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IN THIS ISSUE:

THE PHILIPPINE SOCIETY OF PATHOLOGISTS, INC.

A Specialty Division of the Philippine Medical Association

proudly presents

2024 UPDATES IN SURGICAL PATHOLOGY

HYBRID FORMAT

(IN PERSON & LIVE VIRTUAL via ZOOM Webinar)

01.20-21.2024

Carlos Parra-Herran, MD
Gynecologic Pathology
Brigham and Women's Hospital

Natalia Buza, MD
Gynecologic Pathology
Yale School of Medicine

Robert Soslow, MD
Gynecologic Pathology
Cleveland Clinic

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Thoracic Pathology and Cytopathology
Memorial Sloan Kettering Cancer Center

Xiaoyin "Sara" Jiang, MD
Head, Neck and Endocrine Pathology and Cytopathology
Duke University School of Medicine

Seda Hotel at Bonifacio Global City (BGC)

PRC CPD units will be applied

REGISTRATION QR CODES

SCAN THIS

IN PERSON ATTENDANCE

VIRTUAL ATTENDANCE

SEDA ROOM RESERVATION

REGISTRATION DETAILS

In Person at SEDA BGC (limited to 180 participants)

(inclusive of plated lunch, morning and afternoon snacks)

Kindly scan to register for in person attendance

CATEGORY	REGISTRATION BEFORE NOV. 30	REGISTRATION AFTER NOV. 30
Residents	Php6,500	Php7,500
Graduates & Consultants	Php7,500	Php8,500
Senior Citizens (60 and above)	Php6,000	Php6,800
Foreign Delegates	USD200	USD250

Live Virtual via ZOOM

Kindly scan to register for virtual attendance

CATEGORY	REGISTRATION BEFORE NOV. 30	REGISTRATION AFTER NOV. 30
Residents	Php5,500	Php6,500
Graduates & Consultants	Php6,500	Php7,500
Senior Citizens (60 and above)	Php5,200	Php6,000
Foreign Delegates	USD150	USD200

NOTE: *Please deposit your payment prior to registration. The screenshot of payment details needs to be uploaded. For 60 years old and above, kindly upload a picture of your senior citizen ID to avail of the discounted rate.*

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Single or Double Occupancy in a Deluxe Room (Tower 1)
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(inclusive of breakfast for two)
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BPI US Dollar Account: 4254-0095-18
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Kindly scan for room reservation

OPEN ACCESS

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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.

Philippine Journal of Pathology

Philippine Society of Pathologists, Inc.

The PSP Board of Governors and Executive Officers wish all the members of the society a new year characterized by stronger relationships, continued growth, and peace of mind.

Happy New Year!

Defining the Terms of Reference of the PSP's Committee on Academic and Research Pathology

In the landscape of medical science, the role of pathology cannot be overstated. Pathologists play a pivotal role in diagnosing diseases, understanding their mechanisms, and advancing medical knowledge. The Philippines, home to a wealth of talented healthcare professionals, possesses a cadre of skilled and accomplished pathologists. However, the research and publication output within the field of pathology in the country has not reached its full potential.

The Philippine Journal of Pathology is an instrument for disseminating groundbreaking research and insights within the discipline. Yet, it is evident that there is a pressing need to augment the research and publication output of Filipino pathologists. To bridge this gap, a concerted effort from various stakeholders is imperative.

Firstly, fostering a culture of research from the initial stages of medical education is crucial. Medical schools should emphasize the significance of research, encouraging students to engage in investigative projects and providing adequate mentorship and resources. Encouraging budding pathologists to explore research avenues can lay the foundation for a lifelong commitment to scholarly pursuits.

Moreover, institutional support plays a pivotal role in bolstering research endeavors. Hospitals and pathology departments should allocate resources and funding specifically for research initiatives. Establishing research committees, providing access to laboratory facilities, and offering grants can significantly incentivize pathologists to delve deeper into investigative studies. It will not hurt if the Society itself allows a bigger portion of its budget to fund protocol writing, conduct scientific investigations, and even manuscript writing, in the form of competitive scientific grants.

Residency training institutions should underscore the importance of research excellence, and that getting scientific information "out there" through publication—not a mere presentation at conferences—is the ultimate endpoint.

Collaboration and networking within the pathology community are also vital. Encouraging multidisciplinary collaborations between pathologists, clinicians, researchers, and other healthcare professionals can stimulate innovative research ideas and foster a robust exchange of knowledge. Annual conferences, seminars, and workshops dedicated to pathology research can serve as platforms for sharing insights and forging collaborations.

Furthermore, mentorship programs for early-career pathologists can be instrumental. Experienced researchers can guide and nurture the next generation of pathologists, imparting valuable skills in study design, data analysis, and manuscript preparation. Such mentorship initiatives can empower young researchers to navigate the intricacies of academic publishing more effectively.

Additionally, advocating for policies that recognize and reward research contributions is imperative. Acknowledging research productivity in promotion and tenure evaluations can serve as an incentive for pathologists to actively engage in scholarly activities.

The Philippine Journal of Pathology continues to provide a platform for showcasing the work of Filipino pathologists. From the outset it has embraced an open-access publishing model and insisted that no article processing charges are imposed, to amplify the impact and reach of its published articles.

In conclusion, elevating the research and publication output of Filipino pathologists requires a multifaceted approach. It demands a collaborative effort from educational institutions, healthcare facilities, professional organizations, and the broader pathology community. By fostering a research-centric culture, providing resources and mentorship, encouraging collaborations, and recognizing scholarly contributions, we can pave the way for a thriving ecosystem of pathology research in the Philippines.

The time is ripe for a concerted effort to unleash the full potential of Filipino pathologists, and the Philippine Journal of Pathology stands ready to be an integral part of this transformative journey. Facilitating and sparking this may be considered the main terms of reference for the PSP's Committee on Academic and Research Pathology.

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

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OPEN ACCESS – FEATURE ARTICLE

Ethical Concerns and Recommendations for Sharing Anatomic Pathology Images in Online Social Media Networks

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ABSTRACT

Anatomic pathology is a field that relies on visual examination to provide diagnosis. Photos of specimens and microscopic slides play an important role in pathology education. With the internet, sharing and seeing images from different patient cases has become efficient and accessible. However, ethical concerns may be raised since patient images are used for academic purposes in a public setting. Proper de-identification, informed consent and setting professional guidelines for sharing pathology images are suggested.

Key words: pathology, social media, digital pathology, ethics, policy

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INTRODUCTION

Anatomic pathology is a branch of medicine that provides the diagnosis of different diseases by the examination of cells, tissues or body fluids. Anatomic pathology plays a very important role in cancer staging, guiding therapeutics and determining the cause of death. Anatomic pathology has two main subcategories -- autopsy pathology and surgical pathology. In autopsy pathology, the body and organs of a deceased patient are dissected and examined under the microscope to determine the cause of death. Surgical pathology is similar, but the examinations are performed on a surgically resected body part or organ from a living patient.

The field of anatomic pathology is highly visual. Images from different patient cases have great educational value to students, trainees and practicing pathologists. Exposure to different anatomic pathology cases improves the diagnostic skills of pathologists. Currently, many online communities allow sharing of medical images for discussion.[1] Educational medical communities may be seen in social media such as Facebook, Twitter, Instagram and YouTube[1] and social chat platforms such as Discord.[2] The online pathology community has not only provided medical education for everyone but has also provided the privilege of connecting with experts and experienced pathologists all over the world.[3] Getting opinions from other pathologists can help in solving difficult cases and arriving at the proper diagnosis. This is very beneficial for resource-poor countries like the Philippines, where there are plenty of patient cases but pathology subspecialists are few.

Despite the good intention of sharing cases online to promote education, this learning activity does not happen in a private hospital conference room with a limited medical audience.[4] Images from these cases can be publicly viewed. Hence, misinterpreting the academic intent of the images by non-medical users is not unlikely. Moreover, these images are acquired from patients who seek consultation mainly for medical treatment and *not* for promoting medical education.

Ethical issues on patient autonomy, privacy, confidentiality and non-maleficence are raised in the sharing of anatomic pathology images online.

ETHICAL ISSUES

Medical pictures cannot be generated without the patient. Medical pictures may only be captured if a person engages in a clinician-patient relationship or if a family member/ legal entity consents to an autopsy. To receive medical treatment, the patients not only disclose their personal information but also allow a thorough examination of their bodies.[5] Patients also allow examination of their specimens as part of the diagnostics for their treatment work-up. There is an implicit expectation in the clinician-patient relationship that clinicians will respect the patient's privacy and keep all the information in full confidentiality as part of the ethics of their profession.[5]

In the United States, electronic patient information is protected through the standards of the Health Insurance Portability and Accountability Act (HIPAA).[6] Based on the HIPAA guidelines, patient confidentiality in medical pictures can be preserved by deidentifying the images.[1] However, sharing patient images is not only about patient confidentiality but also patient privacy. Privacy is for the person; confidentiality is for information.[4] Privacy is the freedom of a person from unwanted scrutiny. Confidentiality is about keeping information protected from disclosure.[5]

In 2008, a video showing the surgical extraction of a metal spray bottle canister from the rectum of an unidentified patient went viral on YouTube.[5] The video also showed giggling medical staff who were taking a video of the canister extraction using their cellphones.[5] The patient was later informed by a barangay official about the viral internet video.[5] The patient said he was unconscious during the procedure and was not informed that the medical staff would take videos.[5] For this case, the patient was deidentified in the video and there was an attempt to preserve patient confidentiality. However, the patient was eventually identified.[5]

The video itself showed how the patient's privacy was violated and how the patient lost his autonomy to decide if the canister extraction could be documented. Moreover, sharing the video online may have violated the principle of non-maleficence by causing emotional harm to the patient through psychological distress and embarrassment. Getting and sharing photos from patient specimens outside the purpose of medical treatment raises issues on privacy, patient autonomy and non-maleficence.

This scenario depicts an extreme case of how clinicians can use a clinician-patient relationship to take images from patients and how sharing videos or images from patients can lead to emotional harm if done carelessly. But unlike this incident which did not benefit anyone, case sharing as an academic activity benefits the medical community and the general public.[7] But still, using a clinician-patient relationship to get materials for online academic discussions, outside the patient's knowledge, threatens the public trust in the medical profession in protecting their privacy and the patient's right to self-determination.[4]

In the Data Privacy Act of 2002 (Philippine Republic Act 10173), personal information is defined as any form of information whether recorded in a material or not, from which the identity of the person is apparent or may be ascertained by the person who holds the information.[8] The Data Privacy Act states that personal information should only be collected for the specified and legitimate purpose that was declared.[8] Additionally, the person who owns the information has the right to be informed whether personal information about him or her is collected, recorded, stored, retrieved or used.[8] Following the Data Privacy Act, informed consent is necessary if any information from the patient will be used for purposes other than treatment. Informed consent protects the patient's privacy and autonomy.

Non-maleficence in online image sharing may be secured if there are clear professional standards geared toward sharing medical photographs. These standards will help guide medical professionals to avoid causing any accidental harm to patients and to display professionalism and liability even in an online environment.

To give some perspective, Twitter has 166 million daily active users.[9] Facebook, on the other hand, has 2.7 billion daily active users.[10] There is no data on how many Twitter or Facebook users are medical professionals. However, many young non-medical viewers may use medical images for entertainment. Informed consent may especially be important for images that contain culturally sensitive elements like genitalia, female breasts, dead bodies and children. These images are prone to sensationalism and may not be received neutrally by the non-medical audience.[11]

In April 2018, the autopsy of a 16-year-old Dengvaxia™ (Sanofi) patient received online and public comments when the news talked about how the patient's organs were serially sliced and put into the body cavity outside their anatomic location.[12,13] Facebook comments compared the organs to food (such as "morcon," "embotido" and "bopis").[13] Many other Facebook users expressed hatred towards the doctors who performed the autopsy. There are Facebook users who said that the doctors who did the autopsy should be executed.[13] However, few users knew that an autopsy procedure actually requires serial sections of the organs,[14] and organs are not routinely returned to their original anatomic position after the procedure.

Even with the good intention of learning on an online public platform, the online audience is unpredictable. Let us consider this hypothetical situation: A new pathology trainee saw a vulvectomy specimen from a co-worker and took a photo of it. She uploads a picture of a resected vulva with giant warts (described in medical textbooks as "cauliflower-like"). The photograph is poorly taken with a blood-stained background and bad framing. Being a new trainee, she is not aware that vulvectomy is not commonly done and uploading a picture of a vulvectomy specimen immediately after a certain patient undergoes the procedure may potentially identify a patient. The trainee publicly uploaded the image using an anonymous

Twitter account and described the image as "A beautiful case of giant condyloma acuminata from a vulva of an 83-year-old showing the classic cauliflower appearance! Microscopic examination shows the classic koilocytic or raisin-like changes consistent with human papillomavirus infection. #GynePath." A random teenage Twitter user saw the "cringe factor" on the image; so, he downloaded, edited and spread the image on the internet as a meme with the added phrase: "Yummy cauliflower!" The patient saw the meme and was able to identify the specimen as hers. She felt harassed. She also became very anxious to be identified after finding out that a vulva with the same clinical profile as hers is displayed and shared in public. She was also worried about the stigma associated with getting a tumor that originates from a sexually transmitted virus and the conflict it may bring to her private life.

The presence of clear standards on sharing health information outside the purpose of treatment can make medical case discussions safe for both the patient and the healthcare provider. This paper recommends guidelines to promote the online academic activity of case sharing among medical professionals while protecting the patient's privacy, confidentiality, autonomy and non-maleficence.

