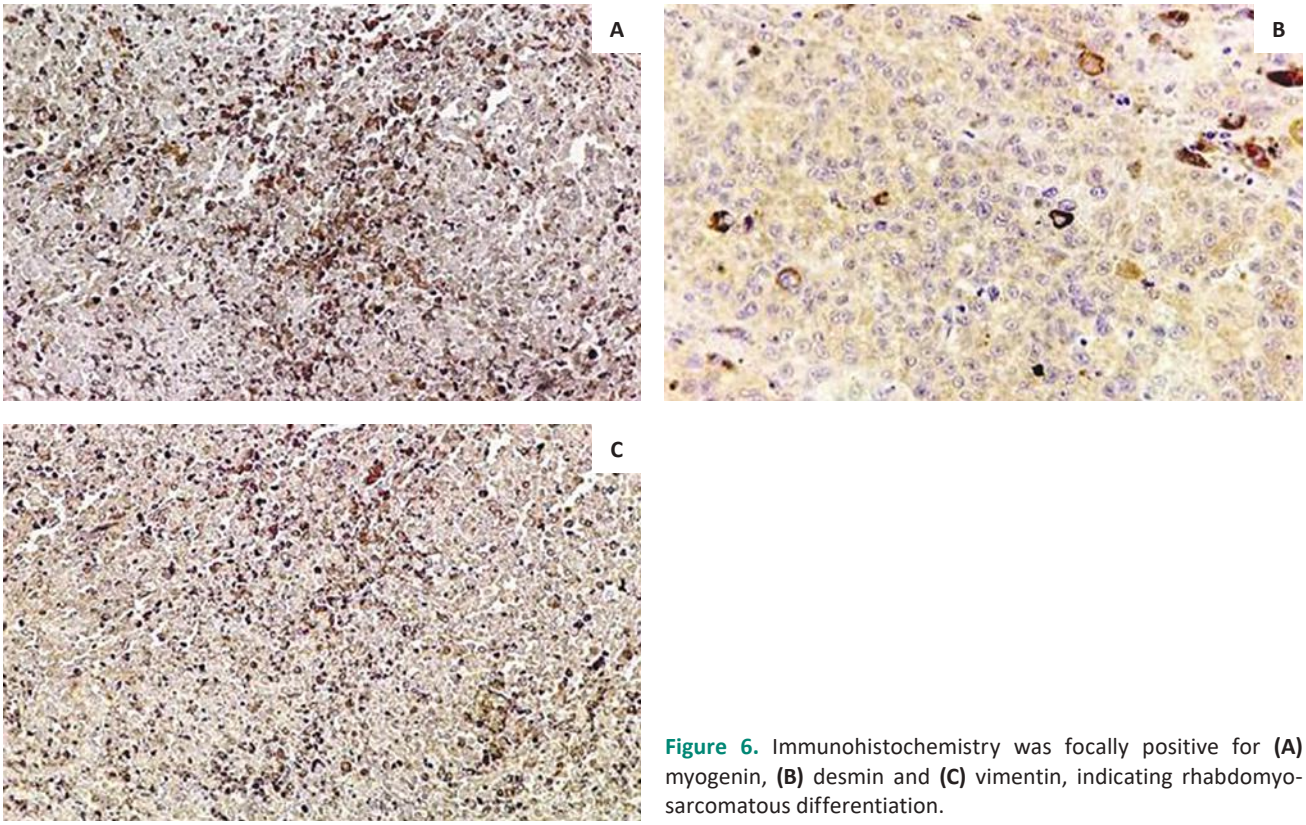

Figure 6. Immunohistochemistry was focally positive for **(A)** myogenin, **(B)** desmin and **(C)** vimentin, indicating rhabdomyosarcomatous differentiation.

Unfortunately, the patient was lost to follow-up after surgical management. The patient was then reported to have expired 11 months after the diagnosis was made.

DISCUSSION

Melanomas can arise in extra-cutaneous regions including the area in and around the eye. Conjunctival melanoma originates from the melanocytes in the basal layer of the conjunctival epithelium and accounts for about 5% of all ocular melanomas.[4] This entity is distinct from uveal melanoma despite both being referred to as "ocular melanomas."[5] Melanomas in this area can occur at any part of the conjunctiva, but often appear at sun-exposed areas such as the bulbar conjunctiva.[4,5] About 75% of cases arise from precursor lesions such as primary acquired melanosis (PAM) or a pre-existing nevus. The patient's tumor arose from a mole that had been present since childhood. *De novo* cases occur in 15–25% of cases.[4] The differential diagnosis for this tumor includes other melanocytic lesions such as PAM, conjunctival nevus and acquired melanoses, as well as malignancies such as pigmented squamous cell carcinoma, uveal melanoma, or metastatic melanoma from a cutaneous site.[6] The malignancies in the differential diagnoses are ruled out as there are no other body sites affected by a malignant tumor, as well as the absence of other component tumor cells in the mass (in the case of pigmented squamous cell carcinoma). The distinction of melanomas from other melanocytic lesions includes stromal invasion along with severe cytological and architectural atypia exceeding those expected in a nevus as essential criteria.[7] The prominent cytological atypia in the examined specimens rules out any benign lesions in the differential diagnosis and qualifies the tumor as a malignancy as opposed to a nevus with atypical features.

The biopsy was initially signed out as "consistent with malignant round cell neoplasm, consider (1) melanoma, (2) rhabdomyosarcoma" with suggestions for immunohistochemistry with myogenin, desmin, vimentin, S100, HMB-45, and MART-1 for additional evaluation. The presence of polygonal, eosinophilic cells in the specimen prompted the testing for muscle markers to rule out rhabdomyosarcoma.

This case of conjunctival mass on a 50-year-old male has shown positivity for desmin, vimentin and myogenin on the same area of tumor cells that has shown positivity for melanocytic markers S100 and Melan-A. This is consistent with the other documented cases of melanomas with rhabdomyosarcomatous differentiation, where foci of tumor cells were reactive to skeletal muscle markers (Table 1). Moreover, no other documented cases of melanomas with rhabdomyosarcomatous differentiation have been reported in the conjunctiva. This makes the current case possibly the first of its kind to be reported.

It should be noted that a melanoma with rhabdomyosarcomatous differentiation is distinct from a rhabdoid melanoma. A rhabdoid morphology in a tumor is described with features such as a polygonal shape, eccentric nuclei, large nucleoli, and abundant eosinophilic cytoplasm containing hyaline filamentous inclusions.[8,15] First described in a variant of Wilms Tumor, rhabdoid differentiation has been seen in other neoplasms and is thought to be a common endpoint of dedifferentiation of a variety of tumors.[10]

Table 1. Cases of malignant melanoma with rhabdomyosarcomatous differentiation

Reference	Clinical Information	IHC	Clinical outcome
Reilly, et al.[8]	59/M skin mass at anterior abdominal wall with right axillary lymph node metastasis	(+): Desmin, Myogenin, S100, HMB-45, Melan-A	Underwent surgery + adjuvant radiotherapy. Treated with vemurafenib with complete metabolic response. Small volume metastasis detected after 12 months.
Gharpuay-Pandit, et al.[9]	21/F submandibular mass (not biopsied) and cervical lymph node metastasis	(+): Desmin, Myogenin, MyoD1, S100, Melan-A	Underwent surgery + radiotherapy; developed chest metastasis and died of disease 10 months after presentation.
Gharpuay-Pandit, et al.[9]	90/M skin mass at the back of pinna	(+): Desmin, Myogenin, MyoD1, S100, HMB45 (-) Melan-A	Lesion was excised; Lost to follow-up.
Shenjere, et al.[10]	67/F Skin mass at chest	(+); Desmin, myogenin, MyoD1, S100, HMB-45, Melan-A	Underwent wide local excision; developed pulmonary metastasis; died of unrelated causes 2 years after diagnosis.
Shenjere, et al.[10]	51/F Mucosal melanoma at cervix with lymph node metastasis	(+): Desmin, Myogenin, S100, HMB-45, Melan-A	Underwent surgery + adjuvant chemotherapy. Developed widespread pelvic disease 10 months after surgery and considered for experimental treatment. Alive with disease.
Antonov, et al.[3]	75/M skin mass behind right ear with cervical lymph node metastasis	(+): Desmin, Myogenin, S100, Melan-A	Underwent wide local excision + chemotherapy. Developed chest metastases and died of disease 7 months later.
Kuwadekar, et al.[11]	72/M scalp mass	(+) Desmin, vimentin, myogenin (-) HMB-45, Melan-A	Underwent wide local excision. Re-biopsy was done 4 months post-op. Referred for external beam radiation therapy.
Campbell et al.[12]	52/F upper back mass with axillary lymph node and vertebral metastasis	(+) Desmin, myogenin, S-100, MART-1	Wide local excision + adjuvant chemotherapy. Died of disease 4 years after diagnosis.
Gupta, et al.[2]	72/M left lateral scalp mass	(+) Desmin, Vimentin	Wide local excision + immunotherapy and radiation; currently with disease.
Baltres, et al.[13]	2/F congenital nevus at lumbosacral region	(+) S-100, SOX10, HMB45, (+) myogenin, myo-D1, desmin, (+) hyperdiploidy with high-level gain of chromosome 8	Complete surgical excision + adjuvant chemotherapy. Pulmonary and hepatic metastases were found after treatment.
Tran, et al.[14]	96/M right forearm mass	(+) S-100, HMB-45, desmin, Myo-D1	Complete surgical excision. On adjuvant radiation therapy 5 months after excision.
Current case	50/M conjunctival mass	(+) Desmin, myogenin, vimentin, S-100, Melan-A	Exenteration, lost to follow up. Died 11 months after diagnosis.

Despite similar appearances, a rhabdoid melanoma lacks immunohistochemical markers for skeletal muscle (e.g., myogenin) and will only contain intermediate filaments (e.g., vimentin, desmin)[9,10]. Melanomas can also undergo transdifferentiation, in which a dedifferentiated melanoma acquires heterologous elements.[16] The loss of melanocytic markers in a transdifferentiated melanoma can obscure the diagnosis and may require molecular testing for confirmation. While a definitive progression sequence of malignant melanoma to produce rhabdomyosarcomatous elements has not been characterized, a proposed progression includes dedifferentiation of the melanoma and acquisition of nonmelanocytic phenotypes[14]. Sarcomatoid melanoma has been proposed as a "transition stage" of this tumor.[14]

The lack of funds and the patient being lost to follow-up has precluded molecular characterization of the current case. The molecular pathogenesis of melanoma has been extensively documented.[17] The use of *BRAF* and *NRAS* testing can be used to identify undifferentiated melanomas.[18] Conjunctival melanomas share similarities with cutaneous and mucosal melanomas at the molecular level, such as the presence of *BRAF*, *NRAS*, *NF1* and *KIT* mutations.[19] Only about one-third of conjunctival melanomas harbor a *BRAF* mutation, with the mutation itself associated with sun-exposed sites and as a target of therapy in primary and recurrent tumors[4]. *NRAS* mutations are common in conjunctival nevi but are only seen in 20% of conjunctival melanomas.[4] *NRAS* mutations in conjunctival melanomas are associated with an increased risk of metastasis and death.[20] *NF1* mutations are present in one-third of conjunctival melanomas but have no association with clinicopathologic features or prognosis.[4] Mutations in *KIT* are seen in conjunctival melanomas in non-sun-exposed areas. Like *NF1*, no association has been seen with *KIT* mutations and survival.[4]

Molecular markers sought as therapeutic targets for conjunctival melanoma include *BRAF*, *NRAS*, *NF1*, *KIT* and PD-1/PD-L1.[4,19,21] Other targets being explored for therapy include enhancer of zeste homolog 2 (EZH2) and the mTOR pathway.[21]

Genetic studies specifically for melanomas with rhabdomyosarcomatous differentiation showed features shared with embryonal rhabdomyosarcoma, such as a hyperdiploid genome and a high-level gain of chromosome 8.[13] An *NRAS* mutation and "shared genetic alterations (loss of chromosome 1q31, amplification of 1q32, and gain of 12q23-qter)" has been found in both the melanoma and rhabomyosarcomatous tumor cells in two cases,[15,22] suggesting a clonal relationship between the two components. The rhabdomyosarcomatous cells were also shown to express rhabdomyogenic RNA transcripts, correlating with morphology and immunohistochemistry.[13]

Conjunctival melanoma by itself has a 10-year mortality rate of 25–35%. Prognostic factors include a *de novo* origin, non-bulbar conjunctival location, nodular growth, multifocal location, and lymph node spread. Increased mitotic rate, lymphatic invasion, and angiotropic metastases microscopically are also negative prognostic factors.[7] The presented case showed a non-bulbar conjunctival location and a mitotic rate of 10 mitoses per 10 high-power fields, but no lymphovascular invasion was identified.

Due to the paucity of cases, no standard treatment has been formulated for melanomas with rhabdomyosarcomatous differentiation. The cases documenting the disease used a combination of wide excision of the tumor with radiotherapy or immunotherapy (Table 1), with varying results. Survival from the time of diagnosis ranged from 7 months[3] to 4 years[12]. The presented case was lost to

follow-up, and the patient expired 11 months after the diagnosis was made. The disease remains to have a rapidly progressive course with a poor prognosis. Most of the documented cases rapidly developed distant metastases.[2]

CONCLUSION

This report discusses a case of malignant melanoma with rhabdomyosarcomatous differentiation located in the right conjunctiva of a 50-year-old male patient. Limited literature review has shown the aggressive nature of the entity in other locations, therefore, thorough examination and testing to identify and document this entity is necessary. Genetic studies have been performed but have limited value in diagnosing the entity and are more useful in identifying alterations targetable for immunotherapy. Due to its rarity, there is a lack of clinical trials aimed at developing standard treatment protocols, ultimately contributing to lower survival rates.

ACKNOWLEDGMENT

The authors acknowledge their Chairperson, Sheila May N. Ramos, MD, FPSP, Training Officers, Aije Hope D. Bruzon-Hortel, MD, DPSP and Ma. Theresa A. Fedoc-Minguito, MD, DPSP of the Department of Pathology and Laboratories of the Southern Philippines Medical Center, and Dr. Kristin J. Estores for her vital technical support during the completion of this paper.

ETHICAL CONSIDERATION

Patient consent was obtained for this case report.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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OPEN ACCESS – CASE REPORT

Nephroblastoma in a 51-year-old Male: An Exceedingly Rare Occurrence of Malignant Embryonal Tumor in Adulthood

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ABSTRACT

Nephroblastoma is an uncommon renal malignancy primarily observed in the pediatric population, with its occurrence in adults being exceedingly infrequent. We describe an extremely rare case of a malignant embryonal tumor presenting in an adult patient with right renal mass. Final histopathologic diagnosis was nephroblastoma with favorable histology. Use of immunohistochemistry studies is generally unnecessary but its rarity in the adult population raises uncertainty in diagnosing this malignancy by histomorphology alone.

Key words: adult nephroblastoma, immunohistochemistry, Wilms tumor, kidney tumor

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 20 November 2024.
Accepted: 8 December 2024.
Published online first: 21 December 2024.
https://doi.org/10.21141/PJP.2024.17

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INTRODUCTION

Wilms tumor or nephroblastoma is the most frequent renal malignant neoplasm in the pediatric population with a peak incidence between 2 and 5 years.[1] On the contrary, this is extremely rare in the adulthood accounting for less than 1% of all renal malignancies. Metastatic disease within diagnosis is more common in adults. Up to 50% of the cases are in the advanced stage (Stage III-V).[2] Establishing the diagnosis has been a great challenge for both clinicians and pathologists, who are not accustomed to considering nephroblastoma as a potential differential diagnosis in adults. Histomorphologic characteristics alone can be sufficient to confirm the diagnosis of nephroblastoma, particularly when the three distinct components—epithelial, blastemal, and stromal—are clearly identifiable. However, use of immunohistochemistry studies may be necessary to rule out other differential diagnoses especially if one or more components predominate than the others. Only less than 200 cases have been documented worldwide. Because of its rarity, standard management guidelines are not available for adult population and are solely based on the established treatment guidelines for pediatric patients by the International Society of Pediatric Oncology (SIOP).[3]

CASE

This is a 51-year-old male who presented with flank pain for 8 months associated with gross hematuria and gradually enlarging abdomen. Three months prior to admission, these symptoms persisted which prompted the patient to consult in a private clinic. CT urography was requested which revealed a right renal mass, predominantly endophytic, extending from the superior interporal region to the inferior pole, measuring at least 15.2 x 19.6 x 13.6 cm. The mass is well-circumscribed and does not invade the adjacent organs. The contralateral kidney and other organs such as urinary bladder, adrenal glands and para-aortic lymph nodes are unremarkable. Eventually, patient was referred to our institution for radical nephrectomy.

Patient is a known hypertensive and adherent to his maintenance medications. Pertinent physical examination findings include pale palpebral conjunctiva and tender mass

palpable in the right upper quadrant. Routine laboratory investigations including complete blood count, renal function tests and bleeding parameters were unremarkable except for the decreased red blood cell count, hemoglobin, and hematocrit, which denote anemia.

The specimen submitted for pathology consists of a single, intact, tan yellow to brown, soft to firm, smooth to rough right kidney weighing 2, 108 grams which measures19.5 x 16.0 x 14.0 cm. The attached ureter is grossly unremarkable which measures1.5 x 0.6 x 0.5 cm (Figure 1.) Serial sections of the right kidney show a well-delineated, tan cream to tan brown, complex, solid to cystic mass which measures 19.0 x 14.0 cm. The mass is predominantly solid with microcystic areas, areas of hemorrhage and extensive necrosis (80%). The mass is pushing the renal capsule but grossly uninvolved by the tumor (Figure 2).

Histopathologic examination of the right renal mass shows three distinct populations of tumor cells (Figure 3). One population represents the epithelial component of the tumor. These are in glandular or tubular architecture and rosette-like formation in a background of fibromyxoid stroma (Figures 4 and 5). The second population represents the blastemal component which consists of small blue round tumor cells in diffuse sheets. This is a highly cellular focus consisting of small to medium-sized undifferentiated cells with overlapping, relatively small, regular, and hyperchromatic nuclei with inconspicuous to visible nucleoli and scant cytoplasm (Figure 6). The third population consists of densely packed undifferentiated mesenchymal cells in fibroblastic stroma. These tumor cells

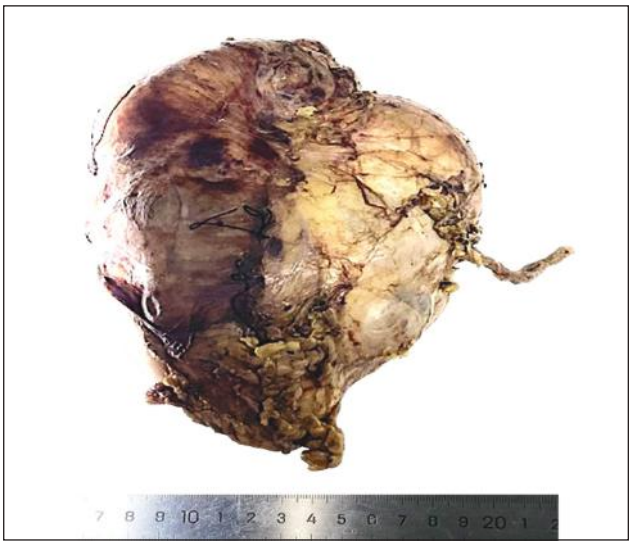

Figure 1. Gross appearance of the right kidney.

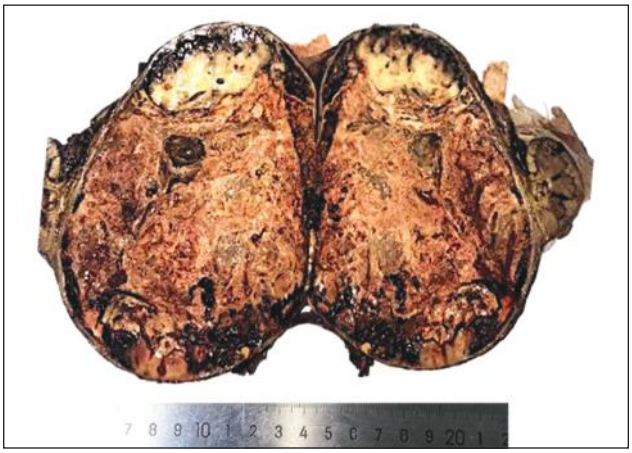

Figure 2. Cut section of the right kidney mass.

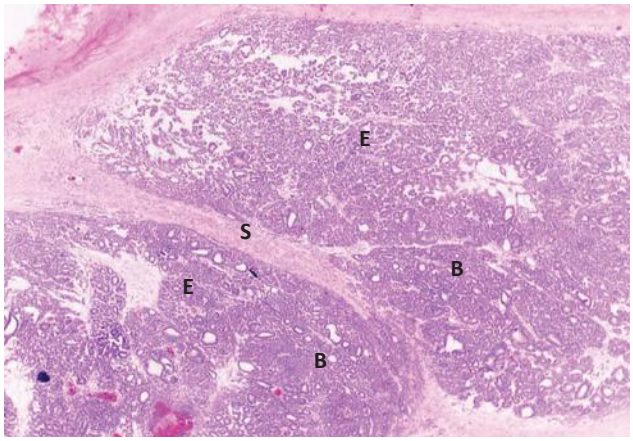

Figure 3. Triphasic tumor composed of epithelial **(E)**, blastemal **(B)** and stromal **(S)** components (H&E, 40x).