RECOMMENDATIONS

Deidentification

Confidentiality is the top priority when sharing any form of patient information publicly. To protect patient confidentiality on image sharing, a patient should not be identified in any way through their images. Based on HIPAA standards, patient data may only be shared publicly once they are de-identified.[1]

The HIPAA Privacy Rule has described **eighteen (18) personal health identifiers** that should be removed for deidentification.[15] These identifiers are:

1. Names
2. Geographical subdivisions smaller than a state
3. All elements of dates directly directed to the individual (date of birth, date of admission, date of discharge and date of death. Also, all ages over 89 years or elements of dates indicative of such age)
4. Telephone numbers
5. Fax numbers
6. E-mail addresses
7. Social security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identification or serial numbers including license plate numbers
13. Device identification or serial numbers
14. Web universal resource locators (URLs)
15. Internet protocol addresses
16. Biometric identifiers including finger and voice prints
17. Full face photographs and any comparable images
18. Any other unique identifying number or code

Aside from the identifiers specified by the HIPAA Privacy Rule, any other potential identifiers should be removed or modified to completely protect the patient's information.

Potential identifiers on photos should be removed. These include identifiers intrinsic to the patient (anatomic anomalies, birthmarks, scars), on the patient (unique clothing, jewelry, piercing, tattoos) and around the patient (unique setting, surroundings or location).[16]

Sufficient alteration of clinical details is recommended to obscure any potential detail that may lead to patient identification.[16] Potential identifying clinical details include date, unusual or newsworthy circumstances and small geographic subdivisions.[16] Approximating the age instead of using the actual exact age is also recommended.[16]

Exchangeable image file format (EXIF) data in the images should also be removed.[17] These are embedded technical meta-data that are created by the digital camera when a photo is created. These may include the camera model, photography settings and the specific date and location when the image was taken.[17]

Informed consent

Informed consent is important to protect patient autonomy and privacy. Informed consent should be voluntary. However, patients may feel coerced or obliged to give their consent to their physicians. Patients may be concerned that denying their consent may affect the quality of treatment they will receive. Hence, it may be necessary that informed consent is requested before the patient engages in the clinician-patient relationship through outright declaration of hospital/clinic guidelines.

If the consent was not requested before establishing the clinician-patient relationship, separate informed consent for specimen photography may routinely be requested for all patients who will undergo surgery/autopsy.

This paper suggests that the acquisition of consent be a part of a routine workflow procedure and be facilitated by a staff or committee who is not directly involved in the patient's medical consultation or treatment. This is to avoid coercion of the patient, relative, or guardian, to have medical images uploaded for online academic purposes.

The informed consent should emphasize the following points:

- The patient has the right to decline specimen photography unless the photography is needed as part of the treatment protocol. Declining will not affect the clinician-patient relationship, or the quality of medical care given to the patient.
- Anatomic pathology images are highly valuable in medical education, training and advancement. Sharing images of actual patient cases will indirectly but greatly benefit the general masses.
- Capturing anatomic pathology images does not pose any medical risk or will not affect the patient's treatment/procedure.
- The images will be photographed by qualified professionals capable of doing proper medical photography. The images will be handled professionally and treated with respect.
- Patient confidentiality will be protected by removing all identifiers and any potential identifiers from the images. Clinical details which may potentially identify

the patient will be altered. Images will not be shared immediately if the time of upload itself may potentially identify a patient.
- The images will be available not only to the medical audience but to the public audience.
- The images may permanently be available on the internet. Once posted, the image may be downloaded by any internet user or be transferred to another website.

This paper would also like to suggest a forum regarding the ethical standards for collecting and using microscopic images for academic reasons. Microscopic images are not identifiable and may only be captured using specialized tools. The possibility of waiving the informed consent for this type of anatomic pathology images may be debatable, however, this paper suggests opening this topic for discussion by legal authorities, medical communities and public representatives.

Online professionalism

To maintain nonmaleficence in sharing photos of specimens, standards should be set on how sharing should be done properly and professionally. All medical professionals should be educated on how they should act online, especially when handling patient information. Trainees and students should be informed about the proper dissemination of information materials and the standards on image sharing in classroom settings, conferences, publications, symposia and the internet.[5]

The following guidelines and standards are recommended to uphold medical professionalism among pathologists and other medical professionals in sharing medical images online:
- Uploaders of anatomic pathology images should not be anonymous. The medical professional should show good intention, transparency and liability by displaying their name, nature of work and/or institution on their online account.
- A professional account, separate from a personal account, is suggested to set the medical context of a medical or academic post.
- Images should follow institutional or societal guidelines for medical photography.
- The storage device containing the photographs should be secured.
- The pathologist should be always respectful when presenting or discussing a case online. A good reputation should be set so as not to undermine public trust in the medical profession.[18]
- Language or images that may provoke sensationalism should be avoided since the internet has an audience coming from all ages and backgrounds.[11]
- Patient confidentiality should be protected by deidentification. All identifiers and potential identifiers from the images and the clinical information should be properly removed. Once an image is uploaded, it should be assumed that the image will be on the internet permanently.[11]
- The images should be watermarked with the pathologist's name or username to ensure that the pathologist will be recognized or liable if the image is detached from the original post. Watermarking prevents plagiarism and using images without referencing has legal implications.[4]
- Since there are no enforcers of online professionalism in image sharing, pathologists should privately and politely inform a medical professional or trainee who commits online misconduct.
- Assigning credible pathologists as moderators (if applicable) in these social network platforms will help in enforcing online professionalism. For severe misconduct, a moderator can report a user to the social media administrator or ban a user from using a social network platform/server.
- Professional agencies and medical societies should enforce online professionalism and apply penalties for online misconduct that involves patient information.

Other recommendations

Medical societies should collaborate with social networking companies to enforce ethical standards in sharing and discussing medical images. Online social platforms should develop clear policies and guidelines on patient-related images. If this type of image is allowed, the platform should specify rules to maintain good ethical standards (such as deidentification, watermarks, and proper language) for this type of content. The consequences for violation of these rules should also be implemented. Features may be developed to confirm the identity of a user to prevent malicious fake accounts from taking advantage of the images shared in the online discussions. Confirming the identity of the user will also increase the reliability of the academic information shared by the user. Furthermore, a specific platform for medical professionals to share patient cases may also be specifically designed to optimize medical discussions while maximizing privacy and security.

CONCLUSION

Uploading pathology images for academic use may seem harmless with patient de-identification. However, the ethical concerns of uploading patient images on the internet go beyond confidentiality. Patient images are not meant to be shown publicly on the World Wide Web by their healthcare provider (Figure 1). Furthermore, patient images are not created to be immortalized digitally in the global system of interconnected computers. Using patient material for educational purposes is a sensitive matter. While no standards have been established for posting anatomic pathology images online, it is our responsibility as medical professionals to protect patients. Any post, tweet, pin or share can stay on the internet permanently or can be downloaded privately by anyone. Nothing should be posted that may be inappropriate in any public forum or can undermine patient privacy, confidentiality and autonomy.

On the other hand, sharing anatomic pathology images with the international medical community provides immense learning opportunities and growth for medical professionals and trainees. It also provides a medical network that provides connections in seeking expert opinions from all over the world and for starting research collaborations.[19] With the continuous development of online social networking, more possibilities unfold for medical professionals that may help in improving health services and for medical advancement.

Figure 1. Imagine (Vyro) AI-Generated image using the prompts "patient confidentiality and privacy," "social media," "doctor uploading patient images."

With the growing online community of pathologists, ethical standards on the proper use of the internet for non-clinical purposes are suggested. Establishing standards will protect every patient's privacy, confidentiality, autonomy and maintain non-maleficence while doing online academic activities using images from patient specimens. Suggested standards focus on informed consent, deidentification and online professionalism. With defined guidelines, overall medical professionalism is maintained not only in the real-world environment but also in the Internet environment.

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STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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OPEN ACCESS – ORIGINAL ARTICLE

Impact of the COVID-19 Pandemic on Blood Supply: A Comparative Cross-Sectional Study of the Pre-Pandemic and Pandemic Era

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ABSTRACT

Objective. The study aimed to determine the impact of the COVID-19 pandemic on local blood supply management in the Davao Region, Philippines from 2019 to 2021 through the analysis of trends in blood supply in Davao Region, Philippines.

Methodology. Secondary data from two blood centers in the Davao Region for the years 2019 to 2021 were used to determine the trends on blood donation supply. To evaluate trends, the overall number of blood donors and the quantities of various types of blood components in whole blood, packed red blood cells (PRBCs), fresh frozen plasma (FFPs) and platelet concentrate have been compared between pre-pandemic, pandemic periods and as restrictions eased.

Results. A substantial decrease of 51.6% in the number of blood donors was seen during 2021 in comparison with 2019. The trend in collection by blood components also showed a significant trend from 2019 to 2021, whole blood (200.8%), packed RBCs (37.1%), fresh frozen plasma (113.6%). While the platelet concentrate supply declined by 34.9% from 2019 to 2020, an increase of 10.7% was noted onwards to 2021.

Conclusion. The results demonstrate that during the COVID-19 pandemic, there was a major reduction in donation and supply of blood. The challenges faced by blood banks in ensuring a stable and sufficient blood supply are highlighted by the decrease in the number of donors and by the different trends in the supply of blood components. The targeted efforts to promote blood donation and enhance the resilience of the blood supply during and after the pandemic is important.

Key words: COVID-19 pandemic, blood donors, Philippines, fresh frozen plasma, whole blood, packed RBC, platelet concentrate, Davao City

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) of the *Coronaviridae* family was detected on January 7, 2020, following the discovery of a pneumonia outbreak that had been reported on December 31, 2019, in Wuhan, Hubei Province, China.[1] The World Health Organization (WHO) classified the COVID-19 pandemic new coronavirus outbreak a global pandemic on March 11, 2020.[2] The Filipino community was extremely alarmed as soon as the first patients who tested positive for COVID-19 pandemic were detected.[2] The priority of the healthcare system has changed to treating people who may be contaminated with COVID-19 pandemic and putting plans in place for patients to be tested as directed by the World Health Organization.[3] Due to the perceived contagion risk and progressively difficult circumstances (i.e., easing and tightening of restrictions), this might especially affect blood donation behavior and lead to a decrease in perceived capacity and eligibility to donate blood.[3]

In many regions of the world, blood donation centers have largely shut down.[4] Donors who engage in social isolation or self-quarantine are dwindling. As concerns about the safety of blood linger, drastic public health activities have concentrated on containment and "flattening the curve" while priceless resources are being severely depleted.[6]

Although the virus primarily causes mild to severe respiratory illnesses, the possibility of transmission through transfusion should be considered. Most blood banks or blood centers in China have implemented the following measures to combat the current outbreak: calling back all blood donors and asking them about their current physical condition as well as asking additional questions about whether the donors or their relatives have recently traveled to areas with local transmission (Wuhan or Hubei Province).[7]

According to the Chief Executive Officer of the New York Blood Center, during these times, the outbreak caused companies, schools, and religious organizations to close, interrupting almost 75% of the incoming blood supply.[8] In the United Kingdom, transfusion specialists are responding to erratic patterns of blood component demand, declines in donation rates, and the loss of critical staff due to illness.[8] The blood transfusion services (BTS) in the region of Saudi Arabia are dependent on hospital blood banks, which are in charge of blood supplies and blood testing, at the donor centers of King Khalid University Hospital Blood Bank and King Saud University Students Health Center in Riyadh, direct donation (mostly from patients' relatives), voluntary unpaid donors, and mobile blood drives are the main sources of given blood.[9]

The pandemic had an impact on clinical transfusion as well as pre-transfusion testing in labs in China.[10] The appropriate changes were made to deal with the circumstances. As a result, the availability of blood and blood products continues to be a bottleneck in the clinical work of hospitals, especially for people needing regular blood transfusions due to blood disorders like thalassemia, sickle cell anemia, hemophilia, obstetric patients, cancer patients, and others in dire need, such as victims of accidents, who need blood products on an emergency basis.[10] In all branches of medicine, blood transfusions are a necessary component of medical care. The adequate and safe supply of blood to meet patient needs became a major worry with the spread of the COVID-19 pandemic.[11] Indeed, the pandemic has had a hugely negative effect on the blood community by decreasing the number of donations, thus, influencing blood transfusion services worldwide.[12]

In the Philippines, the first case of COVID-19 pandemic was detected in January 2020 and a total of 460,000 infections were reported by the end of 2020.[13] On March 15, 2020, the virus made its way to the Davao Region after the first instance of the illness was identified in Davao del Norte, Tagum City.[14] By that time, Davao City and all the provinces have at least one verified COVID-19 pandemic case each. As a result, several strategies were maintained to restrain and slow the virus's spread. These might involve wide-scale lockdowns, intervals of quarantine, regular hand washing, and social seclusion. Although the number of cases has undoubtedly decreased in 2020 as a result of these policies, they have also had an impact on the supply and demand of the economy as well as the availability of medicine and other necessities for health. Blood supply is one component that must be measured because of the need for this supply to all other processes. Assessing and managing blood supply is a critical component of the pandemic response, as it helps ensure that healthcare systems can meet the increased demand for blood products and maintain the safety and integrity of the blood supply chain. Effective blood supply management is essential for saving lives and providing necessary medical care during public health crises like the COVID-19 pandemic.[15]

It is important to carefully monitor the supply of blood during these uncertain times to prevent significant interruptions in blood reserves, which could have severe ramifications for healthcare systems.[16] Blood services are finding it difficult to keep their inventory in check during the current COVID-19 pandemic since it is a perishable good with a very limited shelf life.[4] Since local settings have adopted comparable blood donation practices from other nations, it is critical to assess the blood supply.[17] There is currently limited information available regarding the early impact of COVID-19 pandemic focusing on blood donation in the Philippines. As a result, the current investigation was undertaken.

This study aims to determine the impact made by the COVID-19 pandemic on blood supply. The results of this study will fill in any information gap and will lead to the understand the importance of availability of blood products to clients of Davao Blood Center Philippine Red Cross - Davao City Chapter. Furthermore, this study intends to derive crucial lessons for blood supply management both now and in the future. Moreover, the outcome of this study can be used by concerned institutions in making a contingency plan in times of emergency, calamity or pandemic in the Davao Region and the Philippines in general.

METHODOLOGY

The study utilized a double-center retrospective study to determine the impact of COVID-19 pandemic on blood supply. Secondary data were collected from the Philippine Red Cross - Davao City Chapter and Davao Blood Center for the years 2019 to 2021. The collected data included the following: Number of Whole Blood, Number of PRBCs, Number of FFPs, and Number of Platelet concentrate.