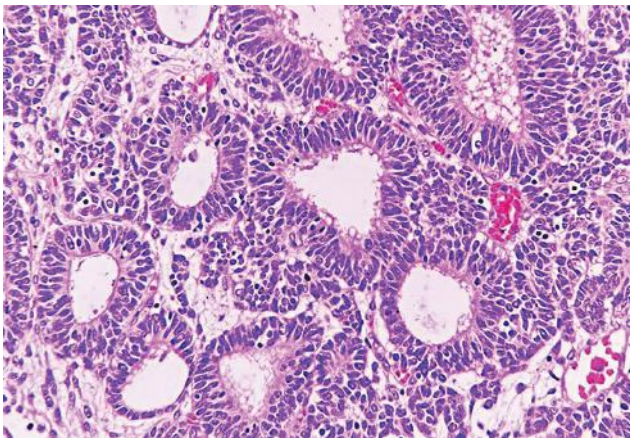

Figure 4. Epithelial elements composed of primitive tubular structures in a fibromyxoid stroma (H&E, 400x).

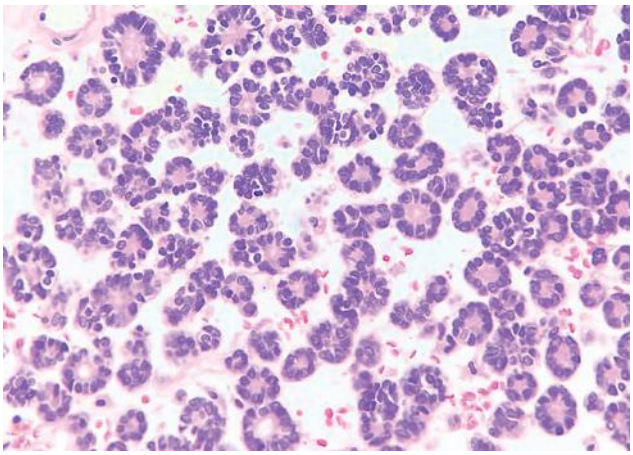

Figure 5. Epithelial component of the tumor in rosette-like formation (H&E, 400x).

have oval to spindle-shaped nuclei with bland nucleoli and indistinct cytoplasmic membrane (Figure 7). There are no areas with anaplasia. However, extensive necrosis and hemorrhagic areas are noted.

Histomorphologic features are very consistent with Nephroblastoma, but this is extremely rare in adult population. Due to its rarity, an accurate diagnosis requires careful exclusion of other potential differential diagnoses. The following are considered such as clear cell renal cell carcinoma with sarcomatoid differentiation, neuroblastoma, Ewing sarcoma, desmoplastic small round cell tumor, rhabdoid tumor, clear cell sarcoma, malignant germ cell tumor and metanephric adenoma. Despite the clear presence of the classic triphasic histologic features of nephroblastoma, immunohistochemistry studies were still done to support the diagnosis such as WT1, Vimentin, Pancytokeratin, Desmin, S100, CD34, Synaptophysin, SALL-4, CD99, CD10 and BCL2. CD10 is negative which rules out renal cell carcinoma. The positivity of WT1 and negativity of BCL2 rules out clear cell sarcoma. CD99 and synaptophysin are negative which rule out Ewing sarcoma and neuroblastoma, respectively. Negativity of Desmin and CD99 rule out rhabdoid tumor as well as desmoplastic round cell tumor. WT1 and vimentin positivity support the diagnosis of metanephric adenoma while BRAF and CD57 immunostains can help in excluding this differential diagnosis. However, it can be ruled out based on histomorphologic finding alone. Metanephric adenoma is a highly cellular tumor, characterized by its typical appearance of tightly packed small, and round to angulated acini and tubules.[4] The presence of the three components (epithelial, blastemal, and stromal), along with high mitotic activity and atypia, helps in excluding metanephric adenoma. Both epithelial and blastemal components are positive for WT1 (Figure 8). The epithelial component is positive for AE1/AE3. The stromal component is positive for Vimentin. Other immunostains such as Desmin, S100,

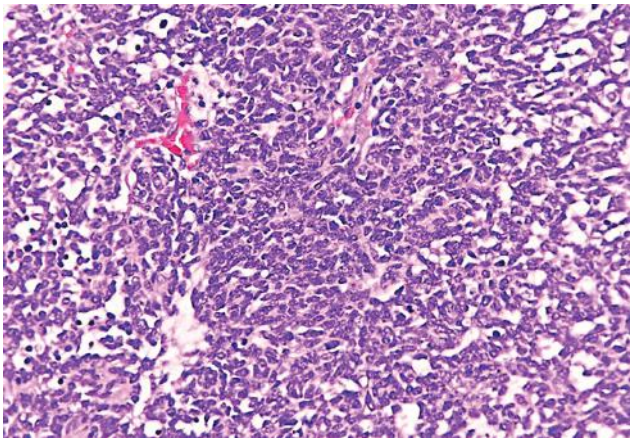

Figure 6. Blastemal component of the tumor arranged in diffuse sheets (H&E, 400x).

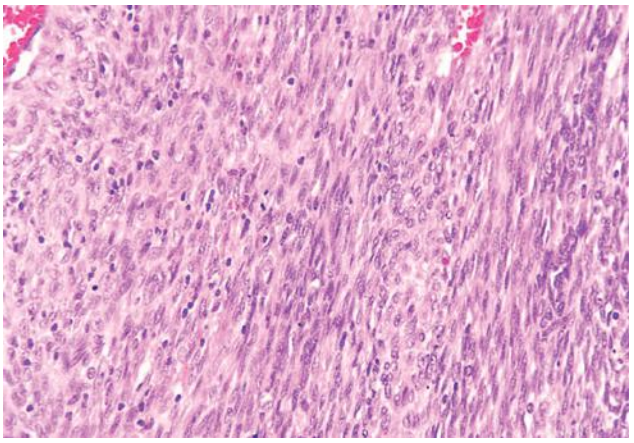

Figure 7. Stromal component composed of densely packed undifferentiated mesenchymal cells in fibroblastic stroma (H&E, 400x).

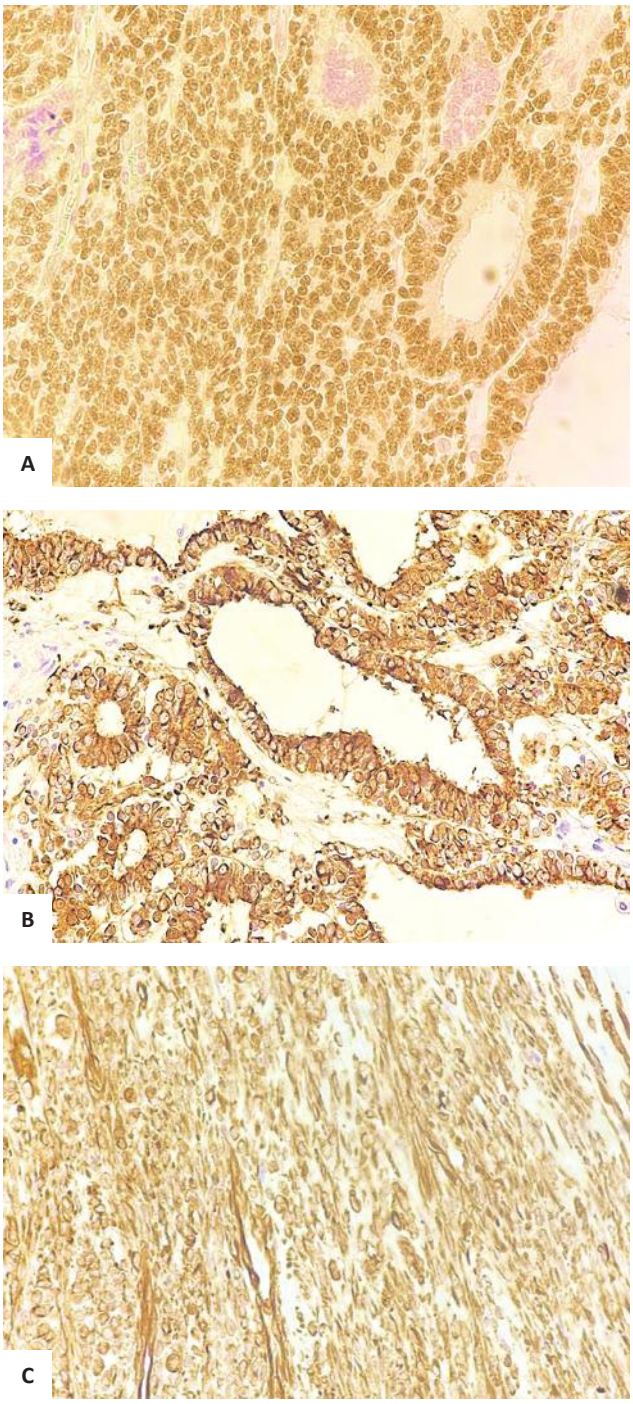

Figure 8. Immunohistochemistry showing: strong and diffuse, nuclear staining for WT1 **(A)**; strong and diffuse cytoplasmic staining for AE1/AE3 **(B)** and Vimentin **(C)**.

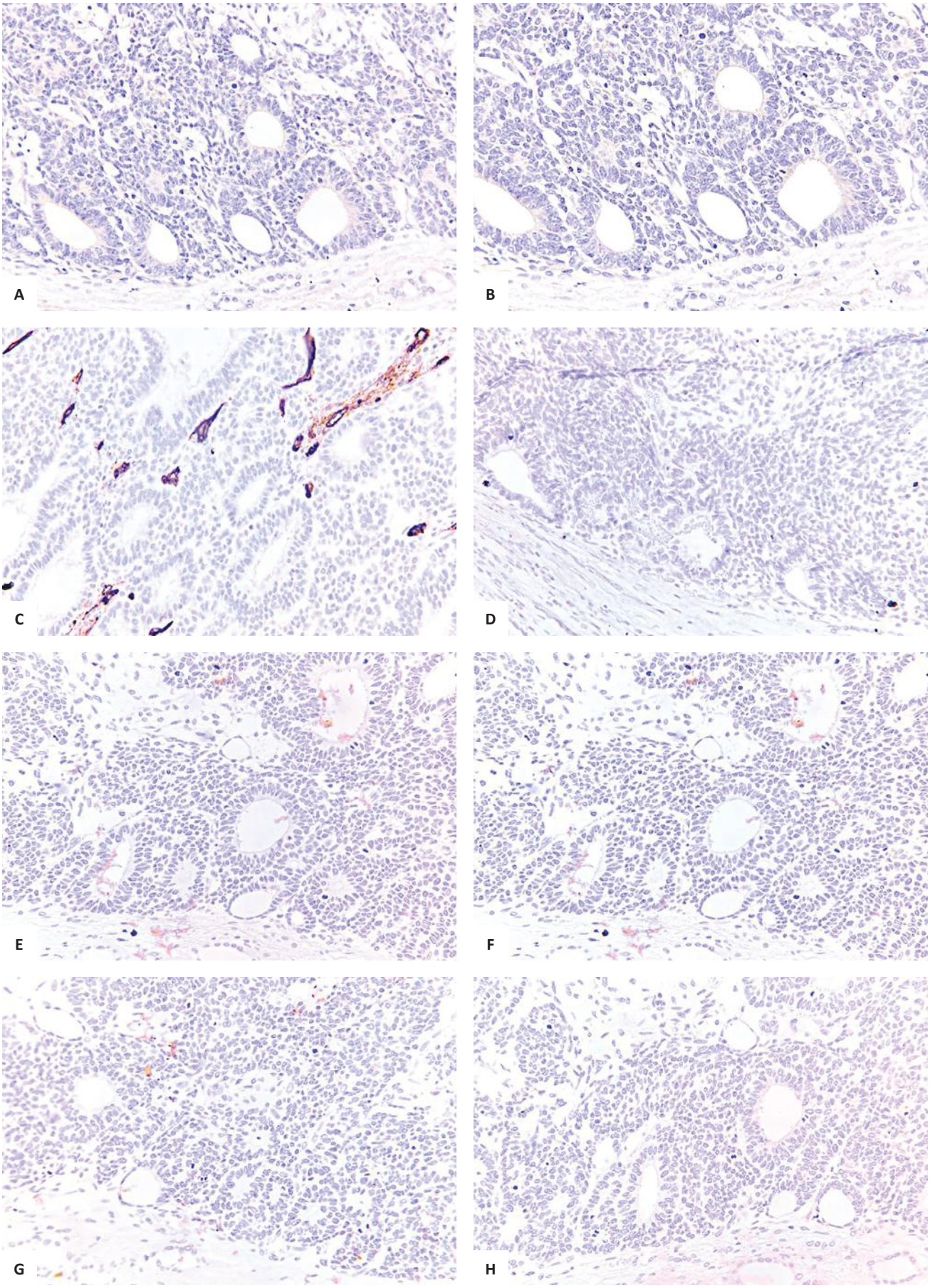

Figure 9. Negative immunohistochemical stains of the right renal mass: Desmin **(A)**; S100 **(B)**; CD34 **(C)**; Synaptophysin **(D)**; SALL-4 **(E)**; CD99 **(F)**; CD10 **(G)**; BCL2 **(H)**.

CD34, Synaptophysin, SALL-4, CD99, CD10 and BCL2 are all negative (Figure 9). Given these histomorphologic features and immunoprofile in correlation with the patient's clinical symptoms and physical examination findings, the case was signed out as Wilms Tumor or Nephroblastoma with Favorable Histology.

DISCUSSION

Incidence and clinical presentation

Nephroblastoma or Wilms Tumor represents <1% of all renal malignancies in the adulthood.[2] There has been only one case reported in the Philippines and a few from other countries. Most of the cases are diagnosed following nephrectomy.

Its typical clinical presentation is the same with the pediatric population such as palpable abdominal mass, hypertension, and hematuria.[5] However, findings from other case reports revealed that the main symptom among adults is flank pain associated with weight loss and a sudden drop in performance status.[6,7]

Approximately 10% of nephroblastoma occurs in conjunction with one of several well-defined dysmorphic syndromes.[8] The genetic loci predisposing to nephroblastoma are WT1 and WT2, located in 11p13 and 11p15.5, respectively. Germline point mutations in WT1 are the genetic basis of Denys-Drash syndrome, while deletions of WT1 underlie WAGR syndrome. WT2 is implicated in nephroblastoma associated with Beckwith-Wiedemann syndrome. Inactivation of the WTX gene on the X chromosome occurs in 6%-30% of sporadic nephroblastoma cases. Additionally, activating mutation of the β-catenin gene (*CTNNB1)* is found in 14%-20% of nephroblastoma, leading to disruption of the Wnt signaling pathway.[9]

Diagnosis

The diagnosis of Adult Nephroblastoma is established according to the criteria proposed by Kilton et al (1980). These criteria comprise of the following: (1) The tumor must be identified as the primary renal neoplasm; (2) Presence of primitive blastemal component, spindle or round cell type; (3) Formation of abortive or embryonal tubular or glomeruloid structures; (4) No histologic evidence of renal cell carcinoma within the tumor; (5) Histologic confirmation of the tumor characteristics; and (6) age >15 years old.[10,11] The classic nephroblastoma has three distinct components, making it a triphasic tumor which consists of epithelial, blastemal, and stromal components.[12] These components are present in varying proportions that influence prognosis. Blastemal-predominant nephroblastoma is associated with poor outcomes despite therapy compared to those cases with predominance of epithelial and stromal components.[7]

Prognosis

Prognosis depends on several factors such as age, stage, size, presence of anaplasia, tubular differentiation, post-chemotherapy morphology and TP53 mutation.[9] It has worse prognosis compared in pediatric patients.[13] The prevalence of metastatic disease at the time of diagnosis is significantly higher in adults approximately 30% compared to 10% in pediatric patients. Up to 50% of the cases are already in the advanced stage (Stage III-V). Sites of distant metastasis occur usually in the lungs, liver, and less commonly in the bones, bladder, contralateral kidney, and nervous system.[6,7] Delay in starting chemotherapy within 30 days post-nephrectomy has led to poor event-survival rate of 14.3% (±13%) and overall survivability of 28.6% (±17%) while patients who started treatment within 30 days showed a 5-year event-free survival rate of 60% (±15%) and overall survivability rate of 80%. The National Wilm's Tumor Study Group (NWTS) reported 5-year overall survival rates for adults based on disease stage as follows: stage 1, 100%; stage 2, 92%; stage 3, 70%; and stage 4, 73%. Other published case reports have found poorer outcomes.[14,15]

Additional studies

Immunohistochemistry studies are typically not required for the diagnosis of nephroblastoma but the rare occurrence of this tumor in the adult population raises uncertainty in considering such diagnosis. Several immunostains such as WT1, vimentin, Desmin, CD10, CD99 and other neuroendocrine markers may be helpful in ruling out differential diagnoses of this tumor. In this case, renal cell carcinoma, neuroblastoma, Ewing sarcoma, desmoplastic round cell tumor, and rhabdoid tumor are ruled out by immunohistochemistry studies.

In addition to the routine histopathologic examination, molecular and genetic studies such as cytogenetic analysis may be necessary for clinching the diagnosis.

Treatment

Currently, there is no established treatment guidelines for adult nephroblastoma. Treatment for adult cases is often derived from the already established pediatric protocols. The standard treatment for nephroblastoma involves multimodal approach, with radial nephrectomy and lymph node dissection serving as the foundation of management, typically supplemented by exclusive chemotherapy or concurrent radiotherapy for most patients.[14,15] The limited number of adult nephroblastoma cases results in a lack of clinical studies providing standard management guidelines for this condition.[16,17]

FOLLOW UP AND OUTCOMES

Unfortunately, the patient sought follow-up care after a considerable delay. Treatment has not been initiated yet, as the patient is still undecided.

CONCLUSION

The extreme rarity of nephroblastoma among adults warrants thorough documentation. The limited number of cases worldwide complicates both diagnosis and management. Use of immunohistochemistry studies may be necessary to rule out other differential diagnoses. Prognosis is worse compared in the pediatric population. A standardized model of care and management in adult population needs to be established.

ETHICAL CONSIDERATIONS

Patient consent was obtained for this case report.

ACKNOWLEDGMENTS

The authors would like to express their sincere gratitude to all the consultants and clinicians who contributed to the preparation of this case report. Their expertise and collaborative efforts were invaluable. They also appreciate the dedicated efforts of the histopathology staff involved in the processing of the immunostains, which played a crucial role in the accurate diagnosis and management of the case. Their contributions were essential to the success of this report.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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Focus Group Discussions on Enhancing Laboratory-based Surveillance Capabilities for Emerging Infectious Disease Response: Project for Strengthening the Philippine National Health Laboratory Network for Infectious Diseases (PHeLNIDs)

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ABSTRACT

The COVID-19 pandemic highlighted critical gaps in the Philippine health laboratory system, including limited testing capacities, insufficient trained personnel, and inadequate resource distribution. To address these issues, the Philippine government established the Office for Health Laboratories (OHL) and sought technical assistance from the Japan International Cooperation Agency (JICA) through the Project for Strengthening the Philippine National Health Laboratory Network for Infectious Diseases (PHeLNIDs). This project aims to enhance the National Health Laboratory Network's (NHLN) capacity for infectious disease surveillance and response. Phase 1 of the PHeLNIDs project included focus group discussions (FGDs) conducted across 17 regions to assess challenges and develop recommendations for a tier-based laboratory network. Key findings revealed logistical, workforce, transportation, and data management challenges that hinder the effectiveness of specimen referral workflows. Recommendations emphasized decentralizing diagnostic capabilities through subnational reference laboratories, strengthening logistics, and implementing an Integrated Laboratory Information Management System (ILIMS). This article underscores the importance of laboratory decentralization, capacity building, and improved resource management to enhance laboratory-based surveillance and response to emerging infectious diseases. The proposed interventions aim to bolster the Philippine laboratory network, reduce turnaround times, and improve public health outcomes.

Key words: health laboratory, laboratory-based surveillance, laboratory network, emerging infectious disease

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 17 December 2024.
Accepted: 17 December 2024.
Published online first: 20 December 2024.
https://doi.org/10.21141/PJP.2024.18

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INTRODUCTION

The COVID-19 pandemic has severely affected the Philippine health sector as well as its economy. Although the Philippine government has taken strong countermeasures against COVID-19 including the expansion of molecular testing for the people, some challenges have been observed, such as the limited number of accredited molecular laboratories, the low capacities of testing centers, the lack of trained personnel, and the inadequate supply and distribution of resources across the country. To address these issues, the government has considered a centrally governing body focusing on the standards, policies, and operations of the laboratory network, stand-alone National Reference Laboratories without being lodged under hospital operations, and the clear delineation between clinical laboratory and public health services. As a result, the government established the Office for Health Laboratories (OHL) under the Health Facilities and Infrastructure Development Team in 2021.[1] The Philippine government has been exerting efforts to strengthen the National Health Laboratory Network (NHLN) through establishing the National Framework of NHLN by virtue of Administrative Order 2012-0021,[2] and drafting a "National Action Plan on Health Security in

2020" to bolster the capacity of NHL and expand NHLN in alignment with the International Health Regulation thematic areas.

The PHeLNIDs project

Under this background, the Department of Health Philippines (DOH) requested technical support from the Japanese government to enhance the capacity of NHLN for infectious diseases. As a result, the Project for Strengthening the Philippine National Health Laboratory Network for Infectious Diseases (PHeLNIDs) was initiated to prepare for a future pandemic through a functional network of health laboratories and improved public health response. PHeLNIDs was formulated with a two-step planning method, which means that Project activities immediately started as phase 1 once a basic plan was formulated, and then its detailed plan for phase 2 was to be prepared based on baseline survey results. The Japan International Cooperation Agency (JICA) and the DOH signed the Record of Discussions in May 2022 and Japanese experts were subsequently dispatched in July 2022.

The Project for Strengthening the Philippine National Health Laboratory Network for Infectious Diseases (PHeLNIDs) was initiated to prepare for a future pandemic through a functional network of health laboratories and improved public health response. PHeLNIDs was formulated with a two-step planning method, meaning that Project activities immediately started as phase 1 once a basic plan was formulated, and then its detailed plan for phase 2 was to be prepared based on baseline survey results.

Initiation of PHeLNIDs Phase 1

Phase 1 involved a baseline survey across various testing facilities to evaluate their capacity to detect infectious agents at national, regional, and local levels. Additionally, focus group discussions (FGDs) were conducted with Disease Reporting Units (DRUs) across 17 regions to identify challenges and develop recommendations for a tier-based laboratory network system.

Objectives of the focus group discussions

The FGDs aimed to:

- Assess practices for specimen referral from DRUs to National Reference Laboratories.
- Identify on-the-ground challenges faced by DRUs.
- Inform the development of tier-based laboratory networks at national, sub-national, and regional levels.

METHODOLOGY

Key personnel from selected DRUs, including RESU (Regional Epidemiology and Surveillance Unit), PESU (Provincial Epidemiology and Surveillance Unit), MESU (Municipal Epidemiology and Surveillance Unit), CESU (City Epidemiology and Surveillance Unit), and HESU (Hospital Epidemiology and Surveillance Unit), participated in FGDs from October to December 2022. Discussions were conducted via online platforms such as Zoom and Webex using semi-structured interviews (sample screenshots of Zoom meetings conducted for two [2] regions, Figures 1 and 2).

The topics raised and discussed during the FGD mostly revolved around the most vital functions and processes of the specimen referral system in the Philippines (Table 1).

Figure 1. Screenshot of FGD (Davao Region).

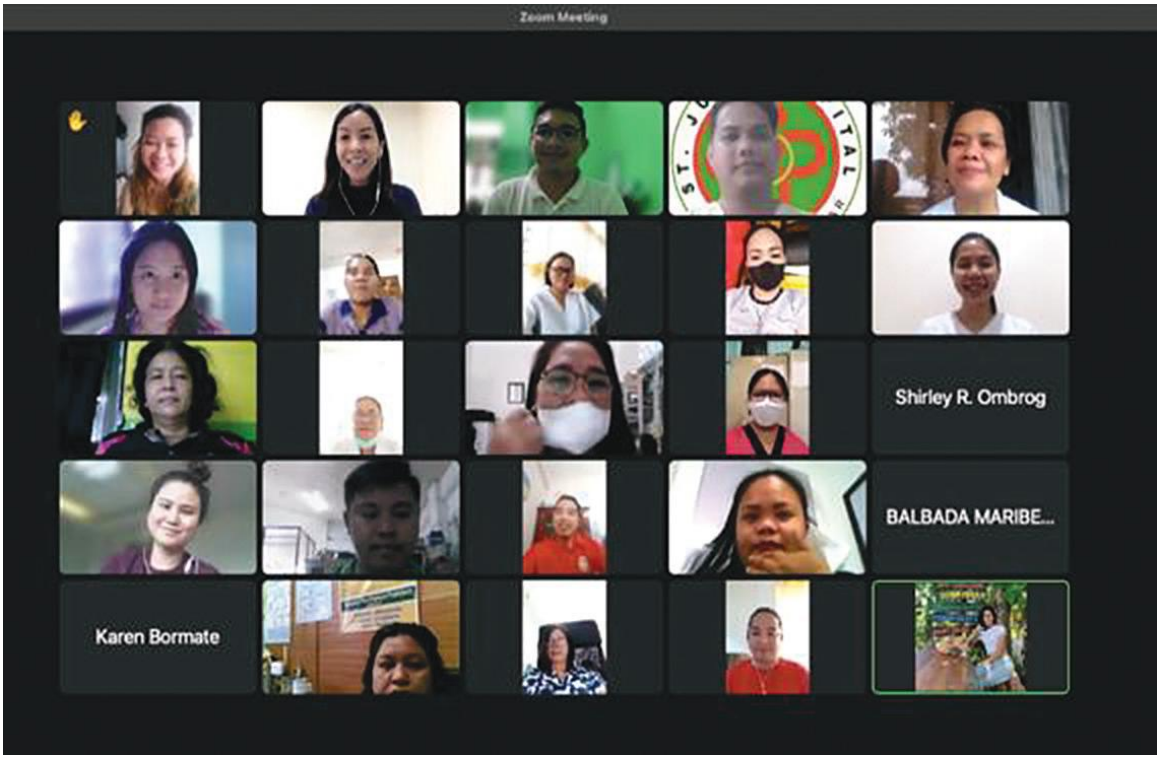


Figure 2. Screenshot of FGD (Eastern Visayas Region).

Table 1. Discussion topics and FGD questions

Discussion topic	FGD questions
Specimen referral workflow	*"What are the DOH referral laboratories in your region?"* *"Discuss the specimen referral form and workflow* *-From where;* *-For what purpose (Clinical or Public Health Surveillance);* *-To which laboratory;* *-For what specimen;* *-How often;* *-Mode of transportation; and* *-Referral budget"*
Guidelines implemented in the laboratories or testing facility	*"What are your existing guidelines in the handling and transport of specimens?"* *"Do you follow the triple packaging model?"*
Data management or the information system used related to specimen referral	*"What are your current practices for information management of infectious diseases?"*
Challenges in the specimen referral system	*"What challenges are you facing during specimen referral?"*
Recommendations for the improvement of the laboratories or testing facility, to include what tests are suggested to be performed if a subnational reference laboratory will be established in the region	*"What kind of laboratory examinations should be included or performed if a sub-NRL is to be established in your region?"*
Prevalent diseases in the region or locality pre- and/or post-pandemic	*"What are the most prevalent diseases in your area?"*

RESULTS

The specimen referral workflow

Specimen referral workflows varied depending on the DRU's capacity and location. Proximity to Epidemiology and Surveillance Units (ESUs) and reference laboratories/testing facilities significantly influenced these workflows (Figure 3). Tables 2a to 2c elaborate the specific steps in the specimen referral workflow relevant to the DRU's proximity to the ESU and testing facility.

To further analyze and determine the current capacity or effectiveness in specimen referral, other specific points were discussed with the FGD participants (Table 3).

Guidelines implemented in the laboratories or testing facility

Most participants adhered to guidelines issued by the Research Institute for Tropical Medicine (RITM) and the DOH. Island provinces also often relied on IATA guidelines due to air transport requirements. However, logistical challenges, such as high costs, insufficient funds, and unavailable local suppliers, necessitated modifications, and use of alternative materials:

- Secondary container: Resealable plastic bags (e.g., Ziplock™ bags)
- Specimen Transport Box: Styrofoam boxes/containers
- Parafilm: Packaging tape
- Cold packs: Frozen bottled water

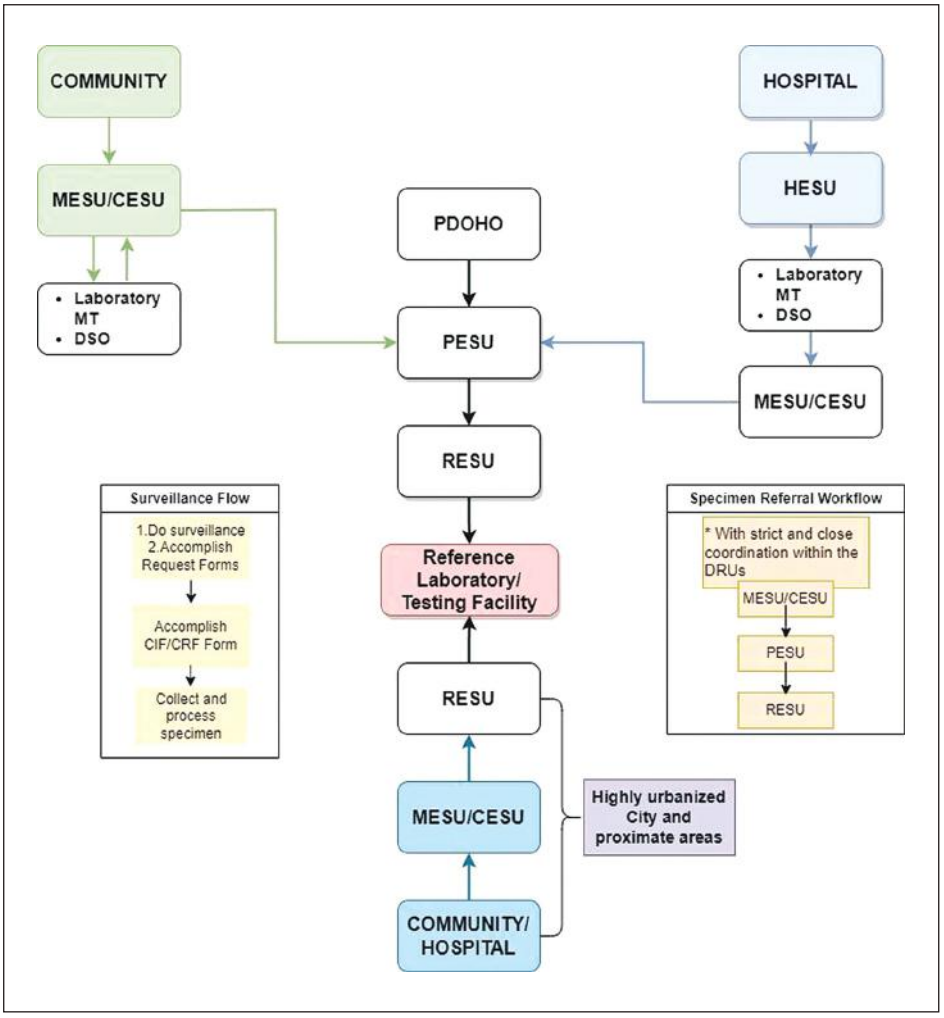
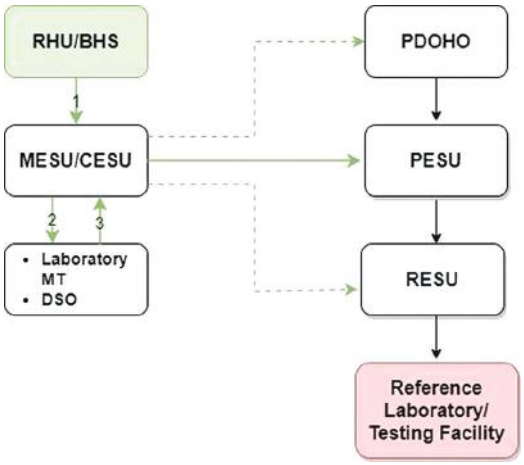


Figure 3. General workflow of referral from collection to receipt at the testing laboratory. There are multiple starting points for the DRUs (Hospital ESUs and City or Municipal ESUs), as illustrated on the swim lane, but their destination is their respective Regional ESUs before they are sent to the relevant recognized testing facility or laboratory.

(HESU – hospital epidemiology and surveillance unit; CESU – city epidemiology and surveillance unit; MESU – municipal epidemiology and surveillance unit; RESU – regional epidemiology and surveillance unit; PDOHO – provincial DOH office; CIF – case investigation form; CRF – case report form; MT – medical technologist; DSO – disease surveillance officer)

Table 2a. Specimen referral workflows depending on DRU (RHU/BHS in remote areas)

Specimen referral workflow	Flow diagram
RHU/BHS in remote areas All cases under investigation by the RHU (Rural Health Unit) or BHS (Barangay Health Stations) will be reported to their respective Municipal ESUs or City ESUs. ↓ The MESUs or CESUs will then be in charge of filling out the corresponding LRF (laboratory request form), CRF (case report form), and CIF (case investigation form), whichever is necessary and required. This will then be coordinated with their corresponding laboratory or DSO (Disease Surveillance Officer) for collection of specimens. ↓ All collected specimens will be processed, including the packaging of specimens by the laboratory or DSO in charge. Laboratory staff or the DSO-in-charge will send back the packed specimen with its corresponding pertinent forms to their respective MESUs or CESUs. ↓ The MESUs or CESUs will send the packed specimen with its corresponding pertinent forms to their respective Provincial ESUs. ↓ The Regional ESU will do the final processing of the specimens submitted to them, including quality assessment and necessary packaging reinforcement if needed. The RESU will also be responsible for the coordination and transport of specimens to each respective and corresponding testing facility. ↓ Reference laboratory/testing facility	

Data management

The PIDSR (Philippine Integrated Disease Surveillance and Response) system was the most used information system, supplemented by tools such as EDCS (Epidemic-prone Disease Case Surveillance) and ESR (Event-Based Surveillance and Response). For COVID-19, platforms like COVIDKaya and Tanod Kontra COVID were widely employed.

Challenges in the specimen referral system

For the fourth item, challenges were categorized into four most common subjects: logistics, manpower, transportation, and data management (Table 3).

Recommendations for the improvement of the laboratories or testing facility

Participants suggested establishing sub-national reference laboratories to enhance diagnostic capacity and reduce reliance on centralized facilities. They also recommended performing tests for locally prevalent diseases and improving logistical support (Figure 4).

Local prevalent diseases

The last item discussed in the focused group discussion was about the most prevalent disease in their locality. Almost all 17 regions and participating DRUs have similar prevalent disease occurrence in their localities pre pandemic and post pandemic (Figure 5).

Table 2b. Specimen referral workflows depending on DRU (RHU/BHS in highly urbanized settings or proximate to the ESUs and reference laboratory/testing facility)

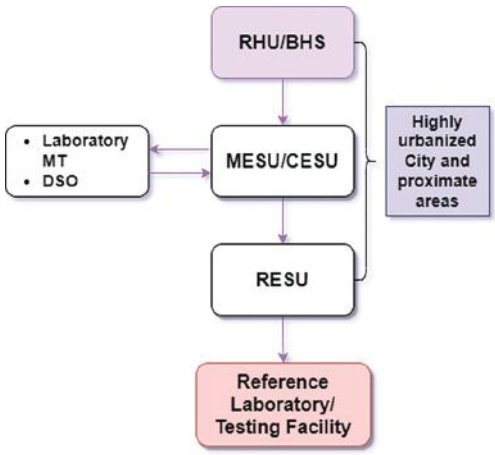
Specimen referral workflow	Flow diagram
RHU/BHS in highly urbanized settings or proximate to the ESUs All cases under investigation by the RHU (Rural Health Unit) or BHS (Barangay Health Stations) will be reported to their respective Municipal ESUs or City ESUs. ↓ The MESUs or CESUs will then be in charge of filling out the corresponding LRF (laboratory request form), CRF (case report form), and CIF (case investigation form), whichever is necessary and required. This will then be coordinated with their corresponding laboratory or DSO (Disease Surveillance Officer) for collection of specimens. ↓ All collected specimens will be processed, including the packaging of specimens by the laboratory or DSO in charge. ↓ Laboratory staff or the DSO-in-charge will send back the packed specimen with its corresponding pertinent forms to their respective MESUs or CESUs. ↓ The MESU or CESU will be responsible for coordinating and submitting specimens directly to the RESU. ↓ The Regional ESU will do the final processing of the specimens submitted to them, including quality assessment and necessary packaging reinforcement if needed. The RESU will also be responsible for the coordination and transport of specimens to each respective and corresponding testing facility. ↓ Reference laboratory/testing facility	

Table 2c. Specimen referral workflows depending on DRU (Hospital or in-patient specimen referral)

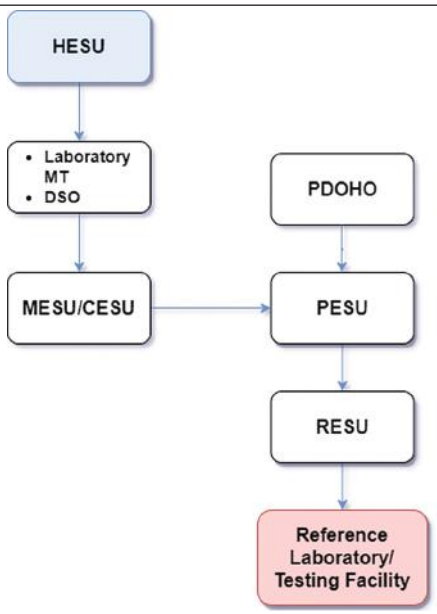
Specimen referral workflow	Flow diagram
Hospital or in-patient specimen referral In patient cases under investigation identified by the attending physician will be reported to the Hospital ESU. ↓ The HESU will then be in charge of filling out the corresponding LRF (laboratory request form), CRF (case report form), and CIF (case investigation form), whichever is necessary and required. This will also then be coordinated with attending physician or hospital laboratory or DSO (Disease Surveillance Officer) for collection of specimens. ↓ All collected specimens will be processed, including the packaging of specimens by the hospital laboratory or DSO in charge. ↓ Laboratory staff or the DSO-in-charge will send the packed specimen with its corresponding pertinent forms to their respective MESUs or CESUs. ↓ The MESU or CESU are the ones responsible in coordinating and submission of specimens to the PESU and PESU will then be the one to consolidate all collected specimen from the Hospital and are the ones to coordinate and transport it to the RESU. ↓ The Regional ESU will do the final processing of the specimens submitted to them, including quality assessment and necessary packaging reinforcement if needed. The RESU will also be responsible for the coordination and transport of specimens to each respective and corresponding testing facility. ↓ Reference laboratory/testing facility	

Table 3. Other points of discussion on specimen referral workflow

Other points of discussion	Responses from FGD participants
Origin of specimen	• DRUs; RESU; CESU; HESU; MESU; BHS; RHU
Purpose of referral	• Public health surveillance • Clinical diagnostics
Referral Laboratory	• Molecular laboratory • Subnational reference laboratory • National Reference laboratory (e.g., RITM) • Philippine Genome Center (PGC) • Sentinel hospitals or facilities (e.g., UP-PGH, SLH) • DOST and FDA
Type of Specimen	• Sputum • Blood • Stool
Frequency of Referral	• Case-to-case basis or as needed based on the specimen to be referred • Once a week/weekly • Some are based on the number of specimens for referral
Mode of Transportation	• CHD or LGU vehicle • Public utility vehicles (PUVs) • Public transportation (vans, bus, boat, airfreight)
Referral budget (if available)	• CHD/RESU • LGU Work and financial plans

CONCLUSIONS

The FGDs provided critical insights into the challenges and opportunities for strengthening the Philippine laboratory network system. Key findings include the need to address logistical constraints, workforce shortages, transportation issues, and data management inefficiencies.

Decentralizing testing capabilities to sub-national levels emerged as a significant recommendation. This approach would alleviate the burden on RITM, improve turnaround times, and enhance surveillance and response to emerging infectious diseases. Additionally, prevalent disease data collected during FGDs will inform the development of tier-based laboratory networks.

Despite resource constraints, DRUs have shown resilience and commitment to fulfill their responsibilities. Addressing the identified challenges and implementing the proposed recommendations will not only improve operational efficiency, but more importantly, strengthen laboratory-based surveillance, leading to faster response times and improved public health outcomes.

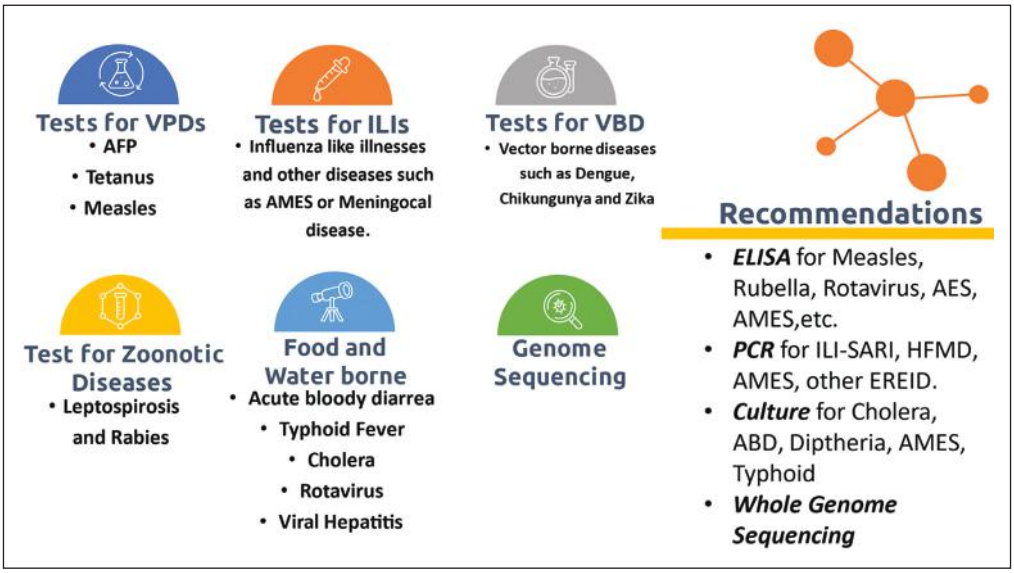


Figure 4. Tests perceived as needed or suggested to be included in a subnational reference laboratory.