The study included the blood collected, screened, and fit for distribution. This also included the blood collected as Whole Blood and processed into Packed Red Blood Cell, Platelet Concentrate, and Fresh Frozen Plasma. Excluded in the study were the blood collected that did not pass the quality standards of the blood facility for distribution. This study does not also include the blood collected that is reactive for the serologic tests done in the blood facility as well as Plasmapheresis.

After obtaining ethical approval from the Davao Center for Health Development Joint Research Ethics Committee (DCHD JREC) of the Southern Philippines Medical Center, the study was conducted by the principal investigator. A retrospective blood collection records review from the year 2019 to 2021 was done for the data collection. The principal investigator ensured the completeness of the record. The type of blood products such as packed red blood cell (PRBC), number of fresh frozen plasma (FFP), and number of platelet concentrate (PC) were noted for

comparison across the study groups. All data were encoded in Microsoft Excel for tabulation and organization.

All data were tabulated for organization and were analyzed using statistical tool SPSS. Categorical variables were summarized using frequencies, ratios, and proportions, along with the 95% confidence interval. Continuous variables were summarized using mean and standard deviation. Qualitative variables were computed using Pearson Chi-square and Fisher's exact test and reported as frequency (%). Quantitative variables were compared using non-parametric Mann-Whitney or Kruskal-Wallis test and reported as mean and standard deviation. A p-value of 0.05 was set as significant.

RESULTS

The total number of donors, whole blood, PRBC, FFP, and platelet concentrate distribution from 2019 to 2021 in Davao Blood Center and Philippine Red Cross - Davao City Chapter, Blood Center was recorded (Table 1).

The p-values of all components are less than 0.01 showing a highly significant result. There was a significant result in terms of total donors, whole blood, PRBC, FFP, and platelet concentrate distribution from 2019 to 2021 in Davao Blood Center. For the number of Total donors, there was a drop of 33% from 2019 to 2020 or equivalent to a reduction of 10,802 donors. For the number of Whole Blood, there was a drop of 147% from 2019 to 2021 or equivalent to a reduction of 3,015 donors. For the Number of PRBCs, there was a drop of 26% from 2019 to 2021 or equivalent to a reduction of 7,787 donors. For the number of FFPs, there was a drop of 37% from 2019 to 2021 or equivalent to a reduction of 1,442 donors. For the number of Platelet concentrate, there was a drop of 15% from 2019 to 2021 or equivalent to a reduction of 2091 donors (Table 2).

The total donors, whole blood, PRBC, FFP, and platelet concentrate distribution from 2019 to 2021 in the Philippine Red Cross - Davao City Chapter reflected a p-value of less than 0.01 proving a highly significant result. For the number of Total donors, there was a drop of 264% from 2019 to 2021 or equivalent to a reduction of 7,408 donors. For the number of whole blood, there was a drop of 317% from 2019 to 2021 or equivalent to a reduction of 2,980 donors. For the number of PRBCs, there was a drop of 247% from 2019 to 2021 or equivalent to a reduction of 4,131 donors. For the number of FFPs, there was a drop of 6235% from 2019 to 2021 or equivalent to a reduction of 3,055 donors. For the number of platelet concentrate, there was a drop of 233% from 2019 to 2021 or equivalent to a reduction of 3920 donors (Table 3).

The p-values of all components are less than 0.01 showing a highly significant result on the total donors, whole blood, PRBC, FFP, and platelet concentrate distribution from 2019 to 2021 from both blood centers in Davao City. For the number of total donors, there was a drop of 201% from 2019 to 2021 or equivalent to a reduction of 5,995 donors. For the number of PRBCs, there was a drop of 37% from 2019 to 2021 or equivalent to a reduction of 11,918 donors. For the number of FFPs, there was a drop of 114% from 2019 to 2021 or equivalent to a reduction of 4,497 donors. For the number of platelet concentrate, there was a drop of 39% from 2019 to 2021 or equivalent to a reduction of 6,011 donors (Table 4).

In Davao Blood Center, for 2020, it is noted that among the years indicated, 2019 had the greatest number of blood donors, followed by 2021, and the least number of donors in 2020. In the Philippine Red Cross - Davao City Chapter, Blood Center in 2020, the highest number of donors was registered, followed by 2020 and 2021 respectively. Before the pandemic, the highest number of donors was registered in 2019, followed by 2021 and 2020 respectively. The earliest phase of the pandemic saw the lowest number of donors.

Table 1. Total donors, whole blood, PRBC, FFP, and platelet concentrate distribution from 2019 to 2021

Davao Blood Center			
Characteristics	**2019**	**2020**	**2021**
Number of Total Donors	43,289	29,276	32,487
Number of Whole Blood	5,061	1,840	2,046
Number of PRBCs	38,228	27,436	30,441
Number of FFPs	5,351	3,307	3,909
Number of Platelet concentrate	15,916	12,101	13,825
Rank	1	3	2
Philippine Red Cross - Davao City Chapter, Blood Center			
Characteristics	**2019**	**2020**	**2021**
Number of Total Donors	10,209	3,520	2,801
Number of Whole Blood	3,919	1,359	939
Number of PRBCs	5,804	1,953	1,673
Number of FFPs	3,104	1,657	49
Number of Platelet concentrate	5,601	1,910	1,681
Rank	1	2	3
Total From Both Facilities			
Characteristics	**2019**	**2020**	**2021**
Number of Total Donors	53,498	32,796	35,288
Number of Whole Blood	8,980	3,199	2,985
Number of PRBCs	44,032	29,389	32,114
Number of FFPs	8,455	4,964	3,958
Number of Platelet concentrate	21,517	14,011	15,506

Table 2. Comparison of blood supply inventory at Davao Blood Center from January 2019 to December 2021

Table	2019	2020	2021	p	2019 vs 2020	2020 vs 2021	2019 vs 2021
Number of total donors	43,289	29,276	32,487	<0.01	-32.4%	11.0%	-25%
Number of whole blood	5,061	1,840	2,046	<0.01	-63.6%	11.2%	-147.4%
Number of PRBCs	38,228	27,436	30,441	<0.01	-28.2%	11.0%	-25.6%
Number of FFPs	5,351	3,307	3,909	<0.01	-38.2%	18.2%	-36.9%
Number of Platelet concentrate	15,916	12,101	13,825	<0.01	-24.0%	14.2%	-15.1%

Table 3. Comparison of blood supply inventory at Philippine Red Cross - Davao City Chapter from January 2019 to December 2021

Characteristics	2019	2020	2021	p	2019 vs 2020	2020 vs 2021	2019 vs 2021
Number of total donors	10,209	3,520	2,801	<0.01	-65.5%	-20.4%	-75.6%
Number of whole blood	3,919	1,359	939	<0.01	-65.3%	-30.9%	-317.4%
Number of PRBCs	5,804	1,953	1,673	<0.01	-66.4%	-14.3%	-246.9%
Number of FFPs	3,104	1,657	49	<0.01	-46.6%	-97.0%	-6234.7%
Number of platelet concentrate	5,601	1,910	1,681	<0.01	-65.9%	-12.0%	-233.2%

Table 4. Comparison of blood supply inventory in Davao City from January 2019 to December 2021

Characteristics	2019	2020	2021	p	2019 vs 2020	2020 vs 2021	2019 vs 2021
Number of total donors	53,498	32,796	35,288	<0.01	-38.7%	7.6%	-51.6%
Number of whole blood	8,980	3,199	2,985	<0.01	-64.4%	-7.2%	-200.8%
Number of PRBCs	44,032	29,389	32,114	<0.01	-33.3%	9.3%	-27.1%
Number of FFPs	8,455	4,964	3,958	<0.01	-41.3%	-20.3%	-53.2%
Number of platelet concentrate	21,517	14,011	15,506	<0.01	-34.9%	10.7%	-38.8%

DISCUSSION

The COVID-19 pandemic has had a significant impact on the supply of blood.[18] Studies have shown that during the pandemic era, there has been a decrease in blood donations, which has resulted in a shortage of blood supply in many parts of the world.

It is worth noting that blood centers have implemented various measures to ensure a safe and adequate blood supply during the pandemic. These include the implementation of social distancing measures, the use of personal protective equipment, and the screening of potential donors for COVID-19 pandemic symptoms.[17]

Indeed, the pandemic has been a major factor in the decline in blood donations around the world. Governments and health authorities have taken steps to prevent the spread of COVID-19 pandemic, including the implementation of social distancing measures. These measures have led to the cancellation or postponement of many blood donation drives, which are usually held in public places such as schools, workplaces, and community centers. This had a negative impact on the number of donors available to the public, as many people have been deterred from donating due to the potential risk of contracting the virus. Additionally, restrictions on travel have also contributed to a decrease in donations, as individuals who usually donate blood while traveling or during vacation periods have been unable to do so. The COVID-19 pandemic brought about a range of changes to healthcare systems around the world, including the introduction of new eligibility criteria for blood donors and the temporary deferral of blood donation for those diagnosed with or in close contact with the COVID-19 pandemic patients.[19] This policy was intended to ensure the safety of donors and recipients, as well as to prevent the spread of the virus. Moreover, the pandemic caused shortages of supplies and equipment in some healthcare facilities, further limiting their capacity to collect and manage blood donations.

In many parts of the world, the pandemic had a significant impact on the supply of blood. One of the main reasons for this is the fear of contracting the virus, which has discouraged people from donating blood. Additionally, many blood drives and donation centers have been canceled or postponed due to restrictions on public gatherings and social distancing guidelines, further reducing the number of blood donations.

As mentioned, blood donations have decreased significantly because of reduced blood drives, social distancing measures, and general hesitation from donors due to concerns about the virus. This problem on shortage of blood supply has affected many areas, making it difficult for healthcare providers to meet the demand for blood transfusions. Moreover, patients with severe COVID-19 may require blood transfusions as part of their treatment, particularly if they experience severe complications such as acute respiratory distress syndrome (ARDS).[8]

Many other patients with various medical conditions also require blood transfusions, such as those undergoing cancer treatment or surgery. The shortage of blood supply has created challenges for healthcare providers in effectively managing their patients' conditions, which can have significant implications for patient outcomes.

The comparative study between the pre-pandemic and pandemic era in a cross-sectional design has highlighted the significant impact of the pandemic on the blood supply. The study has shown that the number of blood

donations has decreased significantly during the pandemic era as compared to the pre-pandemic era. However, it is important to note that this shortage of blood supply is not limited to any specific region but is a global issue that needs to be addressed.[8]

In terms of the collection of different blood components, the pandemic has had varying effects. For instance, the collection of whole blood has seen a decline during the pandemic. The reduction is mainly due to the reduction in blood donation activities caused by restrictions on public gatherings and social distancing guidelines. Hence, decrease in the overall supply of whole blood.

Moreover, the collection of packed red blood cells has also declined during the pandemic era. The widespread outbreak of the virus and subsequent public health measures, such as lockdowns and social distancing, have significantly impacted blood donation drives, resulting in decreased donor participation and reduced availability of blood products such as packed red blood cells. Platelet concentrate collection has also seen a decline, but not as drastically as whole blood. Platelets have a shorter shelf life than red blood cells and need to be used within 5 days of collection. As such, the reduction in platelet donations has resulted in a critical shortage of this component in some regions, making it challenging for healthcare providers to manage patient conditions effectively. Lastly, the collection of fresh frozen plasma has exponentially declined from pre-pandemic to pandemic levels.

In the Philippines, the COVID-19 pandemic has had a significant impact on the blood supply. This study particularly focuses on the Davao Region and is no exception to the effects of the pandemic on the supply of blood. Blood donations have decreased significantly due to social distancing measures, quarantine restrictions, and the reluctance of donors to go to blood donation centers over fears of contracting the virus. To address this issue, the Department of Health has implemented various measures to encourage blood donation, such as setting up blood donation booths in public places, implementing mobile blood donation drives, and launching information campaigns to educate the public about the importance of donating blood.

In the Davao Region, local government units and blood centers have also taken action to mitigate the impact of COVID-19 pandemic on blood supply. The Davao Blood Center, which covers the majority of blood supply in the region, for instance, has implemented a scheduling system for blood donation to ensure that there are enough donors to meet the demand for blood. The Philippine Red Cross-Blood Center has also implemented safety protocols, such as disinfecting equipment and providing personal protective equipment to donors and staff.

Despite these efforts, the blood supply in the Davao Region and the rest of the Philippines remained limited. This can have significant consequences for patients who require blood transfusions for various medical conditions, including COVID-19. The shortage of blood supply can make it difficult for healthcare providers to effectively manage patient.

Overall, the impact of the COVID-19 pandemic on the blood supply has been significant, and more research is needed to understand the long-term effects of the pandemic on blood donation.

CONCLUSION AND RECOMMENDATIONS

This study conforms with most literatures that there is significant decrease in blood supply between the pre-pandemic year of 2019 against the pandemic year of 2020. Moreover, a steady increase is seen as restrictions ease by the year 2021.

The study has gathered valuable information that could have a significant positive impact on blood service facilities, particularly during times of pandemics. First, the study has provided crucial insights and data that can be used by blood service facilities. This information is likely to be related to the challenges faced during pandemics, particularly in regard to blood collection. Such data can be vital for understanding the implications of pandemics on blood supply and the various factors that may affect blood donation rates. Second, by utilizing the information obtained from the study, blood service facilities can make informed decisions and develop strategies to effectively handle blood collection processes during pandemics. This could involve identifying potential obstacles and finding innovative solutions to overcome them. Moreover, contingency plans for blood collection should be constructed. With the insights gained from the study, blood service facilities can create contingency plans specifically designed to tackle issues related to blood collection during pandemics. These plans might include ways to engage with potential donors, ensuring the safety of both donors and staff, and addressing any logistical challenges that might arise during such times. The primary objective of developing contingency plans is to prevent any significant decline in the availability of blood. This is crucial as the demand for blood may increase during pandemics due to medical emergencies, while the willingness of donors to donate might decrease due to fear or restrictions. Lastly, the findings of this study could be used to establish a standardized protocol that blood service facilities can follow during pandemics or similar calamities. This protocol would be based on best practices identified through the study, ensuring a consistent and efficient response to maintain a stable blood supply. The findings could help in offering a data-driven approach to cope with the unique challenges presented during the pandemic. By developing contingency plans and implementing a standard protocol, these facilities can work toward maintaining a stable blood supply even in times of crisis, ultimately saving lives and ensuring better healthcare outcomes for patients.