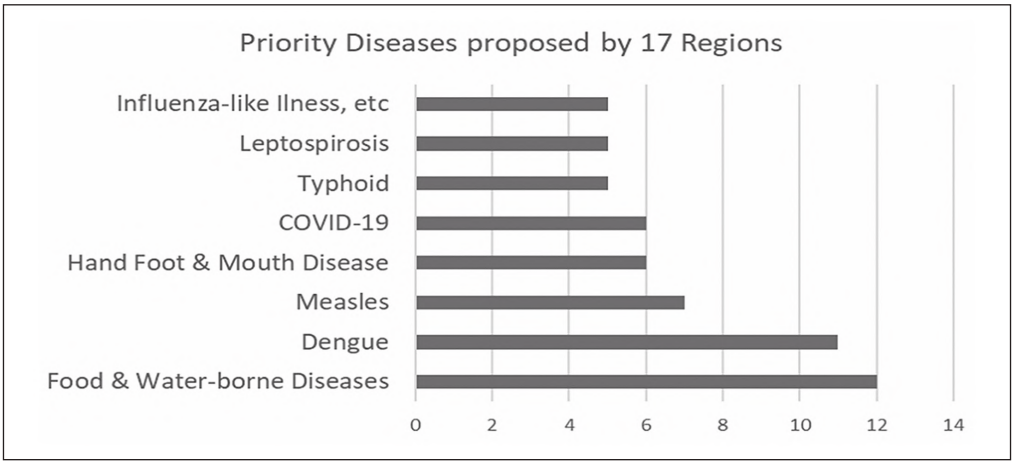


Figure 5. Top 8 prevalent diseases based on the FGD.

RECOMMENDATIONS

Based on the FGD findings and discussions, the following recommendations were made:

1. The establishment of subnational reference laboratories is a critical issue to consider when examining the roles and responsibilities between central and regional or subnational levels in various countries. Subnational reference laboratories can play a crucial role in enhancing public health, disease surveillance, and response capabilities at the local level. Establishing subnational reference laboratories that ensure diagnostic services are accessible will also help reduce the need for samples to be transported long distances, thereby reducing turnaround times for test results. This accessibility is crucial for timely diagnosis, surveillance, and response to infectious diseases and other health emergencies.
2. Decentralizing specific testing functions from RITM to subnational levels can have various advantages. As the National Reference Laboratory (NRL), this approach allows RITM to focus on its core roles, such as detecting emerging and re-emerging infectious diseases (ERIDs), performing advanced technologies, and providing recommendations for disease control measures to the Department of Health (DOH). At the same time, it enables the staff at the Regional Epidemiology and Surveillance Units (RESUs) and Epidemiology and Surveillance Units (ESUs) to strengthen their primary duties, including preventive measures and contact investigations.
3. Essential consumables for specimen referral, such as transport media, swabs, and other necessary supplies, should be centrally ensured through a well-managed procurement and distribution system. A well-managed centralized procurement and distribution system for essential consumables ensures standardization, cost-effectiveness, quality control, efficient distribution, and optimal resource utilization. By centrally ensuring the availability of these supplies, the healthcare system can support the smooth functioning of specimen referrals and maintain the integrity of diagnostic testing processes.
4. Implementing ILIMS (Integrated Laboratory Information Management System) with specimen tracking systems is critical for providing a timely and appropriate response to disease outbreaks on the ground. It improves specimen tracking, enables timely outbreak response, data integration and analysis, communication and collaboration, quality assurance and compliance, and data security. Using ILIMS, laboratories and public health authorities can better manage and respond to disease outbreaks, resulting in more effective public health interventions and control measures.

ACKNOWLEDGMENTS

The authors acknowledge all participating DRUs, JICA, and DOH staff for their contributions to the FGDs.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURES

Dr. Amado Tandoc III is the current PJP Editor-in-Chief. The rest of the authors declared no conflicts of interest.

FUNDING SOURCE

The PHeLNIDs project is funded by the Japan International Cooperation Agency (JICA) and the Department of Health Philippines.

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Computer-Assisted Simulations Using R and RStudio to Assist in Operations Research and Analysis in the Context of Clinical Laboratory Management: A Gentle Introduction and Simple Guide for Pathologists and Laboratory Professionals

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ABSTRACT

Operations research (OR) is a valuable yet underutilized field in clinical laboratory management, offering practical solutions to optimize workflows, resource allocation, and decision-making. Despite its potential, the adoption of OR methodologies remain limited due to a lack of training and familiarity among pathologists and laboratory professionals. This paper addresses this gap by presenting an accessible introduction and practical guide to analyzing operations research problems in clinical laboratories using computer-assisted simulations in R, implemented within the R Studio environment.

The proposed framework emphasizes simplicity and flexibility, leveraging the extensive capabilities of base R to model and analyze critical OR questions. The paper outlines step-by-step methods for defining problems, constructing simulation models, and interpreting results, ensuring that readers can replicate and adapt these techniques to their unique laboratory contexts.

Key features of the framework include its emphasis on reproducibility, customization, and the integration of data-driven insights into decision-making processes. Case studies and examples drawn from real-world laboratory scenarios illustrate the application of R simulations to address challenges such as minimizing turnaround times, balancing staffing levels, and managing inventory efficiently.

This guide aims to empower laboratory professionals and pathologists with the tools and skills to integrate operations research into their practice, fostering a culture of innovation and efficiency in clinical settings. By bridging the gap between OR theory and practical application, this paper contributes to the broader adoption of computational approaches in laboratory management, ultimately enhancing the quality and sustainability of healthcare services.

Key words: operations research, clinical laboratory management, simulation modeling, R programming, healthcare resource management

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 26 November 2024.
Accepted: 9 December 2024.
Published online first: 17 December 2024.
https://doi.org/10.21141/PJP.2024.14

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INTRODUCTION

Operations research (OR) is critical in clinical laboratory management as it provides a structured, data-driven approach to optimizing operations, improving efficiency, and ensuring quality service delivery. In modern laboratories, challenges such as high testing volumes, limited resources, and stringent turnaround time (TAT) requirements necessitate robust analytical tools. OR methods such as queuing theory, simulation modeling, and optimization algorithms enable laboratories to identify bottlenecks, optimize resource allocation, and enhance workflow efficiency.[1-3] For example, discrete-event simulation has been used to reduce sample processing delays, improving patient outcomes while minimizing costs.[4] These techniques help laboratories adapt to demand fluctuations, especially during pandemics or seasonal surges, ensuring they remain agile and resilient.

Beyond operational efficiency, OR supports strategic decision-making by forecasting future testing demands,

determining cost-effective inventory policies, and planning laboratory expansions. This is crucial in an era of precision medicine, where diagnostic labs play a pivotal role in healthcare. For instance, predictive analytics informed by OR can help prevent reagent stockouts, avoiding costly delays in diagnostic processes.[5-7] Furthermore, OR enhances the ability to meet accreditation and regulatory requirements by ensuring processes are both efficient and compliant.

Operations research bridges the gap between operational efficiency and strategic foresight, making it indispensable for managing clinical laboratories in today's complex healthcare ecosystem.

Operations research and analysis is an approach to answer questions that arise in the context of clinical laboratory management and focus on efficiency and optimization problems.

Operations research in clinical laboratories is the application of analytical methods to optimize the use of resources, such as staff, equipment, and reagents, to improve efficiency and reduce costs without compromising the quality of diagnostic services.[8] OR involves the use of mathematical modeling, simulation, and statistical analysis to support decision-making processes in laboratory management, such as workload balancing, test prioritization, and process redesign.[2,9,10] In the context of clinical laboratories, operations research focuses on improving workflow efficiency, reducing turnaround times, and ensuring timely delivery of test results to meet patient care demands.[11] OR applies quantitative techniques to manage laboratory quality, predict future testing demands, and design scalable operations to accommodate growth while maintaining high standards of service.

Important questions arise in the conduct of operations management of the clinical laboratory.

Workflow optimization

Workflow optimization issues in clinical laboratories arise in various settings, including high-volume testing centers, specialized labs, STAT and emergency testing areas, and facilities responding to public health crises. Challenges often include bottlenecks in sample processing, resource allocation inefficiencies, and disruptions from urgent test prioritization or sudden demand surges. Small laboratories with limited resources and those transitioning to new technologies also face delays due to constrained capacity or misaligned workflows.[12,13] Addressing these challenges requires tailored strategies, such as leveraging automation, improving resource planning, and implementing dynamic queuing systems. Examples of questions that may arise are:

- *How can we reduce the turnaround time (TAT) for routine and urgent test results?*
- *What is the optimal sequence for processing different types of specimens (e.g., blood, urine, tissue)?*
- *Where are the bottlenecks in the laboratory workflow, and how can they be alleviated?*
- *How can we ensure that critical tests (e.g., STAT tests) are prioritized without disrupting routine workflows?*

Resource allocation

Resource allocation issues in clinical laboratories commonly arise in settings with high variability in demand, such as during peak testing hours in high-volume labs or public health emergencies. Limited staffing, budget constraints, and equipment availability exacerbate these challenges, particularly in rural or small-scale laboratories with fewer resources.[14] STAT and emergency testing areas frequently face resource allocation conflicts, as prioritizing urgent tests can disrupt routine workflows and strain personnel and equipment.[15,16] Additionally, laboratories transitioning to automation or expanding services often encounter temporary inefficiencies as resources are diverted to implement new systems or train staff.[8] These settings highlight the need for optimized resource allocation strategies to balance demand, costs, and service quality. Examples of questions that may arise include:

- *What is the optimal number of staff required for peak and off-peak hours?*
- *How should staff be scheduled to minimize overtime and maximize efficiency?*
- *How can we maximize the utilization of high-cost equipment (e.g., hematology analyzers, mass spectrometers)?*
- *What is the optimal maintenance schedule to minimize downtime?*

Inventory and supply chain management

Issues in inventory and supply chain management commonly arise in clinical laboratories with fluctuating demand, such as during seasonal surges or public health emergencies like pandemics. Laboratories often face challenges in forecasting reagent and consumable usage, leading to overstocking, stockouts, or waste, particularly in high-volume testing facilities.[17] Small or rural laboratories, operating with limited budgets, may encounter difficulties in maintaining optimal inventory levels due to constrained purchasing power and delayed supplier deliveries.[18] Additionally, disruptions in global supply chains, such as those experienced during COVID-19, can exacerbate shortages, affecting both routine and emergency testing capabilities.[19] These settings emphasize the importance of implementing robust inventory management systems and dynamic supply chain strategies to ensure reliable and cost-effective operations. Example of questions that may arise include:

- *What are the ideal inventory levels for reagents to prevent stockouts while minimizing holding costs?*
- *How can we forecast demand for reagents based on historical testing patterns?*
- *What is the most cost-effective way to manage procurement and logistics for laboratory supplies?*

Quality and accuracy

Issues in quality and accuracy in clinical laboratories often arise in settings with high workloads, complex testing protocols, or inadequate quality control measures. Laboratories handling large volumes of routine or specialized tests may encounter errors during pre-analytical, analytical, or post-analytical phases due to rushed procedures or insufficient staff training.[20] Resource-limited laboratories, such as those in rural or underfunded healthcare systems, often face challenges in maintaining consistent quality due to outdated equipment, lack of standard operating procedures, or insufficient quality control practices.[21] Additionally, emergency testing environments or laboratories responding to pandemics may experience a higher risk of errors due to the pressure

to deliver rapid results without compromising accuracy.[22] These settings highlight the critical need for robust quality management systems and ongoing staff education to ensure diagnostic reliability. Examples of questions that may arise are:

- *How can we minimize pre-analytical, analytical, and post-analytical errors?*
- *What is the impact of process changes on the rate of quality control failures?*
- *What is the optimal frequency for running quality control samples to balance cost and error detection?*

Capacity planning

Issues in capacity planning in clinical laboratories arise in settings experiencing unpredictable demand, such as during seasonal epidemics or public health crises like pandemics. Laboratories often struggle to scale resources, equipment, and staffing to meet sudden surges, resulting in delayed turnaround times and service disruptions.[23,24] Additionally, specialized laboratories offering high-complexity tests often grapple with capacity constraints due to the limited availability of skilled personnel and high-cost equipment.[25] These challenges underscore the importance of data-driven forecasting and dynamic resource allocation to optimize laboratory capacity and responsiveness. Example of specific questions that may arise include:

- *How should the laboratory plan for fluctuations in test volumes (e.g., seasonal trends, pandemics)?*
- *What infrastructure investments are needed to handle projected growth in testing demand?*
- *How can laboratory layout be optimized to improve workflow and accommodate growth?*

Cost management

Issues in cost management in clinical laboratories arise in settings where balancing quality and efficiency is critical, particularly in resource-limited environments such as rural or small-scale labs. High operational costs, driven by reagents, equipment maintenance, and staff salaries, often strain budgets, especially when reimbursement rates do not align with testing costs.[26] Large laboratories with high test volumes may face inefficiencies due to overuse or waste of consumables, while smaller labs may struggle with the economies of scale needed to reduce per-test costs.[26] Public health laboratories or those responding to crises often experience cost escalations due to sudden surges in testing demand, necessitating emergency procurement and overtime staffing.[27] These challenges highlight the importance of implementing cost-tracking systems, optimizing resource utilization, and aligning financial strategies with operational goals to ensure sustainability.

- *What is the cost per test for different assays, and how can it be reduced without compromising quality?*
- *How should pricing models be adjusted to remain competitive while ensuring profitability?*
- *How can the laboratory allocate its budget to maximize operational efficiency and quality?*

Patient care perspective type of questions

Issues in patient care arise in clinical laboratories when delays, errors, or inefficiencies compromise the timely delivery of accurate test results, which are critical for clinical decision-making. High-volume laboratories may face bottlenecks or prolonged turnaround times (TAT), particularly during peak testing periods or public health emergencies, leading to delays in treatment initiation.[11,28] Resource-limited or rural laboratories often struggle to maintain consistent quality due to outdated equipment or insufficient staff, increasing the likelihood of diagnostic errors.[29] Laboratories managing STAT and emergency testing may also encounter challenges in prioritizing critical samples without disrupting routine workflows, potentially impacting patient outcomes.[30] These issues highlight the importance of efficient workflows, robust quality control, and reliable communication with healthcare providers to ensure optimal patient care.

- *What is the optimal TAT for different test categories to meet clinical needs?*
- *How can patient satisfaction be improved through better communication of test results?*

Popular methods exist that answer operations research questions in the context of clinical laboratory management

To address operations research (OR) challenges in clinical laboratories, a variety of methods and techniques are employed, each tailored to specific problems. Mathematical optimization techniques, such as Linear Programming (LP), Integer Programming (IP), and Mixed-Integer Linear Programming (MILP), are foundational tools for resource allocation and scheduling.[31,32]

LP effectively allocates resources, including reagents and staff, to minimize costs, while IP focuses on discrete decisions, such as determining the optimal number of instruments or staff shifts. MILP bridges continuous and discrete variables, making it suitable for complex tasks like laboratory expansions or integrating new technologies.[31,32] Despite their precision and scalability, these methods often demand detailed data and advanced expertise, presenting challenges for smaller or resource-constrained laboratories.[33]

Simulation modeling and queuing theory are particularly effective for addressing the dynamic and stochastic nature of laboratory workflows. Discrete Event Simulation (DES) models workflows to identify bottlenecks and evaluate the impact of process changes, while Monte Carlo simulations manage uncertainty by modeling variability in sample arrival rates or test demand.[34,35]

Queuing theory complements these methods by analyzing sample flow and optimizing service capacity, particularly in high-priority settings like STAT labs, where rapid processing is critical.[36,37] Although these approaches offer a risk-free environment for testing scenarios, they require significant time for model development and depend on high-quality data inputs, limiting their feasibility in certain settings.

These approaches, though effective, often require specialized expertise and tools, which can hinder their implementation in laboratories lacking dedicated OR personnel.

Collectively, these methodologies form a robust toolkit for addressing the multifaceted challenges in clinical laboratory management. While each method has its unique strengths and limitations, their strategic application—alone

or in combination—can significantly enhance efficiency, reduce costs, and support data-driven decision-making. By tailoring these tools to specific laboratory needs and investing in the necessary expertise, laboratories can overcome operational hurdles and deliver reliable, high-quality diagnostic services.

Use of computer assisted simulations

Computer-assisted simulations have emerged as a transformative tool for analyzing complex systems, enabling the study of dynamic processes without real-world disruptions. The roots of simulation as a method can be traced back to the 1940s, when the Monte Carlo method was developed during the Manhattan Project to model neutron diffusion in nuclear reactions.[38,39] In the decades that followed, advancements in computing technology significantly enhanced simulation capabilities, leading to the development of discrete-event simulation (DES) in the 1950s and 60s, which became a cornerstone for studying queuing systems and logistics. Early adopters in industries like manufacturing and defense found these methods invaluable for optimizing resource allocation and process efficiency.[34]

The rise in popularity of computer-assisted simulations has been driven by improvements in computational power, accessibility of software, and the growing complexity of systems requiring analysis. Modern simulation tools, including those for system dynamics, agent-based modeling, and hybrid approaches, are now widely used in healthcare, logistics, and engineering. Open-source programming languages like R and Python have democratized access to simulation tools, enabling researchers and practitioners to model real-world problems without the need for expensive proprietary software.[40,41] In clinical laboratory management, simulations have become essential for addressing challenges such as high testing volumes, resource constraints, and demand fluctuations, further cementing their role as an indispensable decision-making tool.[42,43]

Theory behind computer assisted simulations: a brief conceptual description

Computer-assisted simulations in operations research (OR) are grounded in mathematical modeling and probability theory. At their core, simulations replicate the behavior of complex systems by iteratively calculating outcomes based on predefined mathematical rules and probabilistic distributions.[44] DES, one of the most widely used methodologies, models systems as a sequence of events that occur at discrete points in time. These events are governed by probabilistic distributions such as exponential or Poisson, which describe stochastic processes like inter-arrival times or service durations. Monte Carlo simulations, another key technique, use random sampling to solve deterministic or probabilistic problems by exploring a range of possible outcomes under varying assumptions.[38] Both approaches rely on random number generation and iterative computation to model uncertainty and variability, which are central to real-world OR problems.

The mathematical foundation of simulations also incorporates optimization and queuing theory to analyze system performance. For example, queuing models are built using Markov chains and probability distributions to estimate metrics such as average wait times, service utilization, and system capacity.[45] Optimization models, often integrated into simulation frameworks, use linear or nonlinear programming to identify optimal resource allocation strategies. Simulation algorithms are designed to mimic real-world processes iteratively, capturing dynamic interactions among variables while accounting for randomness. This capability makes simulations particularly powerful for modeling complex, interdependent systems like clinical laboratories, where exact analytical solutions may not exist due to high variability and uncertainty. By combining mathematical rigor with computational efficiency, simulations provide actionable insights for OR practitioners.[45]

Popular software used in computer assisted simulations

Operations research employs a variety of software tools to address complex decision-making problems across different domains. Among the most popular software used in OR are optimization and simulation tools. Optimization software such as Solver, POM-QM, and Lingo are frequently utilized in educational settings to enhance students' problem-solving capabilities, as evidenced by their effective use in a public university in Lima, Peru, where they significantly improved student performance in OR courses.[46]

Additionally, Maple is highlighted for its optimization features, which are particularly beneficial in educational contexts for formulating, solving, and visualizing optimization models.[47]

Simulation software also plays a crucial role in OR, with tools like VISSIM, TSIS/CORSIM, and SYNHRO/SIMTRAFFIC being extensively used for traffic operations, each offering unique capabilities for modeling various traffic conditions and providing measures of effectiveness.[48] The widespread use of simulation modeling in fields such as manufacturing, health, and military applications has led to a proliferation of simulation software tools, as noted in a survey by the Operational Research Society of Great Britain.[49]

Furthermore, the development of micro-computer simulation languages has made powerful and inexpensive simulation tools accessible, enhancing the capabilities of OR analysts.[50] The integration of advanced software tools in OR and analytics, such as machine learning in R and algebraic modeling with JuMP, is increasingly important for handling large data sets and complex models, as demonstrated in a course designed to equip students with these skills.[51]

Overall, the diverse range of software tools available in OR, from optimization to simulation, underscores their critical role in facilitating effective decision-making and problem-solving across various industries and educational settings.

Challenges in operations research

Current challenges in applying operations research (OR) to clinical laboratory management stem from both technical and organizational factors. One major issue is the complexity of laboratory workflows, which involve multiple interconnected processes such as sample collection, processing, quality control, and reporting. Modeling

these workflows requires advanced analytical methods like simulation modeling or optimization techniques, which are often beyond the expertise of laboratory personnel.[52] Additionally, clinical laboratories face resource constraints, such as limited access to specialized software and computational tools, further complicating the integration of OR into routine decision-making. High variability in demand, driven by external factors like pandemics, adds another layer of complexity, requiring dynamic models that are challenging to design and implement effectively.[53]

Another significant challenge is the widespread lack of quantitative and analytical skills among laboratory managers and staff. Many professionals in clinical laboratory management are not trained in the rigorous methodologies required for consistent and reproducible OR studies.[54] As a result, even when data are available, there is a risk of oversimplified or inconsistent approaches that fail to capture the nuances of real-world laboratory operations. Moreover, inadequate training in statistical programming languages (e.g., R or Python) and software for simulation and optimization limits the ability to adopt a reproducible framework. This gap in skills leads to missed opportunities for leveraging OR techniques to improve efficiency, reduce costs, and enhance patient care. Bridging this gap requires targeted training programs, cross-disciplinary collaboration, and investment in user-friendly OR tools tailored to the clinical laboratory setting.[55]

Despite challenges, operations research and analysis can be done using accessible open-source software like R and implemented in RStudio.

Operations research (OR) and analysis can be effectively conducted using accessible open-source tools like R in RStudio, provided users follow key simple practices.

R is a powerful statistical programming environment that offers extensive libraries for simulation, optimization, and statistical modeling, making it highly suitable for a wide range of operations research (OR) applications, including resource allocation and workflow optimization. The language is renowned for its flexibility and extensibility, allowing users to perform a variety of statistical analyses such as regression, ANOVA, time series, and multivariate analysis, which are crucial for OR tasks.[56] R's open-source nature and the availability of over 4000 specialized packages further enhance its capabilities, providing users with tools for data manipulation, calculation, and graphical display. The language's ability to handle complex data structures and perform advanced statistical modeling is particularly beneficial in OR, where data-driven decision-making is essential.[56] Moreover, R's algebraic modeling approach, as discussed in optimization contexts, allows for clear formulation and implementation of linear and mixed-integer optimization problems, which are common in OR. The integration of R with data analytics platforms reduces the barrier to entry for professionals, enabling them to leverage data analytics tools effectively.[57]

Furthermore, R's open-source nature and vast community support reduce barriers to entry, allowing clinical laboratory managers to adopt OR techniques without expensive software. By combining these practices with RStudio's user-friendly interface, even individuals with basic programming skills can harness the power of OR to make data-driven decisions in laboratory management.

Computer-assisted simulations in R using RStudio are highly effective and versatile due to the power of the R programming language and the integrated development environment (IDE) provided by RStudio.

Computer-assisted simulations in R using RStudio are highly effective and versatile due to the robust capabilities of the R programming language and the integrated development environment provided by RStudio. R is a preferred choice for simulation studies across various fields due to its extensive library of packages and the ability to write custom functions, which is particularly beneficial in areas like computer adaptive testing (CAT) and item response theory (IRT) simulations.[58]

The RStudio IDE enhances this experience by offering a user-friendly interface that facilitates project management, script writing, and access to comprehensive documentation, making it an ideal environment for empirical research and educational purposes.[59]

In educational settings, R is utilized to teach complex statistical concepts through simulations, such as sampling distributions and hypothesis testing, which help students grasp abstract ideas more concretely.[60] Additionally, R's capabilities extend to large-scale simulation studies, where packages like *simsalapar* enable efficient parallel computing and comprehensive result analysis, crucial for handling complex quantitative risk management problems.[61]

The RxODE package further exemplifies R's versatility by allowing the simulation of differential equation models, which can be integrated into interactive applications for real-time scenario evaluation.[62]

By combining R's statistical prowess with RStudio's integrated environment, users can create flexible, reproducible, and cost-effective simulations to address complex operations research questions in various fields, including clinical laboratory management. This powerful combination democratizes advanced analytics, making it accessible to a wide range of users and applications.

Simulations can be performed using base R functions to answer simple OR questions using loops.

Even if access to custom packages specifically designed for operations research questions are not available, simulations for simple operations research (OR) questions can be effectively performed using base R functions, leveraging its built-in capabilities such as loops (for, while repeat) and vectorized operations.

This approach provides a flexible and straightforward framework for tackling basic OR problems without requiring specialized packages. Base R excels in simulation tasks through its powerful constructs: vectorized operations enable efficient computations over large datasets, while control structures like loops and conditional statements (if, else) support iterative and dynamic process modeling.

Additionally, R's random number generation functions (runif, rnorm, rpois, and sample) facilitate stochastic

modeling, making it ideal for tasks such as modeling queue behavior, conducting Monte Carlo simulations, or analyzing inventory dynamics. These features collectively ensure that base R is well-suited for addressing a range of simple OR challenges.

Step-by-step instructions for installing R and RStudio

To perform simulations using R, you need to download and install the software on a PC or Mac with an active internet connection. The following text is a step-by-step guide to installing and setting up R and R studio.

Step 1: Download R

1. Visit the CRAN (Comprehensive R Archive Network).
2. Choose your operating system:
   - Windows: Click on "Download R for Windows," then select "base" and download the installer.
   - macOS: Click on "Download R for macOS" and choose the appropriate file for your macOS version.
   - Linux: Follow the detailed instructions for your distribution (Ubuntu, Fedora, etc.).
3. Run the installer:
   - Follow the prompts, accept the defaults, and complete the installation.

Step 2: Download RStudio

1. Visit the RStudio Download Page.
2. Select the free version *(RStudio Desktop – Open Source License)* and download the installer for your operating system.
3. Run the installer:
   - Follow the instructions and complete the installation.

Step 3: Verify installation

1. Open **RStudio**.
2. Verify that R is linked to RStudio by typing the following command in the console:

```
================================
Version
================================
```

The output should display the installed R version and platform information.

Good practices when running R in RStudio

1. Organize your workspace

A well-organized workspace is critical for efficient coding in RStudio. Begin by setting a working directory to define the location where your files will be saved and accessed. This can be done using the *setwd()* function or by navigating to *Session > Set Working Directory* in RStudio's menu. For example:

```
================================
setwd("C:/Your/Directory/Path")
================================
```

Note: replace "*C:/Your/Directory/Path*" with the specific path on your computer for your project.

Additionally, keep projects separate by using RStudio's Projects feature, which allows you to create isolated environments for different analyses. This helps maintain a clean and focused workflow, especially when managing multiple tasks simultaneously.

2. Comment your code

Commenting your code is essential for clarity and collaboration. Use comments to explain the purpose of each section, making your script easier to understand for yourself and others in the future. For instance:

```
================================
# Generate 100 random numbers from a normal distribution
random_numbers <- rnorm(100, mean = 0, sd = 1)
================================
```

Comments have the symbol "#" at the start. This practice ensures that your logic and intent remain clear and human readable, even when revisiting code after a long period or sharing it with team members.

3. Use version control

Integrating version control, such as Git, within RStudio is invaluable for tracking changes in your code. Version control allows you to maintain a history of edits, collaborate with others, and revert to previous versions when needed. RStudio's Git integration makes it easy to commit changes, push updates, and manage branches, ensuring a robust development workflow.

4. Save your work

Always save your scripts regularly to avoid losing progress. Use .R files to organize your code and the Source Pane in RStudio to write, save, and run scripts systematically. Working from the Source Pane instead of directly in the console provides better control and allows you to rerun sections of your code easily.

5. Utilize packages wisely

Efficient package management is crucial for a streamlined workflow. Install only the packages you need using:

```
================================
install.packages("ggplot2")
================================
```

At the beginning of your script, load these packages explicitly with library() to ensure they are available for use:

```
================================
library(ggplot2)
================================
```

This practice keeps your environment organized and avoids potential conflicts or redundancies. Note that functions overwrite previously loaded ones if they have the same name.

6. Keep R and RStudio updated

Regular updates to R, RStudio, and installed packages ensure compatibility, improved functionality, and enhanced security.

The version of R used in the preparation of this manuscript is R version 4.4.1 (2024-06-14 ucrt) -- "Race for Your Life" Copyright © 2024 The R Foundation for Statistical Computing. Platform: x86_64-w64-mingw32/x64.[63] The version of RStudio used in this paper is RStudio 2024.09.0 Build 375 "Cranberry Hibiscus" Release (c8fc7aee, 2024-09-16) for Windows.[64] To update all packages at once, use:

```
==================================
update.packages()
==================================
```

Keeping your software up-to-date prevents bugs and ensures access to the latest features and improvements. This can also be done by pointing and clicking.

7. Write reproducible code

Reproducibility is a hallmark of good programming. For simulations results to be reproducible, a random seed must be set:

```
==================================
set.seed(123)
==================================
```

Additionally, avoid hard-coding file paths by using relative paths, which make your code portable across different systems and environments. A relative path assumes that the starting point of the path is the current working directory and will look for the file of interest beginning in the current working directory.

8. Debug effectively

Debugging is an essential part of coding. Use diagnostic functions like *summary()*, *str()*, and *print()* to inspect variables and identify issues. Break your code into smaller sections and test each one before running the entire script. This incremental approach helps isolate errors quickly and ensures smooth execution.

9. Utilize RStudio features

RStudio offers several features to enhance productivity:

- **Code completion**: Autocomplete saves time and reduces typos.
- **Plots pane**: View visualizations directly within RStudio without cluttering your workspace.
- **Environment pane**: Monitor active variables, their data types, and values to keep track of your workspace.

10. Save outputs

Exporting results, such as plots or data, is straightforward in RStudio. For example, save a plot as a PNG file using:

```
==================================
png("plot.png")
plot(rnorm(100))
dev.off()
==================================
```

This ensures your outputs are preserved and accessible for reporting or further analysis.

Maintain an efficient workflow

To optimize your workflow, use shortcuts like Ctrl + Enter (Windows/Linux) or Cmd + Enter (macOS) to quickly run lines of code. Regularly clear your environment using: rm(list = ls()) to avoid memory issues caused by unnecessary variables. Finally, back up your scripts and results in version-controlled or cloud-based environments for security and easy retrieval.

By following these practices, you can create a structured, efficient, and reproducible environment for coding in RStudio, enhancing your productivity and ensuring the quality of your work.

Key steps in performing a computer-assisted simulation study using base R to answer common operations research (OR) questions:

Once you have installed and set up R and Rstudio, you should be ready to perform simulation experiments and analyses to support operations research. The following paragraphs outline a step-by-step guide to perform simulations in R.

Step 1: Clarify the research or study question

Define the problem

Clearly state the objective of the study. Common problems that arise in the setting of laboratory management include optimizing laboratory workflow, minimizing reagent stockouts, or determining optimal staffing levels.

Example: *"What are the chances of a reagent stockout given fluctuating demand and a fixed supply?"*

Specify the outcome

Identify the metric or outcome you wish to measure. Common outcomes of interest for a clinical laboratory include waiting time, cost, or stockout probability.

Step 2: Define variables and assumptions

List input variables

Identify the key inputs of interest relevant to the operations problem, for example, inter-arrival times, service rates, and demand distribution. This part requires prior information about the specific experience of the clinical laboratory. The researcher or manager must make sure that the assumed parameters closely approximate the distributional characteristics of the phenomena under consideration.

Example: *Daily reagent demand follows a normal probability distribution with a mean of 500 units and standard deviation of 50.*

Specify constraints and assumptions

Document any constraints or fixed parameters (e.g., available supply, service capacity). These are factors that usually have the most impact on the decision-making process and pertain to limits on resources.

Example: *Daily reagent supply is fixed at 600 units.*

Step 3: Set up the model

Choose a simulation approach
Decide on the type of simulation (e.g., discrete-event simulation, Monte Carlo simulation).
Example: *Monte Carlo simulation to estimate the probability of stockouts.*

Define logical flow
Create a logical sequence of events (e.g., sample arrival → service start → service completion).

Plan iterations
Decide on the number of iterations to ensure statistical reliability.

Step 4: Draft the code in base R

Initialize parameters
Define all fixed parameters (e.g., supply level, number of iterations).

```
==========
set.seed(123) # Ensure reproducibility of results
simulations <- 1000
supply <- 600
mean_demand <- 500
sd_demand <- 50
==========
```

Generate random data
Use base R functions to model stochastic inputs. This step is the key step in simulation studies as choice of the stochastic (probabilistic) model has direct effect on the results. The stochastic (probabilistic) model should closely mimic the natural evolution of the phenomenon under consideration as much as practically necessary.

```
==========
demand <- rnorm(simulations, mean = mean_demand, sd = sd_demand)
==========
```

Simulate the process
Use loops and conditional logic to simulate the system. The loop section instructs the computer to perform the simulations many times to adequately model the uncertainty of the phenomena.

```
==========
stockouts <- 0

for (i in 1:simulations)  {
  if (demand[i] > supply)  {
    stockouts <- stockouts + 1
  }
}
==========
```

Calculate the outcome
Compute the desired metric or outcome.

```
==========
probability_stockout <- stockouts / simulations
==========
```

Step 5: Run and debug the code

Run incrementally
Run the code block by block to identify potential errors. This method allows the researcher to fine check the code for errors.

Validate logical flow
Print intermediate results (e.g., head(demand)) to ensure inputs and outputs are logical.

Step 6: Interpret results

Analyze the outputs
Examine the computed outcomes in relation to the research question.

```
==========
print(probability_stockout) # Probability of stockout
==========
```

Provide insights
Example Interpretation: *"The simulation estimates a 4.4% probability of stockout. Based on the current operational situation of the clinical laboratory, this result indicates a potentially preventable loss of productivity and is an opportunity to institute pre-emptive action by increasing the supply or buffer stock."*

Step 7: Ensure reproducibility

Set a random seed
Use set.seed() to ensure consistent results in repeated runs. The computer only generates pseudorandom numbers. Setting the seed at the beginning of the code allows others to faithfully reproduce the results even if the code involves several iterations of generating "random" runs or samples from a probability distribution or stochastic model. Any number can be used, but it must be declared to allow reproducibility.

Example: set.seed(123) #setting the seed to 123 is a simple default strategy, but it can be any number.

Document code
Comment code extensively to explain each step. This allows others to understand the flow and purpose of the code. All characters in a line of code after the pound "#" sign is interpreted by R as a comment. Every next line is considered a new instruction by R.

Example:

```
==========
# Generate daily demand using normal distribution
demand <- rnorm(simulations, mean = mean_demand, sd = sd_demand)
==========
```

Export results
Save results for future reference.

```
==========
write.csv(data.frame(demand, supply), "simulation_results.csv", row.names = FALSE)
==========
```

Step 8: Validate and refine

Test for robustness
Run the simulation with different parameters (e.g., supply levels) to test sensitivity.

Compare results
Validate outputs against known benchmarks or expert estimates.

Step 9: Report findings

Summarize key results
Present the simulation results in clear, concise terms.
Example: *"The Monte Carlo simulation revealed a stockout probability of 4.4%, suggesting a moderate risk under current supply conditions."*

Visualize results
Although there are many excellent packages in R for visualization, the base R plotting functions for visualization are already powerful for basic applications. The following is code that generates a histogram of daily demand:

```
==========
hist(demand, main = "Distribution of Daily Demand", xlab = "Daily Demand")
==========
```

Recommend actions
Translate findings into actionable recommendations. This is one of the most important parts of the analysis as it clearly communicates the findings to decision makers.

This step-by-step process ensures clarity, reproducibility, and actionable outcomes for any OR simulation study conducted in base R.

Illustrative case examples using Base R to demonstrate the analysis of simple OR questions

In the following paragraphs, using typical case scenarios, we will walk you through the process of using R to perform operations research and analysis.

A. Patient or sample queue simulation

Vignette
A typical small government clinical laboratory receives a steady stream of patient samples for processing. Due to the limited resources that the laboratory is given, it is unsurprising that there are days when samples pile up and wait to be processed. You, as the laboratory manager wants to estimate the waiting times to identify bottlenecks in the workflow. You intend to use this information to justify increase in budget allocation for the laboratory.

Strategy
Simulate the waiting times of patients (i.e. samples) in your laboratory where there is only one receiving and processing staff. Assume that the service time follows an exponential distribution with rate = 1.5. Run the simulation for 10 samples.

Solution using base R

```
==========
set.seed(123)
arrival_times <- cumsum(rexp(10, rate = 1)) # Inter-arrival times
service_times <- rexp(10, rate = 1.5) # Service times

waiting_times <- numeric(length(arrival_times))
end_service <- 0 # End time of the previous service

for (i in seq_along(arrival_times))  {
  start_service <- max(arrival_times[i], end_service)
  end_service <- start_service + service_times[i]
  waiting_times[i] <- start_service - arrival_times[i]
}
waiting_times
==========
```

Expected output (waiting time in hours)
[1] 0.00000000 0.09327643 0.00000000 0.15576506 0.35096597
[6] 0.15998745 0.41228424 1.30915313 0.00000000 0.36480311

```
==========
```

Interpretation
In a simulation of arrival times and processing times of the next 10 patients/samples, three (3) patients/samples experience no wait time (0 hours), while the rest of the patients/samples experience waiting times ranging from 6 minutes to 79 minutes.

Explanation and notes
This R code simulates a queuing system where patients/samples arrive and get processed, calculating the waiting time for each patient/sample based on their arrival and service times. The random seed is set using `set.seed(123)` to ensure reproducibility, so the generated random numbers remain consistent across runs.

The arrival times of 10 patients (or samples) are simulated using `cumsum(rexp(10, rate = 1))`, where `rexp(10, rate = 1)` generates random inter-arrival times from an exponential distribution with lambda of 1 (1 patient arrives per hour on average), and `cumsum` calculates their cumulative sum to determine actual arrival times.

Similarly, service (or processing) times are simulated using `rexp(10, rate = 1.5)`, which generates random service durations from an exponential distribution with a rate of 1.5 (1.5 patient samples are processed per hour on average).

A numeric vector, `waiting_times`, is initialized to store the waiting times for each patient (or sample), starting with zeros. The variable `end_service` is set to 0 to track when the previous patient's (or sample's) processing time ends.

The `for` loop iterates over each customer, calculating their waiting time.

For each patient (or sample), the processing time starts either at their arrival time or when the previous customer's service ends, whichever is later.

This is computed using `start_service <- max(arrival_times[i], end_service)`. The service end time is updated as the sum of the processing start time and the current patient's (or sample's) processing time. The waiting time for each patient (or sample) is calculated as the difference between their processing start time and arrival time and is stored in the `waiting_times` vector.

At the end of the simulation, the `waiting_times` vector contains the waiting times for all 10 patients. This code models a first-come, first-served queuing system using an exponential distribution for arrival and processing times, a common approach in queuing theory to represent random events such as patient arrivals and processing durations.

B. Monte Carlo simulation

Vignette

A laboratory faces uncertainty in reagent consumption due to fluctuating daily test demands for a cartridge-based PCR assay for an infectious disease. The lab manager uses Monte Carlo simulation to estimate the probability of running out of reagents (stockouts) when supply is fixed at 600 units per day.

Strategy

Estimate the probability of a reagent stockout. Assume that based on the lab's previous 3 months census, the demand follows a normal probability distribution with mean demand of 500 and an SD of 50. Assume that there is no strong reason to believe that the probability distribution of the demand for the next several months shall be significantly different from the previous 3 months.

Solution using base R

```
==================================
set.seed(123)
simulations <- 1000
demand <- rnorm(simulations, mean = 500, sd = 50) # Daily demand
supply <- 600 # Fixed supply

stockouts <- 0

for (i in 1:simulations)  {
  if (demand[i] > supply)  {
    stockouts <- stockouts + 1
  }
}

probability_stockout <- stockouts / simulations
probability_stockout
==================================

Expected output
[1] 0.028
==================================
```

Interpretation

The probability of experiencing a stockout is approximately 2.8%. Depending on the laboratory's operational strategy, this information may represent an unacceptable level of risk (potential income loss), and thus presents as an opportunity to adjust buffer stock levels to reduce the operational risk brought about by insufficient stocks. Provided that the assumptions are reasonably accurate, this information helps the lab manager decide whether to increase the buffer stock levels or not and how much to increase.

Explanation and notes

This R code simulates a scenario to estimate the probability of a stockout, which occurs when customer demand exceeds available supply. The simulation runs 1,000 iterations to approximate this probability under given demand and supply conditions.

The random seed is set using set.seed(123) to ensure that the generated random numbers are consistent and reproducible. The daily demand is modeled as a normal distribution using *rnorm(simulations, mean = 500, sd = 50)*, which generates 1,000 random values with a mean of 500 and a standard deviation of 50. This represents the variability in daily demand. The supply is fixed at 600 units, indicating the maximum quantity available each day.

A variable stockout is initialized at 0 to count the number of times demand exceeds supply during the simulations. A for loop iterates through each simulated day, comparing the daily demand (demand[i]) to the fixed supply. If the demand on a particular day exceeds the supply, the stockouts counter is incremented by 1.