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The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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OPEN ACCESS – ORIGINAL ARTICLE

Needs Assessment for Establishment of Telepathology in the Philippines*

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ABSTRACT

Objective. The Philippines has more than a hundred ten million population with a very limited number of general pathologists and subspecialist pathologists. Consultation of pathologists with other pathologists is important to ensure accurate results for difficult cases. However, pathologists are not always accessible to review slides. Telepathology can provide access to other pathologists by sending microscopic images through the internet. This study explores the needs of pathologists for consultation in their practice that may be aided by telepathology. The status of current pathology practice and subspecialty consultations across the different regions in the Philippines were determined and the readiness of pathologists for telepathology was identified.

Methodology. This is a cross-sectional descriptive study using an 18-item online survey questionnaire based on the World Health Organization guidelines on needs assessment for medical devices. The survey was distributed among anatomic pathologists practicing in the Philippines.

Results. One hundred forty (140) pathologists responded and were included in this study. 5-10% of cases of respondents required subspecialty referral. Diagnostically challenging cases and confirmation of malignancy are the most common reasons for consultation. Respondents practicing outside the National Capital Region (NCR) have fewer subspecialist pathologists available for referrals within their region. Turnaround times for signing out challenging cases are longer outside NCR (>7 days) compared to NCR (4-7 days). Most respondents have access to the basic equipment to perform telepathology, which includes, an internet link, a smartphone with high-resolution camera and a computer. Almost all respondents will use telepathology if it is available.

Conclusion. A hub-and-spoke telepathology network can provide access to subspecialty consultation to reduce the diagnostic turnaround time and to increase the accuracy of results for challenging cases. The availability of the minimum telepathology infrastructure and the positive attitude of the pathologists towards telepathology may be indicators of readiness for a local telepathology system in the Philippines.

Key words: telepathology, Philippines, pathology, needs assessment, telemedicine, informal telepathology

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INTRODUCTION

The Philippines is a low- to middle-income country populated by 110 million people with geographically disadvantaged areas for receiving health care services. Based on the 2019 data from the Philippine Society of Pathologists (PSP), there are 603 registered anatomic pathologists in the country with only less than fifty subspecialist pathologists (unpublished data from the PSP).

Telepathology is driven by the need to provide access to subspecialized pathologists in areas where they are not available.[1] In remote areas with solo general pathologists, telepathology may be the only means of seeking diagnostic assistance from subspecialist pathologists.[1,2] Telepathology consultations can also bring confidence and enhancement of general pathologists' diagnostic skills, which can further help in solving the geographic maldistribution of pathology services.[3] Furthermore, telepathology also facilitates teaching, research and quality assurance in the diagnosis.[4,5]

Telepathology allows the practice of remote pathology by the transmission of images through a telecommunication system.[4] A basic telepathology setup consists of a camera mounted on a microscope linked to a computer connected to the internet.[6] Digital images are then transmitted to a referral center or an expert pathologist for consultation.[5] The biggest advantage of telepathology is the rapid diagnostic support for obtaining expert opinion without compromising diagnostic performance.[2,7]

A meta-analysis of 10,410 histology samples showed that diagnosing cases through digital images is comparable with diagnosing through light microscopy.[7] Discrepancy rates in telepathology consultations are also comparable with traditional pathology consultations.[1,8] Discrepancies in both forms of consultation are attributed to difficulty of cases, unavailability of immunohistochemical stains and lack of training and expertise of the referring pathologist.[1]

In 1993, the Armed Forces Institute of Pathology (AFIP) launched a telepathology program to provide expert consultation to pathologists internationally. AFIP's telepathology service was mostly utilized by solo pathologists rather than pathologists working in small groups or large departments.[1,2] Many of the laboratories that referred cases lacked access to immunohistochemistry studies.[1] The technical challenges encountered in the telepathology consultations include unreliable internet connection and lack of high-resolution camera.[1]

The cost of infrastructure, such as whole-slide imaging, and quality of internet connection are major concerns for implementation of telepathology in developing countries.[9] But with the current technology, use of images or videos taken from smartphones are possible alternatives.[9,10] Contrary to previous concerns, image compression does not negatively affect the accuracy and diagnosis of telepathology and digital images maybe compressed down to one-tenth of its original size.[11] An Android phone with at least 8-megapixel camera mounted to a commercially available adapter may be adequate for telepathology.[9] With smartphones with high resolution cameras becoming more affordable and accessible to developing countries, telepathology has become more feasible in low-resource areas.[9]

In Eastern Africa, telepathology-referral center based in United States enabled 91.7% of surgical pathology cases in four hospitals with limited resources and manpower.[12] A telepathology referral center based in Germany significantly improved the diagnostic procedures in a hospital in Tanzania where a pathologist cannot be employed.[13]

In 2011, a nationwide telepathology consultation was implemented in China where three regional centers and twenty provincial centers participated.[14] Eighty expert pathologists were part of the study. In two years, 16 247 cases were referred, and majority of the cases were submitted due to diagnostic difficulty.[14] The two-year telepathology program indicated that telepathology can provide a solution for the uneven distribution of pathology resource.[14]

Following a hub-and-spoke model, a central hub for subspecialist pathologists can ensure the accuracy and quality of pathologic diagnoses of general pathologists from remote areas.[3] A referral network, consisting of general pathologists (spokes) and subspecialist pathologists (hub), will support general pathologists.[3] Collaboration with international pathology networks can also form telepathology consultation platforms that will not only benefit areas with few pathologists, but also foster education and research among international parties.[15]

The first telepathology consult in the Philippines was performed between University of the Philippines, Department of Pathology and AFIP in 1996.[3] However, despite the advances in technology around twenty-five years later, use of telepathology in the Philippines is still limited.

This study aims to explore the needs of anatomic pathologists in their consultations that may be aided by telepathology. The current practice of anatomic pathologists in the Philippines was ascertained by identifying their place of practice, diagnostic turnaround time and access to immunohistochemistry. The status of pathology consultations was also determined through the consultation turnaround time, methods of consultation, number of cases consulted, reasons for consultation, access to other pathologists and type of practice (solo versus group practice). The readiness for telepathology was assessed by determining the availability of the infrastructures as well as the awareness and attitude of the anatomic pathologists towards telepathology. The perceived barriers for implementation of telepathology were also identified.

The data gathered in this study can guide in designing a local telepathology framework in the Philippines. Establishing telepathology in the Philippines will potentially increase the accessibility of diagnostic services to geographically disadvantaged areas and improve patient treatment by providing earlier and accurate diagnosis.

METHODOLOGY

This is a cross sectional descriptive study through survey questionnaire. An 18-item online questionnaire (based on the World Health Organization's guidelines on needs assessment for medical devices)[16] were distributed among anatomic pathologists practicing in the Philippines.

The online survey was created using Google Forms. The invitation and link to the survey with accompanying informed consent were given to all the members of the online group for anatomic pathologists in the Philippines. The online group has 214 members and was created by the PSP for all anatomic pathologists recognized by the Society. The invitation to the survey was also submitted to the main office of PSP for distribution to other pathologists that may not be reachable through the online group. Only pathologists accredited by the PSP were included in this study. Non-practicing pathologists were excluded. No identifiers were collected, and all responses were anonymized. The survey was available online for two weeks. Microsoft Excel was used to analyze data and generate descriptive statistics.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Data Privacy Act. All

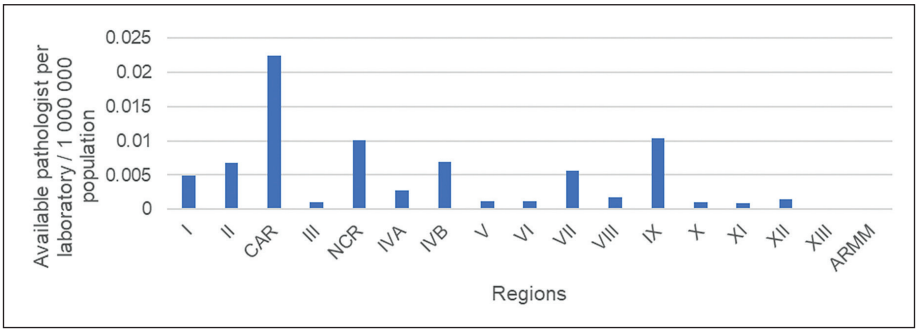

Figure 1. Distribution of practice among the respondent pathologists across different regions.

the respondents provided answered informed consent prior to enrollment. No personal information such as name, address, e-mail address, phone numbers and IP addresses were collected in this study.

RESULTS

Current pathology practice

A total of 140 responses were collected from the survey. Table 1 shows the frequency distribution of practice among the respondents in the different regions of the Philippines.

The majority of the respondents practice pathology in NCR (58.3%, n = 81). The higher number of practicing pathologists in NCR may be attributable to the greater number of laboratories and the population density in the area. The standardized regional distribution of the pathology practice with respect to the number of laboratories (17) and the population of the region (18) (ratio of pathologist to laboratory per one million population) is summarized in Figure 1. Findings showed that CAR has the highest number of pathologists relative to the number of laboratories and population of the area. There is also a notable variation in the distribution of respondent pathologists across the different regions (mean = 0.006 respondent pathologist per laboratory per one million population, SD = 0.005).

Table 1. Distribution of practice among the pathologists across different regions

Region	Frequency	
	Absolute (n)	Relative (%)
Pathologists practicing in one region only	**111**	**79.9**
Luzon	**88**	**63.3**
NCR – National Capital Region	58	41.7
Region I – Ilocos Region	3	2.2
Region II – Cagayan Valley	3	2.2
CAR – Cordillera Administrative Region	5	3.6
Region III – Central Luzon	8	5.8
Region IVA – Calabarzon	8	5.8
Region IVB – Mimaropa	2	1.4
Region V – Bicol Region	1	0.7
Visayas	**16**	**11.5**
Region VI – Western Visayas	6	4.3
Region VII – Central Visayas	9	6.5
Region VIII – Eastern Visayas	1	0.7
Mindanao	**7**	**5.0**
Region IX – Zamboanga Peninsula	4	2.9
Region X – Northern Mindanao	1	0.7
Region XI – Davao Region	1	0.7
Region XII – Soccsksargen	1	0.7
Region XIII – Caraga	0	0.0
BARMM – Bangsamoro Autonomous Region of Muslim Mindanao	0	0.0
Pathologists practicing in multiple regions	**28**	**20.8**
NCR and other regions	**24**	**17.8**
NCR and Region I	1	0.7
NCR and Region III	4	3.0
NCR and Region IVA	18	13.3
NCR, Region III and Region IV	1	0.7
Regions outside NCR	**4**	**3.0**
Region I and III	1	0.7
Region II and III	2	1.5
Region III and IV	1	0.7

*Four to five immunohistochemical stains available

Table 2 summarizes the turnaround time of the pathologists for signing out uncomplicated and challenging cases. In the survey, "turnaround time" was operationally defined as the time from receiving the slide to signing out of the case. The usual turnaround time for uncomplicated cases is 2 to 3 days both in NCR and outside NCR. On the other hand, the turnaround time for challenging cases is higher, ranging from 4 to 7 days to more than a week. The turnaround time is also longer in regions outside NCR which takes more than a week compared to NCR which only takes 4 to 7 days.

Pathologists practicing in NCR have more access to immunohistochemical stains (70.3%) compared to those who are practicing outside NCR (30.5%). More than half of pathologists practicing outside NCR (57.6%) only have very limited access to immunohistochemical stains (one to five stains) and 11.9% have no access to it (Figure 2).

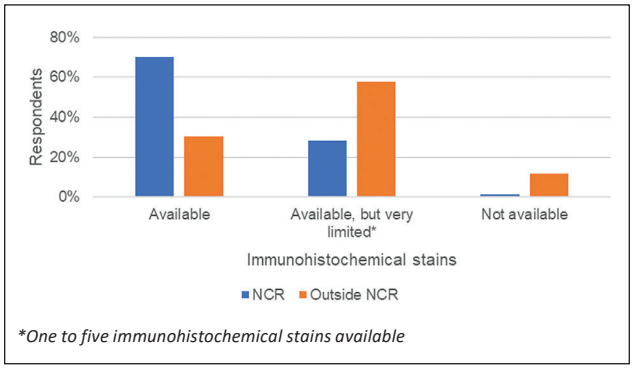

Figure 2. Availability of immunohistochemistry among the pathologists.

Table 2. Turnaround time for uncomplicated and challenging cases in NCR and outside NCR

Turnaround Time*	NCR		Outside NCR		Total	
	Absolute (n)	Relative (%)	Absolute (n)	Relative (%)	Absolute (n)	Relative (%)
Uncomplicated cases						
1 day	14	17.3	7	11.9	21	15.0
2 to 3 days	45	55.6	26	44.1	71	50.7
4 to 7 days	22	27.2	22	37.3	44	31.4
More than 1 week	0	0.0	4	6.78	4	2.9
Challenging cases						
1 day	0	0.0	0	0.0	0	0.0
2 to 3 days	4	4.94	3	5.08	7	5.0
4 to 7 days	42	51.9	26	44.1	68	48.6
More than 1 week	35	43.2	30	50.8	65	46.4

*From receiving the slide to signing out

Table 3. Rate of consultation of the respondents, availability of immunohistochemistry and the number of specialists known to the respondent

Cases consulted	Immunohistochemical stains						Number of subspecialist pathologists known to the respondent							
	Not available		Available, but very limited*		Available		None		Less than 5		5 to 10		More than 10	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Less than 5%	3	37.5	18	32.1	31	41.3	14	37.8	8	36.4	9	45.0	20	33.9
5 to 10%	4	50.0	34	60.7	34	45.3	19	51.4	13	59.1	10	50.0	30	50.8
10 to 50%	0	0.0	4	7.1	10	13.3	3	8.1	1	4.5	1	5.0	9	15.3
More than 50%	1	12.5	0	0.0	0	0.0	1	2.7	0	0.0	0	0.0	0	0.0

*Four to five immunohistochemical stains available

Status of pathology consultation

Most pathologists refer between 5 to 10% of their cases to other pathologists (Figure 3). This is their usual rate of consultation regardless of the accessibility to immunohistochemical stain or the availability of subspecialist pathologists within the region (Table 3).