After completing the loop, the probability of a stockout is calculated as the ratio of the number of stockouts to the total number of simulations (probability_stockout <- stockouts / simulations). This probability provides an estimate of how often demand will surpass supply, helping to assess the risk of insufficient inventory under the given conditions.

Finally, the value of probability_stockout is returned, representing the likelihood of experiencing a stockout based on the simulated data.

C. Inventory Management

Vignette

A clinical laboratory needs to optimize its reagent order quantity for a particular type of PCR cartridges to minimize total costs, which include ordering costs and holding costs. Using a simple inventory model, the lab manager was tasked to determine the optimal order size.

Strategy

Simulate and find the optimum order quantity size using a simple inventory model. Assume that the order cost is 50 (in thousands of pesos) per order, the annual holding cost per unit is 2 (in thousands of pesos), and that the annual demand is 1000 units. Perform a simulation for different order sizes (from 10 per order to 1000 units per order).

Solution using base R:

```
==========
set.seed(123)

order_cost <- 50
holding_cost <- 2
annual_demand <- 1000

total_cost_for_order_size <- function(order_size)  {
  total_cost <- (annual_demand / order_size) * order_cost
  + (order_size / 2) * holding_cost
  return(total_cost)
}

order_sizes <- seq(10, 1000, by = 10)
total_costs <- numeric(length(order_sizes))

for (i in seq_along(order_sizes))  {
  total_costs[i] <- total_cost_for_order_size(order_sizes[i])
}

order_sizes[which.min(total_costs)]

==========
Expected output (optimum order size to minimize total costs)
[1] 220
==========
```

Interpretation

The optimal order size for reagents is 220 units per order, minimizing total costs while ensuring sufficient supply.

Explanation and notes

This R code determines the optimal order size that minimizes the total cost of managing inventory. The optimal order size is calculated by evaluating the trade-off between ordering costs and holding costs for different order sizes.

The code begins by setting a random seed using set.seed(123) for reproducibility.

The fixed parameters include the order cost (order_cost = 50) in thousands of pesos per order, which represents the cost of placing a single order; the holding cost (holding_cost = 2) in thousands of pesos, which represents the cost of holding one unit of inventory annually; and the annual demand (annual_demand = 1000) in units of PCR cartridges, the total number of units required per year.

The function total_cost_for_order_size calculates the total inventory management cost for a given order size. It computes the total cost as the sum of:

1. The ordering cost: (annual_demand / order_size) * order_cost, which depends on how many orders need to be placed annually.
2. The holding cost: (order_size / 2) * holding_cost, which represents the cost of holding the average inventory level (assumed to be half the order size).

Next, a sequence of potential order sizes is generated using seq(10, 1000, by = 10), representing possible quantities from 10 to 1000 units in increments of 10.

An empty vector, total_costs, is initialized to store the total cost for each order size. A for loop iterates through all possible order sizes, calculates the total cost for each using the optimal_order_quantity function, and stores the result in total_costs.

Finally, the code identifies the order size with the minimum total cost using order_sizes[which.min(total_costs)].

This value corresponds to the EOQ, which is the order size that minimizes the combined ordering and holding costs. The result provides a practical decision point for optimizing inventory management.

DISCUSSION

Benefits of using base R for simulations

Accessibility

Base R is inherently accessible, as it is included in every R installation. Users do not need to install or learn additional packages, making it ideal for those new to R or working in environments with limited internet access or system permissions. This simplicity reduces the setup time and ensures that simulations can be executed without technical barriers, streamlining the learning and implementation process for operations research (OR) applications.

Flexibility

Base R's built-in functions and loop structures provide immense flexibility, allowing users to create tailored solutions for specific OR problems. Unlike pre-built packages, which often require users to adapt their problems to fit the package's framework, base R enables the customization of code to address unique scenarios. For example, using for loops and conditional statements, users can model workflows, simulate inventory dynamics, or perform Monte Carlo experiments with parameters that closely match their operational realities.

Transparency

One of the major strengths of using base R is the explicit and transparent nature of the code. Each step of the simulation process is visible and traceable, making it easier to understand the logic behind the calculations. This transparency is particularly valuable in educational settings, where understanding the underlying processes is just as important as obtaining results. For instance, educators can use base R to demonstrate the mechanics of queuing theory or inventory modeling, breaking down complex concepts into manageable steps.

Performance for simple tasks

Base R performs well for small-scale problems, where the computational demands are moderate. For tasks like simulating sample arrival times, calculating resource utilization, or testing simple queuing models, base R executes efficiently without the overhead of loading and running additional libraries. This makes it a practical choice for quick, straightforward simulations that do not require high levels of complexity or scalability.

Limitations and contextual suitability

Scalability challenges

While base R is sufficient for simple OR simulations, its performance can decline when handling large datasets or complex models. Loops in base R, such as for or while, are not optimized for high scalability and may result in slower execution compared to vectorized operations or specialized simulation libraries. For example, simulating thousands of events in a discrete-event simulation might require significant computational time, making package-based solutions like simmer or parallelized approaches more suitable.

Readability concerns

As simulations grow in complexity, the verbosity of base R code can make scripts harder to read and maintain. Unlike specialized libraries that encapsulate intricate operations into single functions, base R requires users to write out each step explicitly. This verbosity can lead to longer scripts that are challenging to debug and interpret, especially for collaborative projects or long-term use.

Lack of specialized features

Base R lacks the advanced functionalities provided by dedicated simulation packages. Features such as parallel processing, pre-built queuing models, and tools for stochastic optimization are not available natively. For instance, simulating real-time laboratory workflows or performing agent-based modeling may require external packages like simmer or SimPy for efficiency and scalability. This limitation makes base R less suitable for highly dynamic or large-scale OR problems.

Balancing benefits and limitations

Simplicity vs. complexity

For basic OR simulations, the simplicity and accessibility of base R often outweigh its limitations. Tasks such as modeling a single-server queuing system or simulating demand fluctuations can be efficiently accomplished using base R's straightforward constructs. However, as the complexity of the problem increases, the advantages of using specialized packages become more apparent. For instance, a laboratory workflow involving multiple servers, priority queues, and stochastic elements would be better addressed with dedicated simulation tools.

Context-driven suitability

The suitability of base R for OR simulations depends heavily on the context. In resource-limited environments or for educational purposes, the transparency and accessibility of base R make it an excellent choice. Conversely, in high-volume industrial settings or research scenarios requiring advanced modeling, the lack of scalability and specialized features may hinder its applicability. In such cases, integrating base R with additional libraries or external software might provide a balanced solution.

Success and utility of simulation depend on accuracy of assumptions

The success and utility of computer-assisted simulations in operations research processes are heavily dependent on accurately modeling the stochastic nature of the phenomena under consideration. Accurate modeling of stochastic processes is essential, as errors in these models can lead to significant consequences, including economic losses and safety risks.[65] Techniques such as observation-enhanced verification and probabilistic model checking have been developed to improve the accuracy of models by incorporating real-world data, thereby refining continuous-time and discrete-time Markov models to better capture process behaviors.[65]

CONCLUSION

In this paper we demonstrated a simple step by step workflow to analyze operations research type of questions arising from clinical laboratory management scenarios.

We showed that even just Base R provides a powerful, accessible, and flexible platform for performing simple operations research (OR) simulations, offering a straightforward framework for modeling diverse scenarios such as queue simulations, inventory management, and basic workflow optimization. Its transparency and ease of use make it particularly well-suited for small-scale problems, educational purposes, or situations where simplicity and minimal setup are priorities. For beginners or users in resource-constrained environments, base R serves as an effective tool to explore OR concepts and conduct meaningful analyses without relying on additional libraries.

However, its limitations in scalability, readability, and advanced features necessitate careful evaluation of the task's complexity. While base R excels in leveraging R's core statistical and mathematical modeling strengths, users must recognize when transitioning to specialized tools is required for addressing more complex OR challenges. Understanding its unique strengths and constraints allows users to harness base R effectively while building a solid foundation for advancing to more robust methodologies.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declare no conflict of interest and associated funding.

FUNDING SOURCE

None.

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OPEN ACCESS – FEATURE ARTICLE

Standardizing Hazard Signage at the Laboratory Research Division of the Research Institute for Tropical Medicine: A Step Towards Improved Safety Compliance

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ABSTRACT

Old signage faced iconography, variable layouts, visual presentations, and contents, as well as degradation issues, undermine the effectiveness of hazard communication in the laboratory. A 2016 project was initiated to standardize all hazard signages at the Laboratory Research Division of the Research Institute for Tropical Medicine, incorporating standard colors and iconography for better compliance and safety. As part of a broader initiative to enhance biorisk practices within the institute, there are plans for improvement and expansion to non-laboratory areas.

Key words: hazard, containment of biohazards, biosecurity, laboratories, communication, laboratory personnel

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 6 December 2024.
Accepted: 8 December 2024.
Published online first: 21 December 2024.
https://doi.org/10.21141/PJP.2024.15

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BACKGROUND

Prior to 2016, various laboratory departments within the Laboratory Research Division (LRD) of the Research Institute for Tropical Medicine (RITM) displayed hazard signages to inform and remind laboratory personnel and visitors of potential risks. However, the existing signages (Figures 1 through 4) had several limitations: minimal use of iconography, excessive reliance on text, non-standardized layouts, and susceptibility to environmental damage. These deficiencies led to ineffective hazard communication, particularly in high-risk environments, such as laboratories where clear and immediate understanding of safety protocols is crucial.

Inspired by the Institute's experience with International Organization for Standardization (ISO) 9001 certification and best practices observed in other institutions (including the San Lazaro Hospital and the University of the Philippines National Institutes of Health), an initiative was launched to address these shortcomings. The goal was to implement a standardized, icon-based hazard signage system that would be easy to produce, cost-effective, and flexible enough to accommodate the specific needs of each laboratory.

STANDARDIZATION OF LABORATORY SIGNAGES

The initiative aimed to create a uniform and functional signage system for all LRD laboratories. Key objectives included:

Cost-effectiveness and ease of replacement

The new signage should be inexpensive to produce and replace, ensuring compliance and ease of revision. Some of the previous signages had comparable properties but lacked consistency and visual impact, while others were directly bought from stores (for example, the middle signage in Figure 2).

Figure 1. Old hazard signage taken 2017, from the main entrance to the P3 Laboratory established in 2008. Signage consisted of a small biohazard label on the door handle and a facility map.

Figure 2. Old hazard signage taken 2017, from the National Tuberculosis Reference Laboratory (NTRL). Signage consisted of several parts, each containing security warnings displayed almost entirely in text. A good point for this sign is the large text size (and large single icon used) and the eye-catching color scheme, even if monotonous.

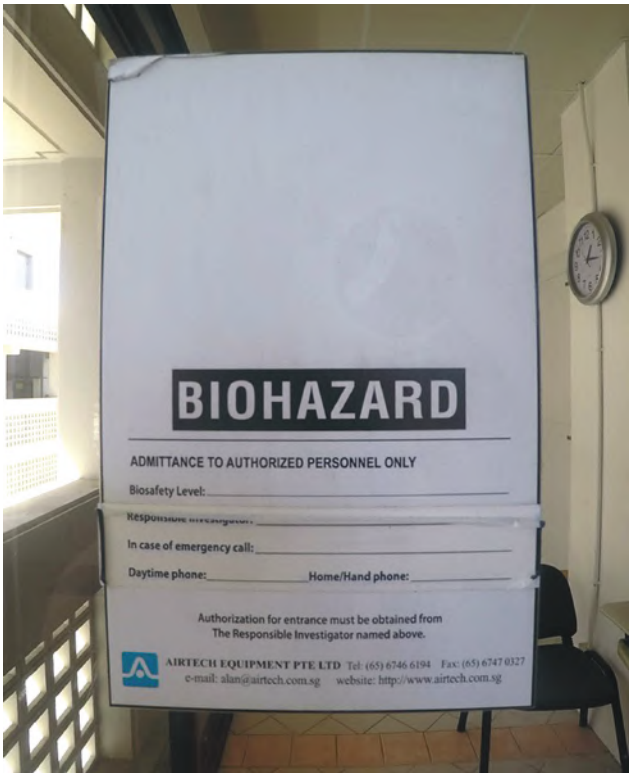

Figure 3. Old hazard signage taken 2017, from the NTRL BSL3 Laboratory established in 2012. Signage is compact and the text is small (except for "BIOHAZARD"). A biohazard symbol is the only pictograph present. But this symbol, as well as the entries in the text fields, has severely suffered from solar bleaching.

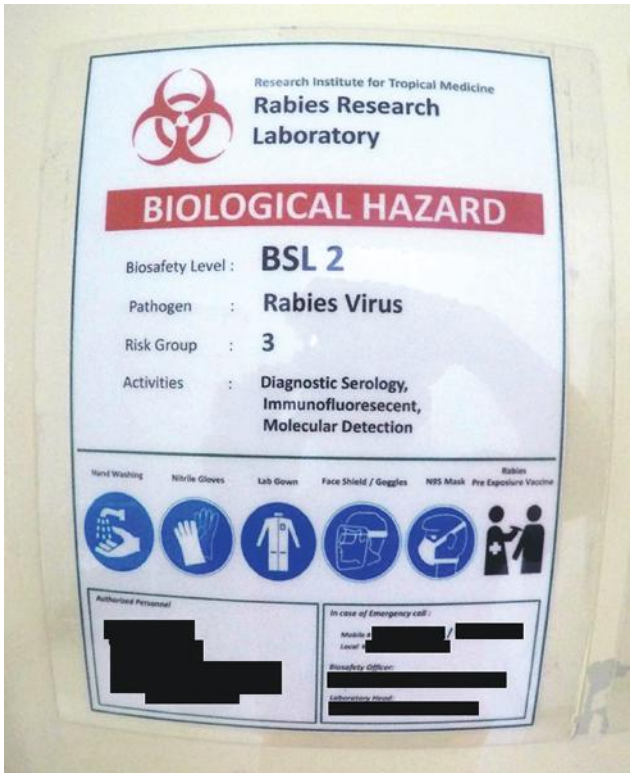

Figure 4. Old hazard signage taken 2016, from the Special Pathogens Laboratory. Usage of ISO pictographs (specifically those for mandatory action) is apparent here. There is also evidence of document control in the form of a supervisor's signature (lost to solar bleaching). Some details are redacted.

Table 1. Safety signage pictographs from ISO 3864 and ISO 7010 [1,2]

Icon Example	Color Scheme (common name and RGB)	Icon Type	Referent (Safety meaning) Example
	Blue (17, 93, 197) White (255, 255, 255)	Mandatory action	Wash your hands
	Red (255, 0, 0) Black (0, 0, 0) White (255, 255, 255)	Prohibition	Do not wear gloves
	Red (222, 0, 41) White (255, 255, 255)	Fire safety	Fire extinguisher
	Yellow (255, 238, 0) Black (0, 0, 0)	Warning	Warning; sharp element
	Green (0, 154, 59) White (255, 255, 255)	Means of escape and emergency equipment	Automated external heart defibrillator (AED)

*Only mandatory action, prohibition, and warning are currently used in the LRD uniform hazard signage.

Design standardization and flexibility

The new signage design was based on that of the RITM Advanced Molecular Technologies Laboratory (AMTL; formerly Molecular Biology Laboratory (MBL)), with a list of standard hazard icons derived from ISO 3864[1] (for pictograph shapes and color schemes) and 7010[2] (for iconography; Table 1). Laboratories were given flexibility to select icons relevant to their specific hazards, with guidelines for creating new icons if needed, as long as if they adhered to standardized shapes, color schemes, and other instructions in the aforementioned ISO documents.

Use of international signage standards

The new system (Figure 5) maximized the use of international signage standards, particularly iconography and color scheme, to communicate hazards clearly and efficiently. This was seen as essential for ensuring that warnings were immediately recognizable to all laboratory personnel, regardless of language proficiency.

Documentation and control

The signage was registered with the Institutional quality management system as a controlled document. This ensures that revisions are well-documented and based on changing laboratory activities and risks. Laboratories were also required to produce a risk assessment document to justify the content of their hazard signage, including any changes to it.

KEY DESIGN ELEMENTS

The new signage format included the following key elements:

Title	Displays the document name, control number, version, and institutional logos. This section allows department-specific branding.
Pathogens tested	Laboratories can choose how much information to disclose about the pathogens they work with, balancing biosecurity concerns with promotional and collaborative opportunities.
Hazards	A primary hazard and biosafety level are identified, with the option to list secondary hazards. The yellow triangle icon is used to signify all hazards.
Personal protective equipment (PPE)	Laboratories define mandatory and additional PPE, with blue circle icons used to indicate such equipment.
Other practices	This section addresses controlled access, prohibited activities, and required preparations before entering the laboratory. It uses prohibition and blue circle icons. Short supporting text may be used to explain some of the items.
Emergency contact information	Includes relevant contacts, such as the department head and lab manager, ensuring swift communication in case of an emergency.
Processes and workflow	Describes the laboratory's workflow, with color-coded sections indicating different rooms and activities. Each laboratory section can have its own signage displaying its unique hazard profile. This is especially important for laboratories where the flow of materials and personnel is critical for minimizing contamination (e.g., PCR or culture laboratories)

IMPLEMENTATION

The signage must be printed, signed by the department head, laminated, and displayed at the main entrance of each laboratory or laboratory section. The responsibility for producing and maintaining the signage lies with individual departments, though the institutional biorisk management office ensures compliance and quality control.

The standardized hazard signage system has significantly improved the clarity and consistency of safety communications across the laboratories. By incorporating internationally recognized symbols, the new signage allowed for immediate recognition of hazards, reducing the reliance on text-heavy signage that may be overlooked. Additionally, the flexibility of the system ensures that each laboratory (and each laboratory section) can tailor the signage to its specific needs, while maintaining overall standardization.

Furthermore, the use of controlled documentation for both the signage and the accompanying risk assessment ensures that safety information remains up to date and aligns with institutional quality management procedures and evolving laboratory practices. This structured approach is expected to facilitate ongoing improvements in laboratory safety and compliance.

CONTINUOUS IMPROVEMENT

Future modifications for the signage system include:

- **Expansion to larger paper sizes**
  To accommodate more detailed information and improve visibility, signage may be printed on larger paper sizes such as A3.

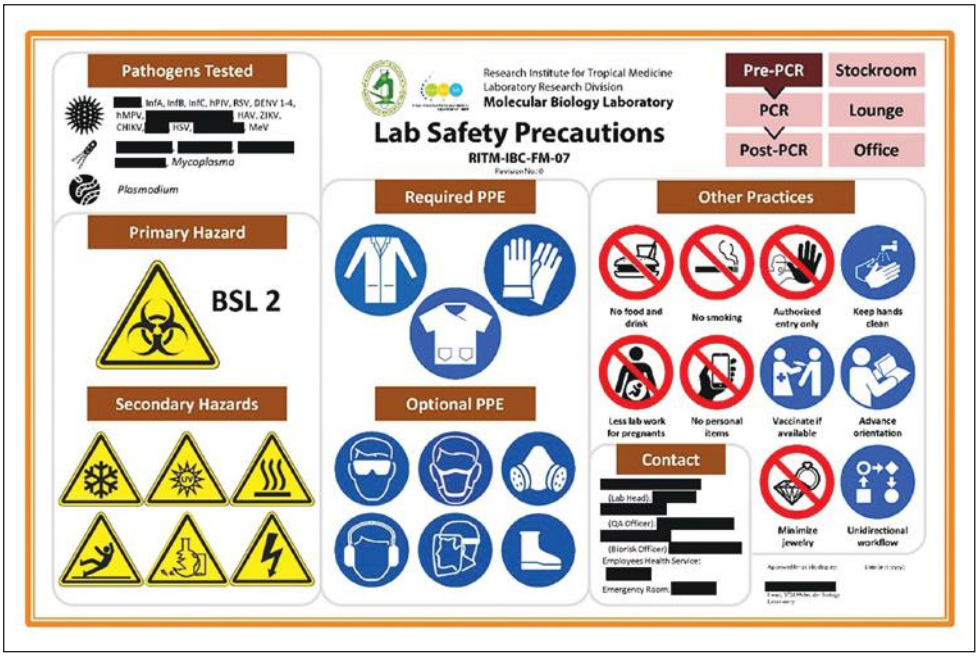

Figure 5. Working version of the uniform hazard signage used by all LRD laboratories today, example above from the Molecular Biology Laboratory (currently Advanced Molecular Technologies Laboratory) Pre-PCR Area. Take note of the document control number (RITM-IBC-FM-07) at the top. Some details are redacted.

- **Incorporation of additional safety standards**
  Efforts are underway to include other signage standards, such as NFPA 704 (fire diamond) and updates to ISO 3864 and 7010.[1,2]

- **Increased compliance with viewing and illumination standards**
  Stricter compliance with viewing distances, angles, and illumination standards is planned to enhance the effectiveness of the signage.

- **Extension to Non-laboratory Areas**
  Similar signages may be extended to non-laboratory areas to further promote occupational safety.