However, most solo pathologists (66.7%) consult only less than 5% of their cases. Among the pathologists with group practice, those who have fewer members in a group practice are also less likely to consult their cases. The immediate availability of another pathologist within the practice maybe affecting the consultation rate.

The majority of the cases consulted are malignant cases (Figure 4). Cases are usually consulted because of difficulty (95.7%). Confirmation of dysplasia or malignancy is another common reason for consultation (75.7%). Table 4 summarizes the reasons for consultation with other pathologists.

In the majority of cases, pathologists practicing in the NCR receive responses for referrals within 2 to 7 days (84%). However, for pathologists practicing in regions outside NCR, whether in solo or with group practice, take longer, between 4 days to more than a week (77.7%).

The longer turnaround time for consultation may be attributable to the availability of other pathologists known to the respondents. The majority of the pathologists (71.3%) in NCR know more than ten subspecialist pathologists

Table 4. Reasons for consultation with other pathologists

Reason for consultation	Frequency (%)
Opinion on known difficult/challenging diagnoses	95.7
Confirmation of dysplasia or malignancy	75.7
Discrepancy with clinical findings	44.3
Disagreement with the original report on an outside case	42.1
Lack of access to immunohistochemical stains	32.1
Advice on wording of report	32.1
Quality assurance	28.6
Mandatory consult	17.1
Coordination of definitive specimen with biopsy finding	<1
Patient requests for second opinion	<1

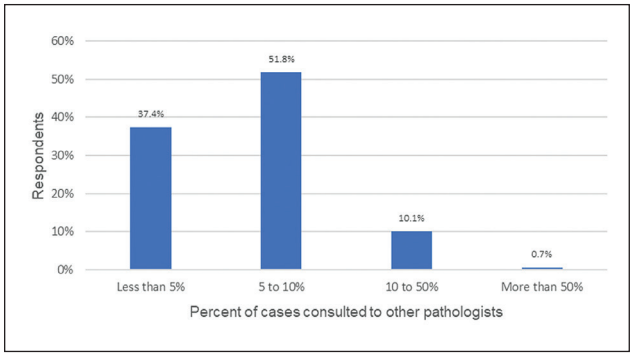

Figure 3. Percent of total cases that need consultation with other pathologists.

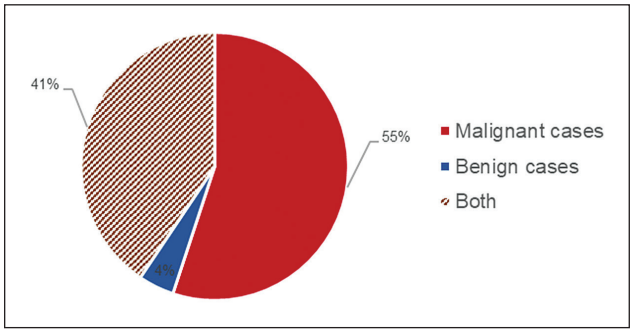

Figure 4. Type of cases that need consultation with other pathologists.

within their region. On the other hand, the majority of the pathologists from the regions outside NCR (60.3%) do not know any specialists in their region. If the respondents wanted to seek the diagnostic opinion of a general pathologist, those from Luzon may have more advantage compared with the other regional groups. In Luzon, most pathologists know more than ten other general pathologists in their region, but for those in the Visayas and Mindanao, most pathologists know only around five to ten other general pathologists in their region.

The most common method of consultation is through direct personal referral (89.3%) followed by sending of images via the internet through mobile phone or e-mail (67.1%). Pathologists who consult through a messenger (39.3%) may ask pathology residents or other pathology colleagues to facilitate the consultation. Only 16.4% of the respondents use courier services. One respondent reported using a slide scanner connected to a server to consult specialists.

Readiness to telepathology

The majority of pathologists from NCR and regions outside NCR already have the equipment to perform a basic telepathology consultation. These include internet access (99.3%), a computer (98.6%) and smartphone with high-resolution camera (81.4%). Other reported equipment includes USB with microscope eyepiece holder, slide scanner and a high-resolution camera for gross pathology.

Figure 5 shows the responses of the pathologists to questions regarding their familiarity and attitude with telepathology. Most pathologists are familiar with telepathology (84.2%, 117 out of 139 responses) and are willing to use telepathology if it is available (98.5%,135 out of 137 responses).

The perceived barriers in the implementation of telepathology are listed in Table 5. The most commonly foreseen barrier is internet speed (88.2%) followed by the availability of equipment for the set-up (65.4%).

DISCUSSION

The distribution of anatomic pathology practice across the regions in the Philippines is highly variable. The longer turnaround time for difficult cases especially in areas outside NCR is a pressing concern. Difficult cases are generally more time-consuming since more thorough slide evaluation, in-depth research and analysis of the case and opinion from another pathologist may be needed. Repeating the preparation of the slides may also be warranted to improve the diagnostic quality of the sample.

In regions outside NCR, the limited access to immunohistochemistry can make cases more difficult to resolve. Additional specimen sampling and consultation with another pathologist or a specialist pathologist may be strongly necessary to increase the diagnostic confidence of a general pathologist. While taking these additional steps may lengthen the turnaround time, they provide the advantage of a more accurate diagnosis in the absence of immunohistochemistry. However, even inter-pathologist consultation can be challenging since many pathologists outside NCR also do not have access to subspecialist pathologists within their area.

Although case consultation is not the sole reason for the longer turnaround time in signing out difficult cases, improving the access to diagnostic assistance from other pathologists can improve turnaround time and minimize diagnostic errors despite minimal use of immunohistochemistry.

Around 5 to 10% of total cases need specialty consultation. Most of these pertain to cases that determine whether a tissue is malignant or not, and therefore a correct diagnosis is crucial. For malignant cases, a fast turnaround time is important to avoid significant disease progression and to facilitate early patient treatment. A general pathologist may be left with the dilemma of delaying the management and spending more time and resources to get a more accurate diagnosis through specialty referral, or to release a result based on the best of her or his ability for the patient to have earlier treatment.

A telepathology network following a hub-and-spoke organization can provide a lifeline to pathologists outside

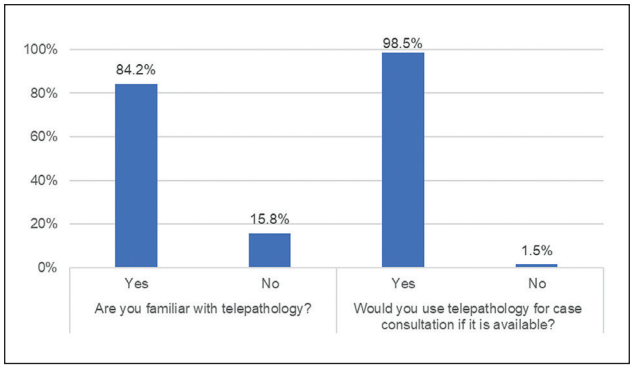

Figure 5. Familiarity and attitude of the respondents towards telepathology.

Table 5. Possible barriers in telepathology perceived by the respondent pathologists

Possible barriers	Responses (%)
Slow internet	91.2
No setup available • Microscope with camera • Slide scanner • High-resolution camera	66.2
Administration barriers	60.3
Reimbursement	39.7
Logistics • Availability of specialist and finding a shared time • Lack of funding • Software and available platforms • Cloud-based storage	
Digitalization of slides • Time consumed on slide scanning • Potentially large file sizes	
User-related • Level of capability with using computers • Learning how to use the software with ease • Trustworthiness on the proficiency of the residents taking the representative samples and appropriate photomicrograph	
Lack of standardized telepathology protocol	
Privacy issues	
Concerns on diagnostic accuracy (i.e., discrepancy in tissue appearance in real life and in camera)	

NCR who need diagnostic support.[19] If a consultation hub with subspecialist pathologists is accessible to general pathologists via telepathology, the turnaround time and diagnostic accuracy for difficult cases can be improved. A telepathology consultation hub can also provide financial savings for the spoke sites by not having to hire subspecialist pathologists for a low volume of subspecialized cases.[20] On the other hand, subspecialist pathologists at the hub site will have more educational exposure to cases which can further improve their diagnostic skills.[20] Cases referred to the hub site may also be used for academic training of residents.

In this study, around seventy percent of the pathologists already perform an informal telepathology consultation by sending digital images of their cases though the internet. The availability of camera phones, internet connection and messaging applications may have contributed to this practice. Many pathologists have the minimum equipment to connect to a telepathology network suitable for a low-resource setting. The general positive attitude of the pathologists towards telepathology can facilitate its widespread implementation.[15]

Establishing a hub-and-spoke telepathology network can be expensive.[20] In designing a telepathology framework, the infrastructural, logistical, legal, procedural and user-related issues raised by the pathologists in this study should be carefully considered to have a usable, stable and cost-effective system.[20] The local telepathology system should also be designed and developed to coincide with the Philippine e-Health Strategic Framework and Plan. This will help in creating a sustainable system with good national collaboration and directed towards the e-Health goals of the Philippines. It can also be the framework for other image-intensive specialties like radiology and dermatology.

CONCLUSION

Access for consultation with subspecialist pathologists can reduce the turnaround time and improve the diagnostic accuracy for difficult and challenging cases. In the Philippines where there are limited number of subspecialist pathologists, a hub-and-spike telepathology network can provide diagnostic assistance to general pathologists. The availability of the minimum telepathology infrastructure and the positive attitude of the pathologists towards telepathology may be indicators of readiness for a local telepathology system.

Although many pathologists perceive the need for high-speed internet and sophisticated equipment to facilitate telepathology, the gap between the pathologists and establishment of telepathology is not the infrastructure. The gap is the lack of a system that can deal with the administrative and logistical challenges of telepathology in a low-resource setting. These include funding, availability of subspecialists for consultation, standard protocol and legal guidelines. These type of healthcare needs are already identified and addressed in the Philippine e-Health Strategic Framework and Plan. Hence, for telepathology to be established sustainably in the country, future efforts should be directed on designing telepathology framework that fits the national e-Health system.

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STATEMENT OF AUTHORSHIP

The author certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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OPEN ACCESS – ORIGINAL ARTICLE

Attitudes and Perceptions of Filipino Clinicians and Pathologists towards the Autopsy as a Medical Tool

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ABSTRACT

Background. Globally, autopsy rates have been continually declining over the course of several years. Previous studies have shown that the perception of pathologists and clinicians may serve as significant factors which may affect the performance of autopsy and contribute to its decreased rate. This study was conducted to determine the attitudes and perceptions of Filipino clinicians and pathologists toward the autopsy as a medical tool.

Methodology. This is a cross-sectional descriptive survey of two groups of physicians. Forty-four (n = 44) pathologists nationwide and thirty-three (n = 33) clinicians from Central Visayas participated in the study. A total of seventy-seven (n = 77) physicians completed a survey using a standardized online questionnaire.

Results. Of the 77 respondents, 94% of clinicians and 75% of pathologists believed that autopsies could provide relevant findings that could change future clinical practice. Despite this, only 6% of clinicians and 20% of pathologists indicated that the number of autopsy cases in their institutions was sufficient. With regards to their practice, pathologists most strongly agreed (mean = 4.30) that material for medico-legal autopsies should be readily available for teaching and research. However, they most strongly disagreed (mean = 2.00) that residents receive adequate training in performing medico-legal autopsies. The two groups of physicians surveyed determined that there is a deficiency in the number of autopsy cases. This is further influenced by clinicians' concerns about litigation, religious/superstitious beliefs, and the delay in releasing autopsy results. Furthermore, pathologists specified that performing autopsies was excessively time-consuming with an unjustifiable cost. Sixty-two percent of the pathologists signified more strongly than the clinicians that modern diagnostic techniques have diminished the need to perform hospital autopsies. Nonetheless, 86% of Filipino physicians acknowledged that the autopsy is an important medical tool that should be performed for patients with unknown diagnoses and unexpected death. The number of observed and/or performed autopsy cases was a major factor that affected the pathologists' attitudes and perceptions toward autopsy.

Conclusion. In general, there is recognition of the autopsy's usefulness as a medical tool among the pathologists and clinicians surveyed. However, the lack of cases referred for autopsy remains a challenge undermining the benefits that are derived from its performance

Key words: autopsy, pathologists, clinicians, attitudes, perceptions

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BACKGROUND

The autopsy is a specialized surgical procedure which is commonly used to determine the cause and manner of death. The cause of death is a medical reason for the cessation of life, while the manner of death consists of the circumstances surrounding the death of a patient.[1] There is a common notion that autopsies should only be performed whenever there is uncertainty concerning the cause of death. Albeit this is a valid reason, it must be emphasized that the autopsy serves a two-fold purpose: one, it enables the thorough evaluation of the presence and extent of disease; and two, it provides a means by which the effectiveness of therapeutic procedures is evaluated to benefit the patient's family, hospital staff, and the future practice of medicine.

The relevance and value of autopsies have been well documented. The study by Hooper et al., demonstrated that physicians value the autopsy as a relevant clinical tool

and that the results could affect their medical practice.[2] This belief was maintained across various medical specialties, years of practice, and prior experiences with autopsy. Furthermore, the study by Hull et al., reinforced the value of autopsy by demonstrating that internal medicine and pathology resident physicians considered the autopsy to be a necessary procedure which provides answers to clinical questions, reveals information not previously identified by medical imaging or not otherwise known in a patient's life, and affects management decisions of future cases.[3]

In the Philippines, an autopsy is performed under the following circumstances: whenever required by special laws; upon orders of a competent court, a mayor, and a provincial or city fiscal; upon written request of police authorities; whenever the Solicitor General, provincial, or city fiscal as authorized by existing laws, shall deem it necessary to disinter and take possession of remains for examination to determine the cause of death; and whenever the nearest kin shall request in writing the authorities concerned to ascertain the cause of death.[4] For patients who die in accredited hospitals, an autopsy may be performed once permission from the next of kin has been obtained by the director of the hospital. Thus, the decision to perform an autopsy is largely based upon proper appraisal by the clinician, and on the approval by the next of kin.

Autopsy rates have been continually declining over the course of several years. Studies showed that autopsy was once considered the "gold standard" in medical diagnosis such that historical data suggested autopsy rates of 50 to 85% during the 1950s and 1960s in the United States. It has declined in use to just 9.4% in 1994.[5] In 2004, the study by Burton et al., suggested that autopsy rates in US hospitals have declined to less than 6%.[6] By 2011, National Center for Health Statistics data concluded that autopsy rates in the US had declined by more than 50 percent from 1972 through 2007.[1] At a hospital in France, the autopsy rates declined during the last 10 years, which is in accordance with what has been documented in the United States, as well as in England and Wales (a decrease from 8.9% in 1966 to 1.7% in 1991).[7]

The autopsy rate is calculated as the number of deaths undergoing autopsy per all deaths expressed per 100 deaths. Perpetual Succour Hospital registered a total of 2,338 deaths from January 2015 up to December 2019. Of these deaths, only two (2) autopsy procedures have been performed in the institution, both occurring in 2019. Thus, the hospital autopsy rate in a span of five (5) years is 0.08%.

Research suggests that pathologists and clinicians alike have different perceptions and attitudes towards autopsy and the different factors related to its decrease. McManus and his colleagues demonstrated that the decline over the past 20 years is perceived significantly more by pathologists than clinicians.[8] However, another study by Chariot, et al. showed that pathologists were "satisfied" with the current decline of autopsy rate in the conditions in which they are currently performed and that the pathologists did not complain about this decrease.[7]

On the other hand, although Nemetz and his colleagues concluded that the explanations behind autopsy rates are multi-factorial and conditional, studies by Eriksson and Sundstrom, have implied that the attitude and interest of clinicians toward autopsy seemed to be the major explanation for the decline of the rate.[5,9] This was supported by Hooper et al., who also suggested that the most important variable in determining whether an autopsy is performed is the requesting physician's general attitude toward autopsy.[2]

Work from previous studies has indicated that the perception of pathologists and clinicians may serve as significant factors which may affect the performance of autopsy, as well as contribute to its decreased rate. It is the goal of the researcher to be able to determine these perceptions with regards to autopsy in the local setting, and perhaps give light to current conditions.

OBJECTIVES

The researcher aimed to determine the attitudes and perceptions of Filipino clinicians and pathologists towards the autopsy as a medical tool.

Significance of the study

Information gleaned from this study may benefit administrators, clinicians, and pathologists alike in understanding how the autopsy is perceived by medical professionals, as well as in identifying certain perceptions and attitudes that may or may not have contributed to its recession. Furthermore, the number of autopsy cases in our institution has been observed to be decreasing in number, thus, it is the hope of the researcher that determining the autopsy rate will provide the scientific community concrete data of this change in the local setting.

Review of related literature

A decreasing trend in the number of autopsy cases has been documented worldwide. Previous studies have concluded that while the reasons for this decline may be multi-factorial, some articles have implied that the perceptions of physicians towards autopsy indeed have an effect.[5]

In 2004, a study by Burton and his colleagues aimed to determine the relation of physicians' recommendations regarding autopsy, as well as patient and surrogate decision-maker characteristics, to autopsy performance. The researchers investigated the association between autopsy performance and the strength of a physician's recommendation for autopsy. The study concluded that the strength of the postmortem recommendation by the physician was the factor most strongly associated with autopsy performance.[6]

A similar conclusion was obtained in the study by Hooper et al., in 2007, which aimed to investigate the nature of physician attitudes about autopsy in a large and varied population and to relate these attitudes to certain physician demographic variables. The study instrument was a 10-question survey which was designed for distribution to all attending physicians at several institutions. The researchers observed from the literature that the most important variable in determining whether an autopsy is performed is the requesting physician's general attitude toward autopsy. Additionally, their study showed that one

of the most crucial factors influencing this attitude is the physician's level of experience with autopsy in training and practice.[2]

Thus, it could be implied that the physicians' attitudes towards autopsy could be the main determinant for the decline in autopsy rates. It was investigated by the study of Eriksson and Sundstrom in 1993, which aimed to explore the reasons behind the decline in autopsy rate in three hospitals in Sweden. Their study concluded that a change in the attitude and interest of clinicians toward autopsy was suggested as the major explanation for the decline of the autopsy.[9]

Barriers to performance of autopsy

In the study by Nemetz et al., the following were hypothesized reasons for the decline in autopsy rates: improvements in diagnostic technology, fear of litigation, removal of defined minimum autopsy rate standards, a lack of direct reimbursement, and lack of standardization of the autopsy as a medical procedure with resultant lack of credibility as a valid outcome or performance measure. Among the hypothesized reasons for the decline in autopsy rates, hospital administrators identified improved diagnostic technology as the most important cause.[5]

The study by Hull and associates in 2007 compared internal medicine and pathology resident physicians' perceptions of the autopsy. In the study, pathologists identified two factors with high importance in determining autopsy rate. Pathologists suggested that clinicians think autopsies are unnecessary because of medical imaging, and that asking for an autopsy is too much trouble for a clinician. Further, the study implied that it was unclear whether pathologists as a group enjoyed doing autopsies since it was determined that many pathologists do not perform them anymore and that many hospitals no longer have a morgue.[3]

A study by Chariot et al., aimed to analyze the different factors that could influence hospital autopsy rates, such as legal constraints, autopsy reporting times, opinions of physicians requesting autopsies and pathologists regarding the usefulness of autopsy in patient care, and use of autopsy material in research publications. Clinicians agreed that the main reason for their disinterest in autopsy was the long response time, such they were dissatisfied with the delay in obtaining written autopsy reports. Additionally, the clinicians' absence during the procedure also was identified as a reason for their disinterest.[7]

Previous studies on autopsies in Japan have revealed that many physicians do not pursue an autopsy even when they feel that it is necessary. The study by Maeda and his colleagues showed that the low autopsy rates were related to the pursuit of autopsy bringing suspicion of medical error upon the physician respondents. Additionally, physicians regarded other methods such as noninvasive blood testing or tissue sampling as significant factors contributing to low autopsy rates.[10]

Differences in perception

Past articles also brought to light differences in perceptions between the different physician groups, such as differences in perception towards the autopsy rate. In 1992, a study by MacManus and his colleagues determined that significantly more pathologists than clinicians believed autopsy rates have fallen over the past 20 years. This was supported by the study by Nemetz et al., which concluded that despite having recognized the decline in autopsy rates, only 25% of the respondents felt that autopsy rates should be higher.[5]

The study by Hull and his colleagues identified a difference in the intensity of perception between internal medicine physicians and pathologists, such that pathologists were more inclined to agree that autopsies were important to provide closure for families. Another important finding was that the internal medicine physicians felt that they had not received adequate instruction on what occurs during an autopsy, nor could they answer technical procedural questions. Additionally, although internists were comfortable in obtaining consent for autopsies, they did not feel that they were able to receive sufficient guidance on how to request them. Internists also believed that pathologists experienced job satisfaction associated with performing an autopsy more than pathologists reported.[3]

These differing opinions were supported by the study of Chariot and his colleagues which showed that one of the causes of their reluctance to perform autopsies is the fear of contracting an infectious disease. Pathologists also indicated that they were not satisfied with the conditions in which they had to perform the procedure. Lastly, the pathologists in this study agreed that they were "satisfied" with the current decline of hospital autopsy rates in the conditions in which they are currently performed since they felt that autopsies were a low priority and were not stimulated by requesting physicians, who were usually not present during the procedure and who rarely expressed interest in the results.[7]

These different attitudes and perceptions were met with a genuine concern stated in some studies, which contemplated that the pathologists' skill in autopsies could decline if a critical number of cases were not provided to training pathologists, thereby making autopsy reports less useful to the physicians.[3] This same concern was expressed by pathologists who also stressed that the decline in autopsy rate will induce loss of expertise.[7]

Support for autopsy

Despite the previously discussed barriers to the performance of an autopsy, it is still widely believed that the autopsy is a useful medical tool. The study by Start et al., found that senior pathologists strongly agreed with statements relating to the importance of autopsies about workload, medical audit, and accreditation for residency training. Likewise, strong support was given for the attendance of clinicians at autopsy demonstrations and for the suggestion that material from medico-legal autopsies should be made available for teaching and research. On the other hand, the respondents expressed strong disagreement with the statements that advances in diagnostic techniques have diminished the role of autopsies, that performing autopsies does not further pathologists' education, that the cost of autopsies may not be justifiable within a limited budget, and that the autopsy should no longer be part of the pathology board examination. With regard to accreditation, most pathologists supported the

suggestion that accreditation for training should be linked to an adequate autopsy rate.[11]

Additionally, studies showed that both internal medicine and pathology resident groups strongly agreed that autopsies were important for their respective education, research, medical quality control, and public health.[2,3] Moreover, both groups disagreed that autopsies had no value and that they were useless if the findings were not treatable in life. As a final suggestion, internists stated that they would request autopsies more frequently if they had seen one.[3]

METHODOLOGY

Research design
This study employed a cross-sectional descriptive survey design to determine the attitudes and perceptions of Filipino clinicians and pathologists towards autopsy as a medical tool.

Research locale
This study was conducted online in two parts. First, the study survey was distributed nationwide among Filipino pathologists. Second, the study survey was administered among clinicians practicing in Central Visayas. The study was conducted from August 2022 to June 2023.

Sampling design
The first part of the study utilized a purposive sampling technique wherein the respondents of the study were members of the Philippine Society of Pathologists, Inc. (overall national society).

The second part of the study utilized a purposive sampling technique wherein the respondents of the study were members of the Philippine College of Physicians Central Visayas Chapter and the Philippine Pediatric Society Central Visayas Chapter.

Respondents of the study
The respondents of the study were members of the following societies: Philippine Society of Pathologists, Inc. (overall national society), the Philippine College of Physicians Central Visayas Chapter, and the Philippine Pediatric Society Central Visayas Chapter. Respondents of this study included resident doctors, fellows, and consultants who were affiliated with these specialty societies and practicing in the fields of Pathology, Internal Medicine, and Pediatrics, respectively.

Data gathering procedure
An ethical approval for the conduct of the study was secured from the Institutional Review Board of Perpetual Succour Hospital of Cebu. After securing the ethical approval, the researcher gathered pertinent data on the number of autopsies done in our institution, as well as the number of deaths. The researcher acquired consent from the specialty societies and thereafter coordinated with the Secretariat of each specialty society for the distribution of the survey questionnaire. An informed consent was sent online together with the questionnaire. The completed questionnaires were then retrieved and collated; after which, appropriate statistical analyses were applied.

Statement of confidentiality
The records of the study were collected and stored in a secure file accessible by the researchers only. Respondents were not identified by name, social security number, address or phone number. All research data were treated with the utmost confidentiality. In the event of any publication or presentation resulting from the research, no personally identifiable information would be shared.

Research instrument
The study tool that was used in this study was a comprehensive questionnaire adapted from the untitled questionnaire used by Start, et al. and the questionnaire entitled "Autopsy Research Questionnaire" used by Hooper et al. Correspondence from the authors of both questionnaires was secured before using the survey questionnaire. Before the administration of this questionnaire, a pilot study using 10 respondents was conducted using an online survey tool. Modifications were done at the end of the pilot study.

The questionnaire distributed to pathologists consisted of 3 sections with 27 question items in English. The first part of the questionnaire consisted of informed consent and 7 items to determine the profile of the respondent. The second part consisted of 10 questions that explored pathologists' different attitudes and perceptions towards autopsy. Each question in this portion required a response using a 5-point Likert scale (5 = strongly agree, 4 = somewhat agree, 3 = neither agree/disagree, 2 = somewhat disagree, and 1 = strongly disagree) to measure the respondent's degree of agreement to the statements regarding autopsy. The third part consisted of 10 questions that explored the pathologists' attitudes and perceptions towards autopsy. Each question required a response using a 5-point Likert scale (5 = strongly agree, 4 = somewhat agree, 3 = neither agree/disagree, 2 = somewhat disagree, and 1 = strongly disagree) to measure the respondent's degree of agreement with the statements regarding autopsy.

The questionnaire distributed to the Clinicians consisted of 2 sections with 27 question items in English language. Sections 1 and 2 of the clinicians' questionnaire contained identical questions to that of sections 1 and 3 of the pathologists' questionnaire, respectively.

Data analysis
For this study, frequency and percentage distribution were used to describe the demographic profile of the respondents, which include their gender, age, work, number of years of experience, religion, and number of autopsy cases observed or participated. In addition, mean, standard deviation, and relative frequency (in percentage) were utilized to describe respondents' attitudes and perceptions toward autopsy.

Meanwhile, ANOVA or analysis of variance was utilized to determine the difference in respondents' attitudes and perceptions towards autopsy when grouped according to their profile. SPSS Win (Statistical Package for the Social Sciences in Windows) and Microsoft Excel Analysis tool pack were used. An alpha level of 0.05 was used in the statistical treatments.

Scope and limitation of the study

The study was conducted in two parts. The first part was conducted among pathologists nationwide. The second part of the study was conducted among clinicians practicing in Central Visayas only. Physicians without internet access were not included in the study. The study is limited by the number of pathologist and clinician respondents who were able to complete the online survey conducted.