CONCLUSION

The standardization of hazard signage within the Laboratory Research Division at the Research Institute for Tropical Medicine represents a significant step toward improving laboratory safety and compliance. By adopting a flexible yet standardized signage system based on internationally recognized icons and color schemes, the Institute has created a clear, consistent, and cost-effective method for communicating hazards in high-risk laboratory environments. This initiative not only enhances biosafety but also lays the foundation for broader institutional and inter-institutional improvements in occupational safety. The signage system may be adopted by other facilities that wish to adopt the standardized format.

ACKNOWLEDGMENT

The author thanks Plebeian Medina (Head, RITM Biorisk Management Office) and Amado Tandoc III, MD (Chief, RITM Laboratory Research Division) for the encouragement and help.

STATEMENT OF AUTHORSHIP

The author certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The author declared no conflict of interest.

FUNDING SOURCE

None.

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Soft tissue Pathology
Brigham and Women's Hospital

Joseph T. Rabban III, MD, MPH
Gynecologic Pathology
University of California, San Francisco

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THE PHILIPPINE SOCIETY OF PATHOLOGISTS, INC.

A Specialty Division of the Philippine Medical Association

2025 UPDATES IN SURGICAL PATHOLOGY

HYBRID FORMAT (ON-SITE AT SEDA MANILA BAY HOTEL AND LIVE VIRTUAL VIA ZOOM)

SCHEDULE

Day 1 : 30 January 2025 (Thursday)

MASTER OF CEREMONIES: DR. REX MICHAEL SANTIAGO

TIME	ACTIVITY	SPEAKER	VENUE
7:00 - 7:55	REGISTRATION / ATTENDANCE		
7:55 - 8:00	WELCOME REMARKS	DR. MARIA CECILIA LIM (PSP PRESIDENT)	
8:00 - 8:45	LECTURE 1.1 Prostate Pathology - Diagnosis and Grading Simplified	DR. FIONA MACLEAN	Sampaguita 1,2,3
8:45 - 9:30	SLIDE SESSION 1.1 ABCs of Kidney Tumour Classification - How to make it EZ!	DR. FIONA MACLEAN	
9:30 - 9:40	OPEN FORUM		
9:40 - 10:20	COFFEE BREAK / MEET THE EXPERT - DR. JASON HORNICK		Dama de Noche
10:20 - 11:05	LECTURE 2.1 Agressive Mimics of Low Grade Endometrial Endometrioid Carcinoma	DR. JOSEPH RABBAN	Sampaguita 1,2,3
11:05 - 11:50	SLIDE SESSION 2.1 Update on Ovarian Non-epithelial Tumors	DR. JOSEPH RABBAN	
11:50 - 12:00	OPEN FORUM		
12:00 - 12:30	Lunch Symposium - Biosite		Sampaguita 1,2,3
12:30 - 1:00	Lunch Symposium - AstraZaneca		
1:00 - 1:45	LECTURE 3.1 Differential Diagnosis of the Most Common Spindle Cell Tumors of Deep Soft Tissue	DR. JASON HORNICK	Sampaguita 1,2,3
1:45 - 2:30	SLIDE SESSION 3.1 An Approach to the Diagnosis of Pleomorphic Sarcomas: Histologic Clues	DR. JASON HORNICK	
2:30 - 2:40	OPEN FORUM		
2:40 - 3:20	COFFEE BREAK / MEET THE EXPERT - DR. FIONA MACLEAN		Dama de Noche
3:20 - 4:10	LECTURE 4.1 The Differential Diagnosis of Pleomorphic Cutaneous Tumors	DR. THOMAS BRENN	Sampaguita 1,2,3
4:10 - 4:55	SLIDE SESSION 4.1 Challenging Tumors with Melanocytic Differentiation	DR. THOMAS BRENN	
4:55 - 5:05	OPEN FORUM		

MODERATORS: DR. DAVID JEROME ONG, DR. JENNIFER GO, DR. GIO EARNEST DE LA CRUZ, & DR. KEVIN ELOMINA

THE PHILIPPINE SOCIETY OF PATHOLOGISTS, INC.

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2025 UPDATES IN SURGICAL PATHOLOGY

HYBRID FORMAT (ON-SITE AT SEDA MANILA BAY HOTEL AND LIVE VIRTUAL VIA ZOOM)

SCHEDULE

Day 2 : 31 January 2025 (Friday)

MASTER OF CEREMONIES: DR. REX MICHAEL SANTIAGO

TIME	ACTIVITY	SPEAKER	VENUE
7:00 - 8:00	**REGISTRATION / ATTENDANCE**		
8:00 - 8:45	LECTURE 1.2 Updates to genitourinary pathology since the 2022 WHO	DR. FIONA MACLEAN	Sampaguita 1,2,3
8:45 - 9:30	SLIDE SESSION 1.2 Genitourinary Pathology - learn the secrets not in the books	DR. FIONA MACLEAN	
9:30 - 9:40	**OPEN FORUM**		
9:40 - 10:20	**COFFEE BREAK / MEET THE EXPERT - DR. THOMAS BRENN**		Dama de Noche
10:20 - 11:05	LECTURE 2.2 Aggressive uterine mesenchymal tumors that may mimic a leiomyoma.	DR. JOSEPH RABBAN	Sampaguita 1,2,3
11:05 - 11:50	SLIDE SESSION 2.2 Diagnostic pitfalls and classification dilemmas in endometrial biopsies.	DR. JOSEPH RABBAN	
11:50 - 12:00	**OPEN FORUM**		
12:00 - 12:30	**Lunch Symposium - Roche**		Sampaguita 1,2,3
12:30 - 1:00	**Lunch Symposium - MMJ**		
1:00 - 1:45	LECTURE 3.2 Round cell sarcomas: Ewing and beyond	DR. JASON HORNICK	Sampaguita 1,2,3
1:45 - 2:30	SLIDE SESSION 3.2 Mesenchymal tumors of the gastrointestinal tract: is it a GIST?	DR. JASON HORNICK	
2:30 - 2:40	**OPEN FORUM**		
2:40 - 3:20	**COFFEE BREAK / MEET THE EXPERT - DR. JOSEPH RABBAN**		Dama de Noche
3:20 - 4:10	LECTURE 4.2 Cutaneous vascular tumors	DR. THOMAS BRENN	Sampaguita 1,2,3
4:10 - 4:55	SLIDE SESSION 4.2 Novel developments in skin adnexal carcinomas	DR. THOMAS BRENN	
4:55 - 5:05	**OPEN FORUM / AWARDING OF CERTIFICATES**		
5:05 - 5:10	**CLOSING REMARKS**	**DR. JUSTINE ALESSANDRA UY (PSP CHAIR, CME FOR AP)**	

MODERATORS: DR. DAVID JEROME ONG, DR. JENNIFER GO, DR. GIO EARNEST DE LA CRUZ, & DR. KEVIN ELOMINA

2025 UPDATES IN SURGICAL PATHOLOGY

JANUARY 30-31, 2025

(Thursday & Friday)

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Foreign Delegates	USD200	USD250

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CATEGORY	REGISTRATION BEFORE OCT. 31	REGISTRATION AFTER OCT. 31
Residents	Php5,500	Php6,500
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Senior Citizens (60 and above)	Php5,200	Php6,000
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Suicide by Sodium Nitrite Ingestion: An Autopsy Case Report*

May Vell Mañibo[1] and Raquel del Rosario-Fortun[2]

[1]*Department of Laboratories, University of the Philippines – Philippine General Hospital*
[2]*Department of Pathology, University of the Philippines College of Medicine*

ABSTRACT

Sodium nitrite (SN, $NaNO_2$) is a water-soluble, white-yellow crystalline powder with broad applications in food preservation, automotive maintenance, and animal control. It is a strong oxidizing agent that can oxidize hemoglobin iron (Fe) to its oxidized state, leading to methemoglobin formation. An increasing trend of suicide cases by SN ingestion has been reported globally following its popularization in online suicide forums providing detailed instructions of its use solely or as part of a "suicide kit." We report a case of a 21-year-old male who was found continuously vomiting, with blood per orem and cyanosis of the mouth and digits. Within minutes of the onset of symptoms, the patient lost consciousness and was pronounced dead on arrival at the nearest emergency room. Autopsy findings showed lip erosions, hemorrhage, and perioral and peripheral cyanosis. Internal examination showed characteristic bright red muscle discoloration, dark brown arterial blood, red-brown congested visceral organs, and hyperemic esophageal and gastric mucosa. Methemoglobin studies from sampled arterial blood showed elevated levels (17.5%). Further investigation of the decedent's belongings, social media posts, and recent online purchases reinforced the intentional sodium nitrite ingestion. While there are plenty of reported SN poisoning in suicide cases internationally, limited reports have been published locally. Death by SN poisoning is preventable with Methylene blue. The role of forensic pathologists through autopsy may be the last chance to detect such cases. The lack of systemic death investigation, experts, and local laboratories to reliably detect the signs of SN poisoning may have affected the low detection rate of cases locally. Further reporting of cases can raise the awareness of medical professionals that is fundamental to the ultimate saving of lives.

Key words:: sodium nitrite, suicide, poisoning, forensic pathology, autopsy

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 10 July 2024
Accepted: 20 August 2024.
Published online first: 27 September 2024.
https://doi.org/10.21141/PJP.2024.10

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**This was presented at the Philippine Society of Pathologists Annual Convention Poster presentation contest, April 25-27, 2024, at the Makati Shangri-La Hotel, Makati Manila.*

INTRODUCTION

Sodium nitrite (SN, $NaNO_2$) is best known as a food additive preventing the growth of microorganisms in meat. It is an odorless inorganic salt that is a white-yellow, crystalline powder and is highly water-soluble.[1] Being a strong oxidizing agent, SN, when absorbed into the body, can oxidize iron (Fe) in the hemoglobin from ferrous (Fe^{+2}) to ferric (Fe^{+3}) state, producing methemoglobin (MetHb). MetHb is unable to bind and transport oxygen, resulting in cellular hypoxia and ultimately leading to organ damage and death.[1] Recently, an alarmingly increasing trend in the use of SN for suicide purposes has been seen around the world following its popularization online.[2]

CASE

We report a case of a 21-year-old male with no known co-morbidities. Relatives reported previous attempts of self-harm. Minutes prior to his demise, the decedent was seen continuously vomiting with blood per orem and cyanosis of the mouth and digits. He was immediately brought to the nearest hospital where cardiopulmonary resuscitation (CPR) was done but was then pronounced dead on arrival.

An autopsy was done 24 hours post-mortem. External examination findings showed no traumatic injuries or signs of assault. There was significant perioral and peripheral cyanosis (Figure 1). Non-specific grey skin discoloration in the dependent areas of the body was also noted. Lip erosions and hemorrhages were identified, consistent with

caustic burns (Figure 1). Internal examination showed characteristic bright red muscle discoloration, red-brown congested visceral organs, and hyperemic esophageal and gastric mucosa (Figure 2). The gastric contents consisted of brown, mucoid material (80 cc).

Further investigation of the decedent's belongings at the scene revealed multiple-page suicide notes, a black rope, and a suspicious clear fluid in a commercial bottle of water. A review of phone and computer files was done revealing a recent online purchase history of sodium nitrite (1 kg) from a local distributor. Social media posts surrounding the time of death revealed ingestion of a bitter substance and vomiting as the initial symptoms.

Unfortunately, reliable direct assessment of sodium nitrite in the blood sample, gastric contents, and clear fluid in the bottled water is not available in the local setting. Blood sample from the root of the aorta was tested for Methemoglobin eight (8) days postmortem, yielding elevated levels of 17.5% (normal values 1-1.5%).[1] With great efforts but limited resources, other toxicological studies of the gastric contents were not deemed to be any more contributory.

The cause of death is determined to be hypoxia secondary to methemoglobinemia from sodium nitrite poisoning. The manner of death is suicide.

DISCUSSION

Suicide accounts for 1% of all causes of death worldwide and is the 4th most common cause of death in the young (15-29 years old).[2] Since 2017, a significant increase in the use of sodium nitrite for suicide purposes has been seen around the world. Websites such as online suicide forums provide detailed instructions for the use of SN solely or as a part of a "suicide kit."[2]

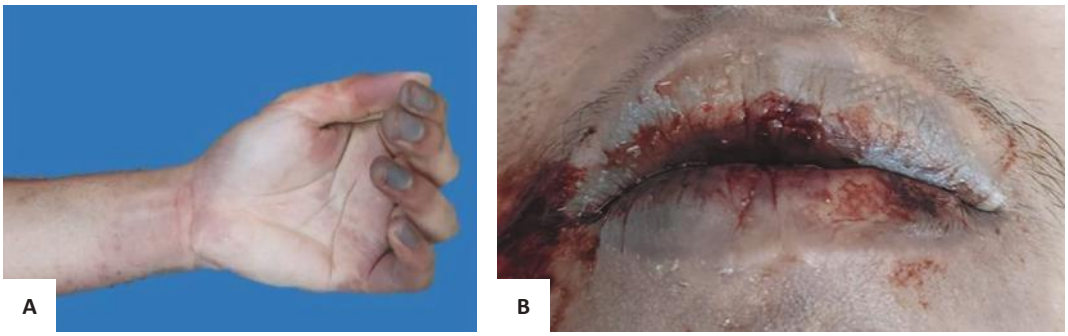

Figure 1. ***External examination findings.*** **(A)** Peripheral cyanosis and **(B)** perioral cyanosis, lip erosions, and hemorrhages.

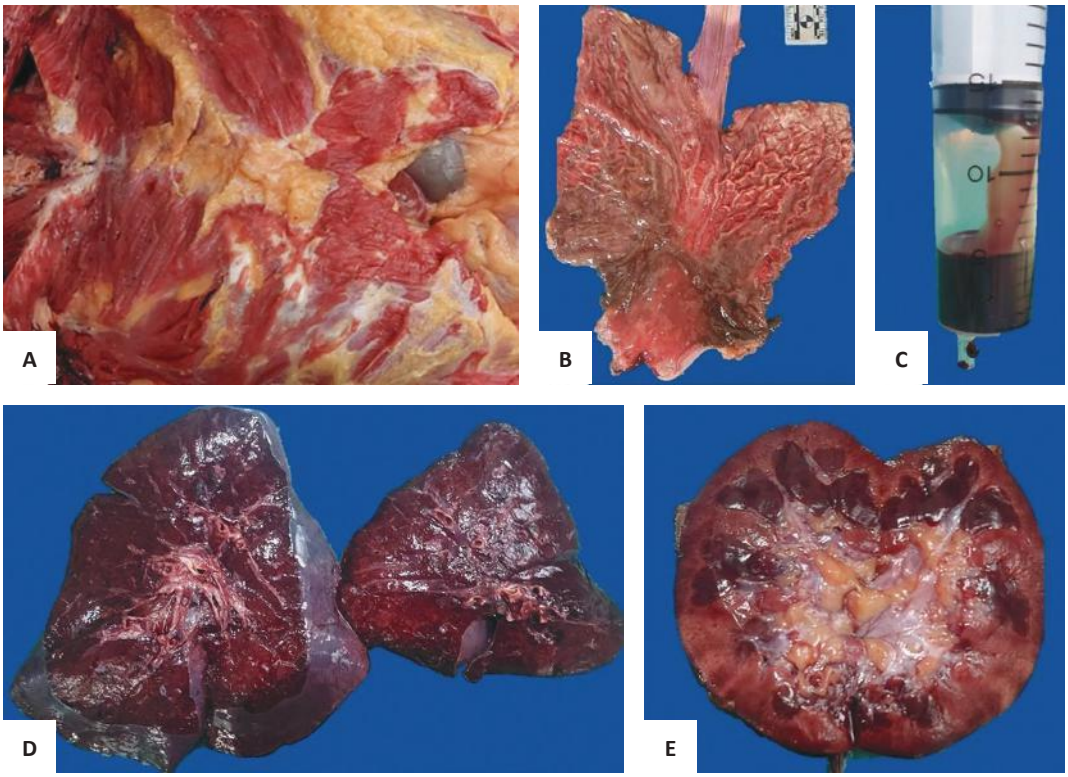

Figure 2. ***Internal examination findings.*** **(A)** Bright red muscle discoloration; **(B)** hyperemic esophageal and gastric mucosa; **(C)** dark-brown arterial blood. Red-brown congested visceral organs **(D)** lungs and **(E)** kidney.

While there are plenty of reported cases internationally, no local report of sodium nitrite poisoning in suicide cases has been published in the Philippines. A local journal article related to SN poisoning was published in 1996.[3] The authors reported a case of accidental SN poisoning of a child after consumption of cured meat. This patient presented with vomiting, abdominal cramps, cyanosis, tachycardia and hypotension within one (1) hour of ingestion and yielded normal methemoglobin levels. The normal methemoglobin result was attributed to late testing (beyond 24 hours). This patient recovered after administration of ascorbic acid and intravenous fluid.[3] To the best of the authors' knowledge and review of literature, no other local case of suicide by SN poisoning has been reported as of date.

Sodium nitrite is a potent oxidizing agent and is popularly known as a meat-curing compound. However, dietary exposure to small amounts is harmless.[1] A maximum level of less than 500 mg/kg (5 to 416 mg/kg) of curated food products has been regulated by the Bureau of Food and Drugs (BFAD) in the Philippines.[4] The estimated fatal dose for humans is approximately 2.6 g, although cases of death from 1g and survival after 6 g ingestion were previously reported. Clinical symptoms of sodium nitrite poisoning include cyanosis, hypoxia, altered consciousness, dysrhythmias, and death.[1] Other uses of SN include corrosion inhibitors found in anti-freeze, antimicrobial, coloring agent and antidote to cyanide poisoning.[2]

A reliable measurement of SN levels in the blood is difficult due to nitrites rapidly converting into nitrates, resulting in a falsely low value.[1] The measurable value of methemoglobin is helpful in the indirect assessment of SN poisoning.[1] Methemoglobinemia is caused by the oxidation of ferrous to ferric iron leading to increased affinity of hemoglobin to oxygen hence reducing oxygen delivery to tissues leading to hypoxia. Increased levels of methemoglobin in blood account for the clinical manifestations. At 10%, cyanosis will be apparent. If the level reaches above 20%, other symptoms such as headache, dizziness, polypnea, tachycardia, and general asthenia may be observed. Values close to 60% may cause loss of consciousness and death at values higher than 70%.[1] Our case presented with vomiting, cyanosis, and loss of consciousness just minutes before death. Although the methemoglobin level of our case is at 17.5%, other factors including delay in testing (8 days) may have contributed to the falsely low levels, that are not compatible with the literature.[1]

In general, methemoglobinemia may be caused by a congenital defect or an acquired disorder.[5] Congenital causes include autosomal recessive variants in the CYB5R3 gene or autosomal dominant variants in the globin genes, collectively known as HbM disease.[5] These conditions present early on in life with cyanosis and hemolysis. Given the age of the decedent in our case, the absence of symptoms during childhood and the lack of family history, a congenital cause of methemoglobinemia is unlikely. On the other hand, acquired causes of methemoglobinemia include consumption of numerous drugs and toxic agents. The most common documented drugs are benzocaine and lidocaine – both of which are local anesthetics administered topically or parenterally and will not present with continuous vomiting and caustic burns such as in our case.[5] Other recreational drugs such as amyl nitrate (poppers), nitrous oxide (laughing gas), and adulterants in cocaine were also reported to cause fatal methemoglobinemia.[5] However, there is no documentation of previous use, possession, and/or purchase of any of these drugs by the decedent.

According to a 2022 systematic review of cases related to SN intoxication and death, there is a concerning 41.67% mortality rate - 80% of which with suicidal intent.[6] Mortality is significantly higher in suicide cases due to greater quantities taken. A longer survival interval with the possibility of accessing an emergency department is reported in cases that took excessive but non-lethal quantities. Given this data, training of health professionals to quickly identify an acute intoxication and to implement necessary treatments is inferred.[6] The antidote for methemoglobinemia from SN poisoning is methylene blue.[1] Methylene blue is given at a dose of 1-2 mg/kg and is infused over 5 min and can be repeated if symptoms persist.[1,7] This antidote acts as a catalyst to reduce methemoglobin to hemoglobin via the enzyme NADPH-methemoglobin reductase.[8] Ascorbic acid, hyperbaric oxygen, exchange transfusion, and extracorporeal membrane oxygenation are some of the additional treatment approaches for methemoglobinemia.[8] There are reported cases of patients surviving from SN poisoning.[9] Unfortunately, the index patient of this case report succumbed to death just minutes post-ingestion.

Documented autopsy findings in SN poisoning include post-mortem signs of methemoglobinemia such as blue-grey hypostasis, cyanosis, and dark-brown discoloration of blood and internal organs.[1,5,6] Most of these are present in our case.

There is a general methodological discrepancy in the diagnostic process, and SN-related deaths represent a challenge for forensic pathologists.[6] An important role in framing SN intoxication as cause of death is played by the investigation of the scene, and an accurately done autopsy.[6] Forensic pathologists involved in such cases are advised to: 1) investigate the scene; 2) ascertain previous web searches, purchases, and consumption of uncontrolled food; 3) pay attention to livor mortis; 4) focus on autopsy findings; and 5) consider nitrite and methemoglobin dosage in suspected cases.[6] With the permission and help from the relatives of the decedent, these tasks were taken by the forensic pathologist in charge of the case.

Distinguishing between manners of death particularly in suicide and accident cases, is a challenge.[10] The role of pathologists in such cases is highlighted during post-mortem examination. Death investigation using autopsy, toxicological and histological examination is ideal if the cause of death is not readily recognized.[11,12] While there are established and collaborative systemic death investigations between the police and forensic pathology experts internationally, the current local setting relies on the autopsy findings by pathologists.[10,12]

CONCLUSION

Sodium nitrite ingestion has an alarming increasing trend of use for suicide purposes around the world. Easy access

to the substance and online forums providing step-by-step instructions on how to use it play a significant role in the continuously increasing number of suicide cases by SN ingestion. We report a case of a young adult who purchased SN online and committed intentional ingestion, with autopsy findings compatible with methemoglobinemia from SN poisoning. The acute, non-specific, and dose-related manifestations of SN poisoning pose a challenge in the clinical recognition and prompt management of cases. The lack of forensic pathology experts, systemic death investigation, and local laboratories to reliably recognize the autopsy signs may have also affected the low detection rate of cases locally. Further reporting of cases can raise the awareness of medical professionals and is fundamental in the ultimate saving of lives.

ACKNOWLEDGMENT

The authors hereby extend their sincerest gratitude to the family of the decedent for their invaluable contribution and cooperation with the case and for spreading awareness on the subject matter.

ETHICAL CONSIDERATION

An informed consent was secured from the index patient's relative before the conduct of the autopsy and a separate informed consent for the writing of the case report. The completed report has been submitted and approved by the Expanded Hospital Research Office (EHRO) of the affiliated institution.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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Mucosal Schwann Cell Hamartoma Mimicking a Colon Polyp: Pathologic Insights

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Key words: Schwann cell, hamartoma, mucosa, polyp, colorectal

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 9 July 2024.
Accepted: 8 August 2024.
Published online first: 27 September 2024.
https://doi.org/10.21141/PJP.2024.11

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A rectal polyp is found during a routine colonoscopy of a 34-year-old male. He has no known significant family history of inherited disorder. Endoscopic findings reveal a 5-mm JNET 2A polyp in the rectum which is removed via forceps polypectomy. The microscopic examination shows a polypoid colonic mucosa with fairly circumscribed proliferation of low-grade spindle cells in the lamina propria, separating the crypts. The individual spindle cells are uniform in size with abundant eosinophilic cytoplasm. No mitotic figures, nuclear atypia, pleomorphism and necrosis are noted. Likewise, the crypts do not exhibit serrated architecture.

Immunohistochemical stain showed that the mucosal-based lesion was strongly and diffusely positive for S100 (Ventana, Roche). The spindle cells show proliferation between the normal crypts and do not form a discrete lesion, hence, in correlation with the S100 positivity, the case is signed out as mucosal Schwann cell hamartoma.

Mucosal Schwann cell hamartoma (MSCH) is a rare, benign mucosal based lesion derived from the Schwann cells.[1] The entity was first described by Gibson and Hornik in 2009. It commonly presents as an incidental polyp in the rectosigmoid during routine screening colonoscopy or endoscopic procedures performed for unrelated reasons. It has no known association with any inherited syndrome, in contrast with other mesenchymal lesions such as gastrointestinal stromal tumors and neurofibroma. Since the initial description of this entity, it has been primarily reported in the colorectum, although it can occur anywhere in the gastrointestinal mucosa and even in the gallbladder.[2] Clinically, MSCHs are asymptomatic and are found incidentally. When incidental, these are usually found in middle-aged women in the left colon. Although it is benign, the correct identification of this lesion is essential for differentiating this benign entity from other gastrointestinal mesenchymal spindle cell lesions, which may entail different prognoses and treatment approaches.[3] As of 2023, only 35 cases have been identified so far and no local case in the Philippines has been reported to date.[4]

Histologically, MSCH exhibits low-grade spindle-shaped cells with tapered nuclei which are positive for S100 protein on immunohistochemistry.[5] It typically lacks the myxoid stroma as well as nuclear atypia, mitosis and necrosis that are associated with other peripheral nerve sheath tumors.[1] Given the histomorphologic features, the main differential diagnoses for this mucosal-based spindle cell lesion include neurofibroma, perineurioma, ganglioneuroma and GIST.

Neurofibroma is a benign nerve sheath tumor composed of a mixture of Schwann cells, perineural cells and fibroblasts. In contrast to MSCH, it typically exhibits a more varied cellular composition, and it can be associated with an inherited syndrome such as Neurofibromatosis type 1.[6] On the other hand, the sporadic cases occur in middle-aged adults without gender predilection and arise most commonly in small or large intestine.[7] Histologically, it is characterized by a loose, myxoid to hyalinized stroma with interspersed collagen fibers which is described as "shredded carrots." Similar to MSCH, it is positive for S100 due to the Schwann cell component. However, the S100 positivity seen in neurofibroma is not as diffuse as MSCH since the former is composed of a mixture of cells. Neurofibroma is positive for CD34, which is less commonly seen in MSCH.[8]

Another differential diagnosis is perineurioma which is a benign neural tumor characterized by perineural cell proliferation. It is clinically asymptomatic and is discovered incidentally during screening colonoscopy. It usually occurs in middle-aged adults with female predominance. The most common site is the rectosigmoid colon.[9] Microscopically, it exhibits elongated spindle cells which are arranged in a storiform pattern, and which expand the lamina propria. A characteristic feature is the uniform entrapment or whirling of the spindle cells around the crypts. Colorectal mucosal perineurioma is also often seen associated with serrated epithelial polyps such as hyperplastic polyps and sessile serrated lesions.[10] Immunohistochemically, the spindle cells are positive for EMA which highlights the delicate staining pattern of the cell processes.[11] Other immunohistochemical stains which may be utilized include Claudin-1 and GLUT1, both of which, however, are not widely available in our local setting.

The third differential diagnosis is ganglioneuroma which is a benign neoplasm composed of mature ganglion cells, Schwann cells and nerves.[9] It has a wide age range and there is no gender predilection. It typically presents as small mucosal polyps on the left side of the colon and the rectum.[9] Majority of the cases are sporadic but when the presentation is that of multiple lesions, a strong association with multiple endocrine neoplasia type 2B (MEN 2b) and neurofibromatosis type 1 is noted.[12] Histologically, it displays a mixture of mature ganglion cells, spindled Schwann cells and eosinophils within the lamina propria, which is different from the pure Schwann cell composition of MSCH. The use of S100 can delineate the mixture of the Schwannian cells and ganglion cells since the former are S100 diffusely positive but the latter cells are negative.[5]

Gastrointestinal stromal tumor is a mesenchymal neoplasm with differentiation towards the interstitial cells of Cajal.[13] More than half of the cases arise in the stomach and approximately 5% occur in the colorectal site.[14] Smaller GISTs are detected incidentally during routine endoscopy. Histologically, it can exhibit a spindle cell, epithelioid or mixed morphology. Immunohistochemically, it is characterized by positivity with CD117 and DOG1. Spindle cell type of GISTs can express CD34 and a minority can also express SMA.[15]

In our case, the main differential diagnosis is neurofibroma due to its spindle cell morphology and S100 expression

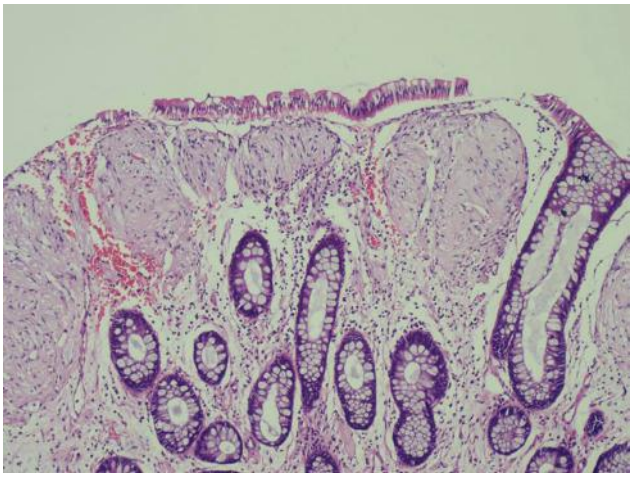

Figure 1. Microsections show polypoid colonic tissue with mucosal-based spindle cell proliferation that is dissecting in between the colonic crypts. The individual spindle cells are uniform in size without cellular atypia, mitosis, and necrosis. There are no associated crypt luminal serrations or distortion (H&E, 100x).

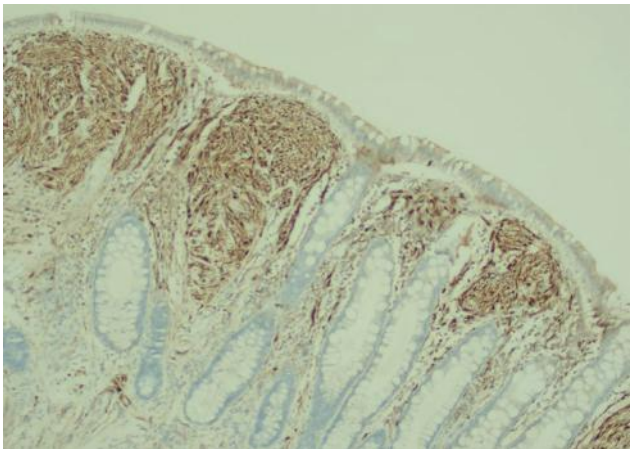

Figure 2. Diffuse and strong nuclear and cytoplasmic staining for S100 in the benign spindle cells (S100, 100x).

(Figure 2). However, the absence of clinical features of NF1, and lack of CD34 positivity has made this entity less likely in our case (Figure 3). The lack of serration of the colonic crypts and the absence of EMA expression rules out perineurioma (Figure 4). Similarly, the absence of mature ganglion cells has excluded ganglioneuroma. Lastly, the lack of CD117 and DOG1 staining dissuades GIST (Figure 5). The final diagnosis of MSCH (Figure 1) is rendered based on the following: uniform spindle cell morphology, absence of cellular atypia and mitosis, confinement to the mucosa, and strong S100 protein expression.

MSCH in the colorectum usually presents as a small polyp (mean = 5 mm) found incidentally in colonoscopy and it is predominantly located in the rectosigmoid. Similar to the other reported cases of MSCH, our case presents as a small polyp (5 mm) located in the rectosigmoid area. Although the majority of the cases are asymptomatic, a few of the MSCH can present as lower gastrointestinal bleeding or occult blood in the stool. This is like our case which

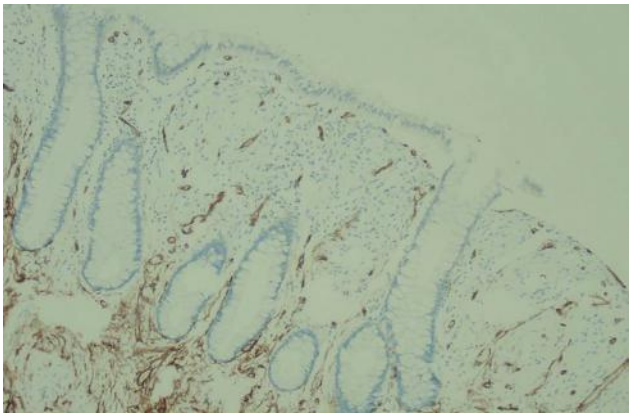

Figure 3. No membranous staining for CD34 is noted in cells of interest (CD34, 100x).

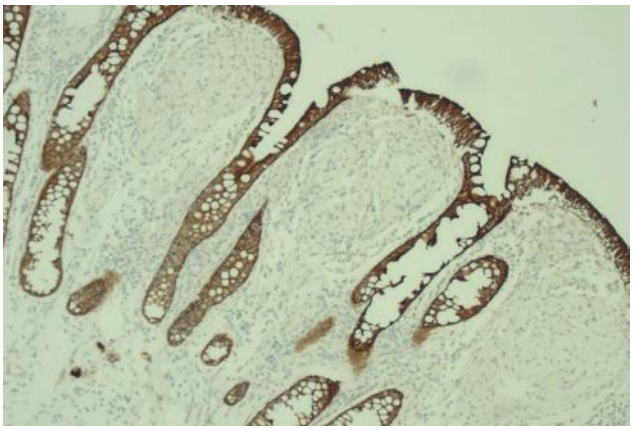

Figure 4. No membranous staining for EMA is noted in cells of interest (EMA, 100x).

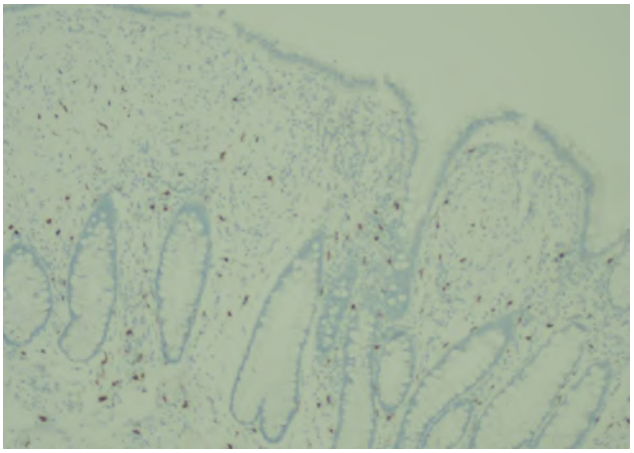

Figure 5. No membranous or cytoplasmic staining for CD117 is noted in cells of interest (CD117, 100x).

clinically presents rectal bleeding. Majority of MSCH cases have a female predilection with a mean age of 62 years old (range 46-88).[4]

This case highlights the importance of histopathological and immunohistochemical evaluation to distinguish MSCH from other spindle cell lesions of the gastrointestinal tract. Even though MSCHs are benign lesions which generally require no further treatment after excision, other mesenchymal neoplasms such as neurofibroma and ganglioneuroma may need additional surveillance or intervention, particularly if the clinical history shows stigma for systemic syndromes. On the other hand, GISTs have the potential for malignancy, hence a different treatment algorithm such as surgical resection, closer follow-up and possibly targeted therapy may be performed. Awareness and understanding of MSCH will help practicing pathologists arrive at the correct diagnosis to guide clinical management.

ACKNOWLEDGMENT

The authors wish to express their gratitude to the Institute of Pathology of Chinese General Hospital and Medical Center for the technical support and assistance.

ETHICAL CONSIDERATION

The authors confirm that due diligence was done in attempting to obtain informed consent from the patient involved in the case report. Despite efforts to contact the patient through different means (checking available addresses and contact via known cell phone and landline number), no response was received. In line with this, the authors ensured that all identifying information had been anonymized to protect the patient's privacy.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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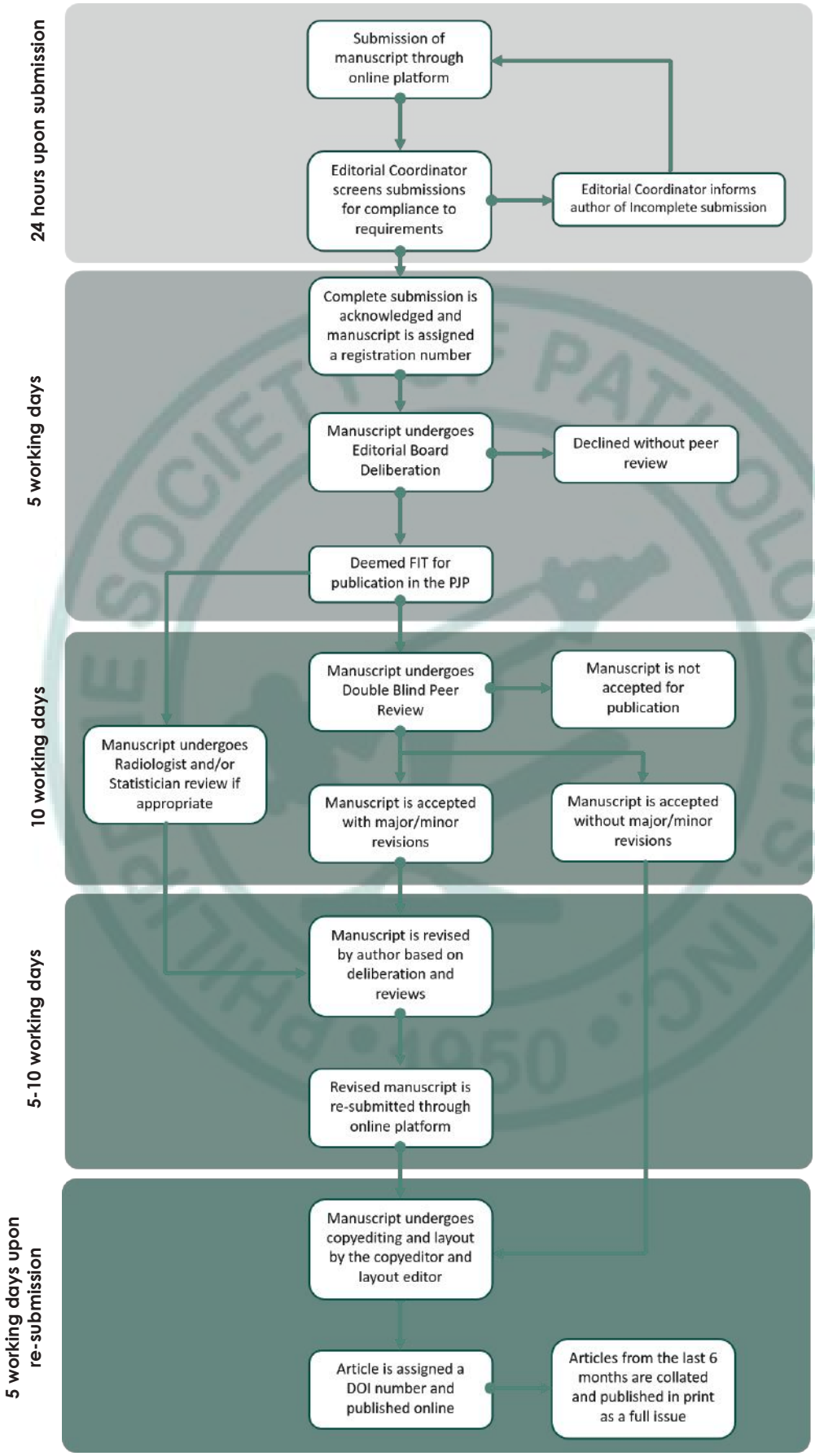

Figure 1. Editorial Process Flow.

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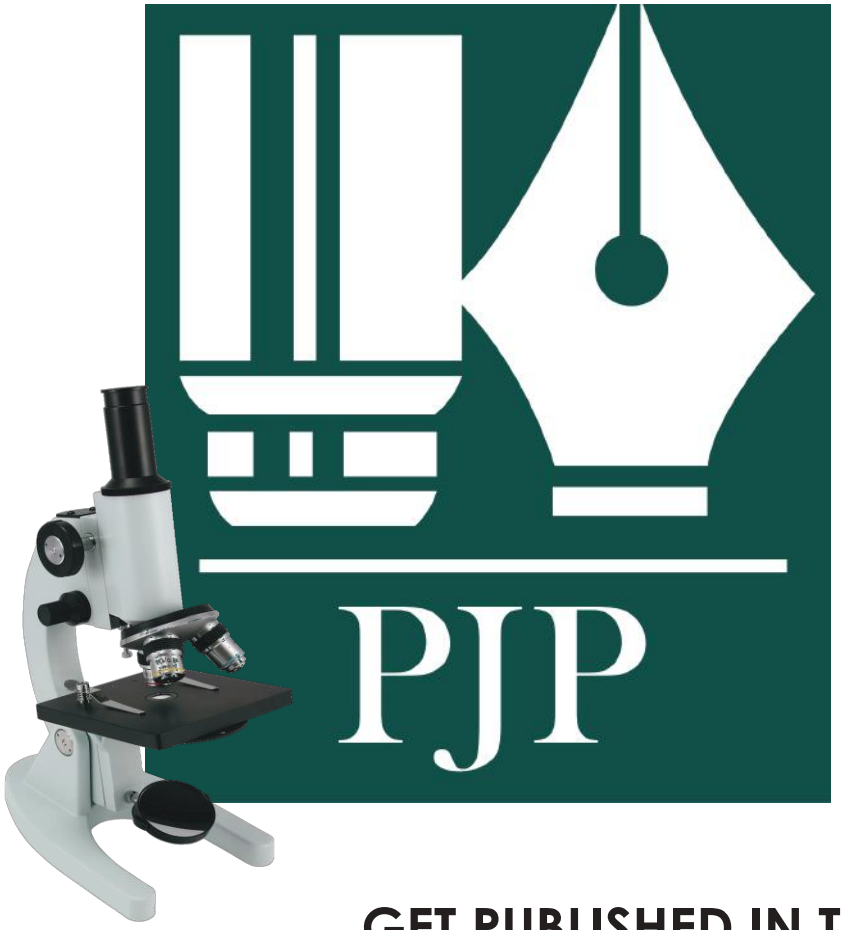

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