RESULTS

Part one – Survey among pathologists

Demographic profile

A total of 44 pathologists participated in this research and completed the online questionnaire. Table 1 presents the profile of the respondents of the study. The majority of the respondent pathologists (n = 44) belong to the 31-34 age group, are predominantly female, and are Roman Catholic. They are comprised mostly of consultant pathologists (56.8%) and resident physicians in training (40.9%). The majority of the respondents had 0 to 3 years of experience (34.1%), followed by those with 4 to 5 years of experience in their profession. Only 2.3% of the pathologist respondents stated that they were not able to observe or participate in any autopsy, while most of the respondents said that they were able to observe or participate in less than 5, 5-10, and more than 20 cases.

Pathologists' attitudes and perceptions toward autopsy

Table 2 presents the pathologists' attitudes and perceptions toward autopsy. The respondents agreed that performing autopsies will further their knowledge and experience in pathology (mean = 4.14). Moreover, while the pathologist respondents agreed that autopsies are an important part of a pathologist's work (mean = 4.16), the respondents agreed that performing autopsies can be excessively time-consuming, considering other demands on their time (mean = 3.53). The table shows that the highest mean score was recorded in item number (8) (mean = 4.30). This follows that most respondents strongly agreed that the material from medico-legal autopsies should be readily available for teaching and research purposes. Pathologists also agreed that medico-legal autopsies arising from post-operative deaths should be performed by an independent pathologist from another center (mean = 3.93) and that a hospital autopsy should be recommended on every tenth death in the hospital as part of the clinical audit.

On the other hand, the lowest mean is in item number (3) (mean = 2.00). This shows us that the respondents disagreed that pathology residents receive adequate training in performing medico-legal autopsies. In addition, respondents showed a neutral (mean = 2.84) response to the statement that pathology residents received adequate supervision and training in hospital autopsies even though most respondents agreed that a minimum number of autopsies per year should be one of the requirements for the accreditation of a pathology residency training program of an institution (mean = 2.64). Lastly, respondents neither agreed nor disagreed that the performance of a minimum number of autopsies should be a requirement for their society's Diplomate examination (mean = 2.91).

Pathologists' general attitudes and perceptions towards autopsy

Table 3 shows the general attitudes and perceptions of pathologists towards autopsies. Among all the statements, the lowest mean score was recorded for statement number 1 (mean of 2.36). This showed that pathologists disagreed that the number of autopsy cases in their institution is sufficient to meet departmental goals for knowledge, research, and education.

Table 1. Demographic profile of the respondents

Total n= 77		Clinicians, n=33		Pathologists, n=44	
	Profile	**F**	**%**	**F**	**%**
Gender	Female	26	78.8	24	54.5
	Male	7	21.2	20	45.5
Age	27 to 30 years old	18	51.72	6	13.6
	31 to 34 years old	7	20.69	19	43.2
	35 to 38 years old	4	13.79	6	13.6
	39 years old and above	4	13.79	13	29.5
Current work	Consultant	8	24.24	25	56.8
	Fellow	5	15.15	1	2.3
	Resident Physician	20	60.61	18	40.9
Number of years of experience	0 to 3 years	23	69.7	15	34.1
	4 to 5 years	4	12.1	13	29.5
	6 to 8years	1	3.03	6	13.6
	9 to 11 years	2	6.06	3	6.8
	12 years and above	3	9.09	7	15.9
Religion	Roman Catholic	30	90.9	39	88.6
	Christian	1	3.0	1	2.3
	Islam	1	3.0	1	2.3
	Protestant	1	3.0	3	6.8
Autopsy cases observed or participated	0 (none)	18	54.5	1	2.3
	Less than 5	14	42.4	12	27.3
	5 to 10	1	3.0	12	27.3
	11 to 20	0	0	7	15.9
	More than 20	0	0	12	27.3
Department	Internal Medicine	20	60.6	-	-
	Pediatrics	13	39.4	-	-

Table 2. Pathologists' attitudes and perceptions towards autopsy

	Statement	Mean	Sd	Interpretation
1	Autopsies are an important part of a pathologist's work.	4.16	1.10	Agree
2	Pathology residents receive adequate supervision and training in HOSPITAL autopsies.	2.84	1.33	Neutral
3	Pathology residents receive adequate training in performing MEDICO-LEGAL autopsies.	2.00	1.10	Disagree
4	A minimum number of autopsies per year should be one of the requirements for the accreditation of a pathology residency training program of an institution.	2.64	1.57	Agree
5	Performing autopsies will further my knowledge and experience in pathology.	4.14	0.93	Agree
6	I find that performing autopsies can be excessively time-consuming, considering other demands on my time.	3.53	1.20	Agree
7	Medico-legal autopsies arising from post-operative deaths should be performed by an independent pathologist from another center.	3.93	1.09	Agree
8	Material from medico-legal autopsies should be readily available for teaching and research purposes.	4.30	0.93	Strongly Agree
9	A hospital autopsy should be recommended on every tenth death in the hospital as part of the clinical audit.	3.45	1.42	Agree
10	The performance of a minimum number of autopsies should be a requirement for our society's (PSP) Diplomate examination.	2.91	1.61	Neutral

Table 3. Clinicians and pathologists' general attitudes and perceptions towards autopsy

	Items	N	Mean	Sd	Interpretation
1	The number of autopsy cases in my institution is sufficient to meet departmental goals for knowledge, research, and education.	Clinicians	1.85	0.97	Disagree
		Pathologist	2.36	1.37	Disagree
2	Autopsy results are available in timely fashion.	Clinicians	2.39	0.97	Disagree
		Pathologist	2.89	1.30	Neutral
3	Autopsies can provide relevant findings that could change future clinical practice.	Clinicians	4.58	0.71	Strongly Agree
		Pathologist	4.09	0.88	Agree
4	Currently, modern advances in diagnostic techniques have diminished the need to perform hospital autopsies.	Clinicians	3.09	0.95	Neutral
		Pathologist	3.73	1.44	Agree
5	The decision to request for an autopsy is affected by concerns about lawsuits due to unexpected findings from the procedure.	Clinicians	3.55	1.15	Agree
		Pathologist	4.09	1.02	Agree
6	Many family members refuse autopsy because of religious objections and/or superstitious beliefs.	Clinicians	3.52	1.35	Agree
		Pathologist	4.16	1.08	Agree
7	Whenever possible, clinicians should attend autopsies that they have requested on their patients.	Clinicians	4.00	1.17	Agree
		Pathologist	4.27	0.90	Strongly Agree
8	Patients with unknown diagnoses and unexpected deaths should always be subjected to autopsy.	Clinicians	4.36	0.90	Strongly Agree
		Pathologist	4.39	0.92	Strongly Agree
9	The autopsy will help the family go through the grieving process.	Clinicians	3.94	0.83	Agree
		Pathologist	3.30	1.11	Neutral
10	The cost of performing an autopsy is justified for training institutions with a limited budget.	Clinicians	3.70	0.88	Agree
		Pathologist	3.09	1.36	Neutral

The statement with the highest mean score—for the pathologists-was observed in statement number 8 (mean = 4.39). The study showed that the pathologist respondents strongly agreed that patients with unknown diagnoses and unexpected deaths should always be subjected to autopsy.

Table 4 shows the relative frequency of pathologists' responses when asked about their general attitudes and perceptions towards autopsy. Responses recorded as "Strongly Agree" and "Somewhat Agree" were added under the column "Agree", while responses noted under "Somewhat Disagree" and "Strongly Disagree" were added under the column "Disagree".

Regarding the perceived lack or decline in cases, 59% of pathologists disagreed that the number of autopsy cases in their institution is sufficient to meet departmental goals for knowledge, research and education.

When asked about the timeliness of autopsy results, the pathologists showed different responses among themselves with thirty-six percent (36%) agreeing that results are delayed while thirty-four percent (34%) felt that results are available on time. This accounted for their mean neutral response of 2.89.

Seventy-five percent (75%) of pathologists agreed that autopsies can provide relevant findings that could change future clinical practice. However, the study showed that the majority (62%) of pathologists agreed that modern advances in diagnostic techniques have diminished the need to perform hospital autopsies.

When asked about possible barriers to the performance of an autopsy, seventy-seven percent (77%) of pathologists agreed that the decision to request an autopsy is affected by concerns about possible lawsuits due to unexpected findings from the procedure. Moreover, eighty-four percent (84%) of pathologists agreed that many family members refuse autopsy because of religious objections and/or superstitious beliefs.

Regarding physician participation in the procedure, eighty-four percent (84%) of pathologists agreed that clinicians should attend the autopsies that they have requested on their patients. Moreover, the majority of pathologists (86%) agreed that patients with unknown diagnoses and unexpected deaths should always be subjected to autopsy.

The study showed that while a majority (41%) of pathologists–agreed that the autopsy will help the family go through the grieving process, thirty-nine percent (39%)

Table 4. Relative frequency of clinicians and pathologists' general attitudes and perceptions towards autopsy

	Statements	Physician Group	Responses (%)		
			Agree (SA+A)	Neutral (N)	Disagree (D+SD)
1	The number of autopsy cases in my institution is sufficient to meet departmental goals for knowledge, research, and education.	Clinicians	6	21	73
		Pathologists	20	20	59
2	Autopsy results are available in timely fashion.	Clinicians	6	45	48
		Pathologists	36	30	34
3	Autopsies can provide relevant findings that could change future clinical practice.	Clinicians	94	3	3
		Pathologists	75	20	5
4	Currently, modern advances in diagnostic techniques have diminished the need to perform hospital autopsies.	Clinicians	39	30	30
		Pathologists	62	9	30
5	The decision to request for an autopsy is affected by concerns about lawsuits due to unexpected findings from the procedure.	Clinicians	51	33	15
		Pathologists	77	11	9
6	Many family members refuse autopsy because of religious objections and/or superstitious beliefs.	Clinicians	60	15	24
		Pathologists	84	9	7
7	Whenever possible, clinicians should attend autopsies that they have requested on their patients.	Clinicians	72	12	15
		Pathologists	84	9	7
8	Patients with unknown diagnoses and unexpected deaths should always be subjected to autopsy.	Clinicians	85	9	6
		Pathologists	86	9	4
9	The autopsy will help the family go through the grieving process.	Clinicians	69	27	3
		Pathologists	41	39	21
10	The cost of performing an autopsy is justified for training institutions with a limited budget.	Clinicians	54	39	6
		Pathologists	34	34	32

Table 5. Difference in clinicians' attitudes and perceptions towards autopsy when grouped according to their profile

Variables	F	p	Interpretation
Gender	0.020	0.891	Not Significant
Age	0.356	0.567	Not Significant
Work	1.129	0.296	Not Significant
Years of Experience	0.990	0.413	Not Significant
Religion	0.611	0.627	Not Significant
Number of autopsy cases observed/participated	0.485	0.632	Not Significant
Department	1.200	0.305	Not Significant

Table 6. Difference between pathologists' attitudes and perceptions towards autopsy when grouped according to their profile

Variables	F	p	Interpretation
Gender	0.044	0.834	Not Significant
Age	2.824	0.101	Not Significant
Work	0.405	0.528	Not Significant
Years of Experience	1.427	0.240	Not Significant
Religion	1.163	0.288	Not Significant
Number of autopsy cases observed/participated	7.915	0.008	Significant

of the pathologists had a neutral response, while only three percent (3%) disagreed, thus accounting for their mean neutral response of 3.30.

The results of this study showed that only thirty-four percent (34%) of the pathologists perceived the cost of performing an autopsy to be justified for training institutions with a limited budget, while–another thirty-four percent (34%) neither agreed nor disagreed.

Difference in attitudes and perceptions towards autopsy when grouped according to profile

Table 6 shows the difference in the pathologists' attitudes and perceptions towards autopsy when grouped according to their gender, age, work, years of experience, religion, and number of autopsies observed/participated. The result revealed no significant differences in the respondents' attitudes and perceptions towards autopsy when grouped according to their gender, age, work, years of experience, and religion. However, a significant result ($p < 0.05$) was noted when associated with the number of autopsy cases observed/participated. This implies that the pathologists' experience in practicing autopsy is a factor that affects their attitudes and perceptions towards it.

Part two – Survey among clinicians

Demographic profile

A total of 33 clinicians from Central Visayas participated in this research. Table 1 presents the profile of the respondents of the study. The majority of the respondent clinicians (n = 33) belong to the 27-30 age group, are predominantly females, and are Roman Catholic. They are comprised mostly of resident physicians in training (60.61%) followed by consultants (24.24%) and practicing in the field of Internal Medicine (60.6%). The majority of

the respondents (69.7%) had experience of 0 to 3 years in their profession. Most of the clinicians were not able to observe or participate in any autopsies at all (54.5%).-

Clinician's general attitudes and perceptions towards autopsy

Table 3 shows the general attitudes and perceptions of clinicians towards autopsy. Among all the statements, the lowest mean score for clinicians was recorded for statement number 1 (mean of 1.85). Like the pathologist group, clinicians disagreed that the number of autopsy cases in their institution is sufficient to meet departmental goals for knowledge, research, and education.

The statement with the highest mean score for the clinicians was noted in statement number 3 (mean = 4.58), which implied that clinicians strongly agreed that autopsies could provide relevant findings that could change future clinical practice.

Table 4 shows the relative frequency of responses from clinicians when asked about their general attitudes and perceptions toward autopsy. Responses recorded as "Strongly Agree" and "Somewhat Agree" were added under the column "Agree", while responses noted under "Somewhat Disagree" and "Strongly Disagree" were added under the column "Disagree".

Seventy-three percent (73%) of clinicians disagreed that the number of autopsy cases in their institution is sufficient to meet departmental goals for knowledge, research and education. This shows congruence with that of the pathologists' perception on the same topic. When asked about the timeliness of autopsy results, forty-eight percent (48%) of clinicians disagreed that autopsy results are available in timely fashion.

Almost all the clinicians (94%) of the study agreed that autopsies can provide relevant findings that could change future clinical practice. The clinicians perceived this more strongly than the pathologists with mean responses of 4.58 and 4.09, respectively.

When asked about the impact of modern advances in diagnostic techniques, thirty-nine percent (39%) of the clinicians agreed that these have diminished the need to perform hospital autopsies. In addition, thirty percent (30%) of the clinicians had a neutral response, while thirty percent (30%) disagreed, thus accounting for their mean neutral response of 3.09.

Fifty-one percent (51%) of clinicians agreed that the decision to request for an autopsy is affected by concerns about possible lawsuits due to unexpected findings from the procedure. Moreover, sixty percent (60%) of clinicians stated that many family members refuse autopsy because of religious objections and/or superstitious beliefs.

Regarding physician participation in the procedure, seventy-two percent (72%) of clinicians stated that clinicians should attend autopsies that they have requested on their patients. Moreover, majority (85%) of clinicians agreed that patients with unknown diagnoses and unexpected death should always be subjected to autopsy.

The study showed that majority of clinicians agreed that the autopsy will help the family go through the grieving process. More clinicians (69%) perceive this than the pathologists (41%).

The results of this study showed that clinicians (54%) perceived the cost of performing an autopsy to be justified for training institutions with a limited budget, while thirty-nine percent (39%) had a neutral stance.

Difference in attitudes and perceptions towards autopsy when grouped according to profile

Table 5 depicts the difference in the clinicians' attitudes and perceptions towards autopsy when grouped according to gender, age, work, years of experience, religion, number of autopsies observed, and department. The result revealed no significant differences in the clinicians' attitudes and perceptions towards autopsy when grouped according to their demographic profile since the computed p values are greater than alpha level 0.05. This entails that their profile is not a factor that affects their attitudes and perceptions toward autopsy.

Statistical difference between two groups

The researchers also compared the attitudes and perceptions towards autopsy of clinicians and pathologist respondents through the Independent T-test. The result revealed a t-value of 0.615 with a computed p-value of 0.541 which is greater than 0.05; hence, there was no significant statistical difference in the attitudes and perceptions of the two groups.

DISCUSSION

Globally, autopsy rates have been observed to be steadily declining for the past years. Although there are no official autopsy registries in our country, the calculated autopsy rate in five years of 0.08% for our institution supports this observation. The autopsy rate considered data from 2015 until 2019 in order to reduce possible effects that could have been brought on by the start of the COVID-19 pandemic in 2020.

This study shows that the lack of cases is felt by both groups of respondents, who perceived that the number of autopsy cases in their institutions was insufficient to meet departmental goals for knowledge, research, and education. This is particularly important for pathologists, wherein the autopsy is regarded as an important part of their work since they believe that performing it will further their knowledge and experience in pathology. In the Philippine setting, a minimum number of autopsy cases is required for the accreditation of the residency training program of an institution. This administrative measure is in fact supported by the respondents of this study, who also advocated that a hospital autopsy be performed for every tenth death in the hospital as part of the clinical audit.

The deficiency in the number of autopsy cases in our institutions perhaps contributes to the pathologists' lack of confidence in the adequacy of supervision and training that residents receive in performing hospital and medico-legal autopsies. In line with this perceived inadequacy in training, the pathologists of this study neither agreed

nor disagreed that applicants who are about to take the Diplomate Board Exam should require a minimum number of autopsies. This perhaps arises from the hesitancy about whether sufficient knowledge could have been gained during residency training before the examination.

The results of this study showed that while pathologists understood the importance and necessity of autopsy in their profession, they also demonstrated several negative perceptions towards it. Most of them felt that performing autopsies was excessively time-consuming, considering other demands on their time. They also felt that the cost of performing autopsies was not reasonable for those with a limited budget. More importantly, the pathologists believed more strongly than the clinicians that modern advances in diagnostic techniques have diminished the need to perform hospital autopsies. This in line with findings from the study by Maeda et al., wherein physicians believed that the cause of death can be determined by other forms of investigation such as blood tests.[10]

The responses of the clinicians in this study also showed that they exhibited some negative perceptions toward autopsy. Together with the pathologists, clinicians agreed that their decision to request for an autopsy is affected by litigation concerns due to unexpected findings from the procedure. They also perceived that family members refuse autopsy due to religious and/or superstitious beliefs. Lastly, in contrast to the pathologists' neutral response, the majority of the clinicians felt that autopsy results were delayed and unavailable on time.

Despite all the negative perceptions exhibited by the respondents, the results of this study also revealed several attitudes and perceptions that supported the performance of the autopsy.

Clinicians believed more strongly than pathologists that autopsies provided relevant findings that could change future clinical practice and that the autopsy would help the family cope with their grief. The respondents also supported that patients with unknown diagnoses and unexpected deaths should always be subjected to autopsy. Meanwhile, pathologists believed more strongly than clinicians that the requesting physician should attend the autopsies of their patients. This is in line with the findings by Start et al., which emphasized that there should be increased participation by clinicians.

The results of this study determined that the clinicians' demographic profile is not a factor that could affect their attitudes and perceptions toward autopsy. Moreover, the number of years of experience also did not appear to be a significant factor in the attitudes and perceptions of both pathologists and clinicians toward autopsy.

On the other hand, this study showed that the number of observed and/or performed autopsy cases was a factor that affected the pathologists' attitudes and perceptions toward autopsy. The results of the study demonstrated that the majority of the clinicians were not able to observe nor participate in any autopsy case, while almost all the pathologists were able to perform or witness at least 1 or more. This implies that actual participation in the autopsy procedure is the main factor that produced an impact on the physicians' perceptions and attitudes towards autopsy. However, determining the presence or absence of a relationship between the number of autopsy cases observed with the attitudes and perceptions of the pathologists could not be done in this study due to the nominal character of the data that was collected in the demographic profile.

CONCLUSION AND RECOMMENDATIONS

In general, there is recognition of the autopsy's usefulness as a medical tool among the pathologists and clinicians surveyed. However, the lack of cases referred for autopsy remains a challenge undermining the benefits derived from its performance. There are also attitudes and perceptions among pathologists that performance of the autopsy may be too time-consuming and costly in a limited resource setting. Clinicians surveyed acknowledged that religious beliefs and concerns about litigation affected their decision to refer cases for autopsy.

The following recommendations are made based on the findings of this study: (1) to generate more robust data, increasing the number of respondents to the online survey, expanding the scope geographically, as well as inviting practitioners beyond internists and pediatricians may be considered; (2) there may be a need to provide information and orientation to clinicians themselves on the value of the autopsy as a medical tool to improve referral of cases, as well as providing them with communication strategies to address concerns or questions on the autopsy from family members of the deceased to improve consent taking.

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STATEMENT OF AUTHORSHIP

Both authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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OPEN ACCESS – ORIGINAL ARTICLE

Correlation of Clinicopathologic Features of Filipino Primary Breast Cancer Patients with HER2 Subgroups Classified according to the ASCO/CAP 2018 Breast Cancer HER2 Testing Guidelines

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ABSTRACT

Background. Guidelines for testing human epidermal growth factor receptor 2 (HER2) in breast cancer using fluorescence in situ hybridization (FISH) were released in 2018. These guidelines were jointly developed by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) to achieve a clearer designation of breast cancer HER2 status. Clinical correlation with other factors was also considered appropriate, especially for those cases classified under ISH groups 2, 3, and 4.

Objective. In this study, we examined clinicopathologic features among Filipino breast cancer patients whose HER2 status was reclassified based on the 2018 ASCO/CAP guidelines.

Methodology. One hundred and thirty-two (132) breast cancer cases with immunohistochemistry (IHC) equivocal results in the Medical City were enrolled from January 2017 up to December 2020. HER2 FISH results classified under groups 2, 3, and 4 were then re-evaluated for HER2-IHC status in accordance with the 2018 ASCO/CAP guidelines. The relationship between clinicopathologic features and HER2 status was analyzed using the Fisher exact test.

Results. Significant differences were found in histologic type, nuclear pleomorphism, mitotic rate, progesterone receptor (PR) status, and regional lymph node involvement among the reclassified ISH groups. In the conv+ group, the tumor cells did not involve the regional lymph nodes as compared to group 5, where the tumor cells were involved. The conv- group had a higher grade for nuclear pleomorphism, mitotic count, and overall Nottingham Histologic Grade than group 5. There was a significant association between progesterone receptors among the conv- group and group 1.

Conclusion. Filipino breast cancer cases whose HER2 status was reclassified to negative following the 2018 ASCO/CAP guidelines had statistically different clinicopathologic features from those classified as group 5.

Key words: breast cancer, ASCO/CAP, HER2, fluorescence in situ hybridization, immunohistochemistry

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INTRODUCTION

Breast cancer is the most common cancer in women and also one of the leading causes of cancer-related deaths worldwide.[1,2] Although Western countries generally have higher incidence rates compared to Asian countries, the Philippines is an exception, with a high incidence rate of 17.7% among Filipino women.[3] Despite being the most vulnerable population in Southeast Asia, there are only a few published studies on breast cancer in the Philippines, most of which are about risk factors.[4-6] There are limited data available on the clinicopathologic details of breast cancer in the country.[7]

Breast cancer is a disease that has different subtypes and is characterized by genetic and clinical heterogeneity.[8] One study was conducted in the Philippines to identify the gene expression profile of breast cancers in different molecular subgroups, such as luminal A, luminal B, HER2, basal, and normal breast-like. Among 36 female participants, luminal A was found to be the most common profile for Filipino women, accounting for 52.8% of cases. The HER2 profile, which is associated with aggressive disease

and poor survival outcomes,[9] was found to be the third most common subgroup, accounting for 8.3% of cases.[10] The Department of Health (DOH) Breast Cancer Control Program has reported a HER2-positivity rate of 23.17% nationwide, with approximately 80% of cases diagnosed early.[11]

HER2 IHC and/or ISH are commonly used in clinical practice to determine the responsiveness to therapies that target the HER2 protein. Guidelines such as those published by the ASCO/CAP are paramount for the performance and accuracy of HER2 testing. However, on the 2007 and 2013 ASCO/CAP guidelines, while a HER2-positive or negative result is straightforward, the inclusion of "equivocal" results in ISH has been a dilemma in clinical decision-making. On the updated 2018 guidelines, the ASCO/CAP HER2 testing Expert Panel overcame this by emphasizing the use of concomitant IHC to guide the interpretation of those previously labeled as equivocal.[12] The recommendations made in the 2018 guidelines were reaffirmed in 2023.[13]

Five categories (ISH groups 1, 2, 3, 4, & 5) have been established based on the HER2/CEP17 ratio and average HER2 copy number. Group 1 is HER2 positive, while group 5 is HER2 negative.[12,13] Cases in group 1 show a higher grade, more frequent occurrence of negative estrogen and progesterone receptor results, and a higher Ki-67 index than group 5.[14] HER2 ISH results that fall under groups 2, 3, and 4 are reported to be approximately only 5% of a large-scale population.[1] Due to the rarity of cases, data regarding groups 2, 3, and 4 are still considered inadequate, especially after reclassifying to either HER2 positive or negative. Limited publications have also been made about the association of clinicopathologic features of groups 2 to 4. And none have been published yet with Filipino breast cancer patients as their population.

The main objective of this study is to compare the clinicopathologic features of converted HER2 status among breast cancer patients with those classified as group 1 and group 5 according to the ASCO/CAP 2018 breast cancer HER-2 testing guidelines. Clinical correlation with other factors is crucial for better treatment management of any patient.

METHODOLOGY

Population and sample

This retrospective study is composed of all patients of either sex in all age groups, with a histopathologic diagnosis of primary invasive breast carcinoma and subsequently underwent IHC testing for ER, PR, and HER2, and FISH testing for HER2 between January 2017 and December 2020 at The Medical City.

Inclusion and exclusion criteria

Included are those with surgically resected specimens from definitive breast cancer surgeries: core needle biopsy with subsequent definitive surgery; excision biopsy with subsequent definitive surgery; total mastectomy with either sentinel lymph node biopsy with or without axillary lymph node dissection; modified radical mastectomy; and partial mastectomy with sentinel lymph node biopsy and intraoperative radiotherapy. Excluded in this study are those who only underwent core needle breast biopsy with no subsequent definitive surgery.

The minimum number of patients is determined based on the assumed proportion of GROUP 5 patients among primary breast cancer patients to be approximately 60% of the preliminary census acquired. The calculation is detailed below:

$$n = \frac{N * \frac{(Z_{\alpha/2})^2 * p(1-p)}{E^2}}{\frac{(Z_{\alpha/2})^2 * p(1-p)}{E^2} + N - 1}$$

where $Z_{\alpha/2}$ is the critical value of the normal distribution at α/2 (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), E is the margin of error, p is the anticipated sample proportion, and N is the population size. Assuming N = 10,000, p = 60%, α = 0.05 and E = 7%, the recommended minimum sample size was 185.

Data collection

Histopathologic and IHC results were collected from the Laboratory Information System (LIS) at the Anatomic Pathology Department, while the HER2 FISH results were collected from the Institute of Personalized Molecular Medicine (IPMM). Clinical data of the patients was collected through the computerized health care information system ORION, Medical Information Documentation and Access System (MIDAS), and Strategic Hospital and Medical Automation on Net (SHAMAN) of The Medical City. Data collection forms were used (Table 1) for data organization. Patients' results included in this study were anonymized and assigned a unique numeric identifier. Investigators involved in data analysis were blinded to patient identity. Accrued data was strictly limited to the primary investigator.

Grouping was based on the HER2/CEP17 ratio and average HER2 copy number (Figure 1). A concomitant IHC review was done for those classified as groups 2, 3, and 4, with a recounting of the ISH test by a second reviewer if IHC 2+, as stated by the updated 2018 ASCO/CAP recommendations (Figures 2 to 4).

- Group 1 – Tumors with HER2/CEP17 ratio ≥2.0 and average HER2 copy number ≥4.0 signals per cell and a final status designation of HER2 positive.
- Conv+ group – Tumors with:
  - HER2/CEP17 ratio ≥2.0 and average HER2 copy number <4.0 signals per cell (group 2), concurrent IHC 3+ and a final status designation of HER2 positive;
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥6.0 signals per cell (group 3), concurrent IHC 2+ or 3+ and a final status designation of HER2 positive; and
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥4.0 and <6.0 signals per cell (group 4), concurrent IHC 3+ and a final status designation of HER2 positive.

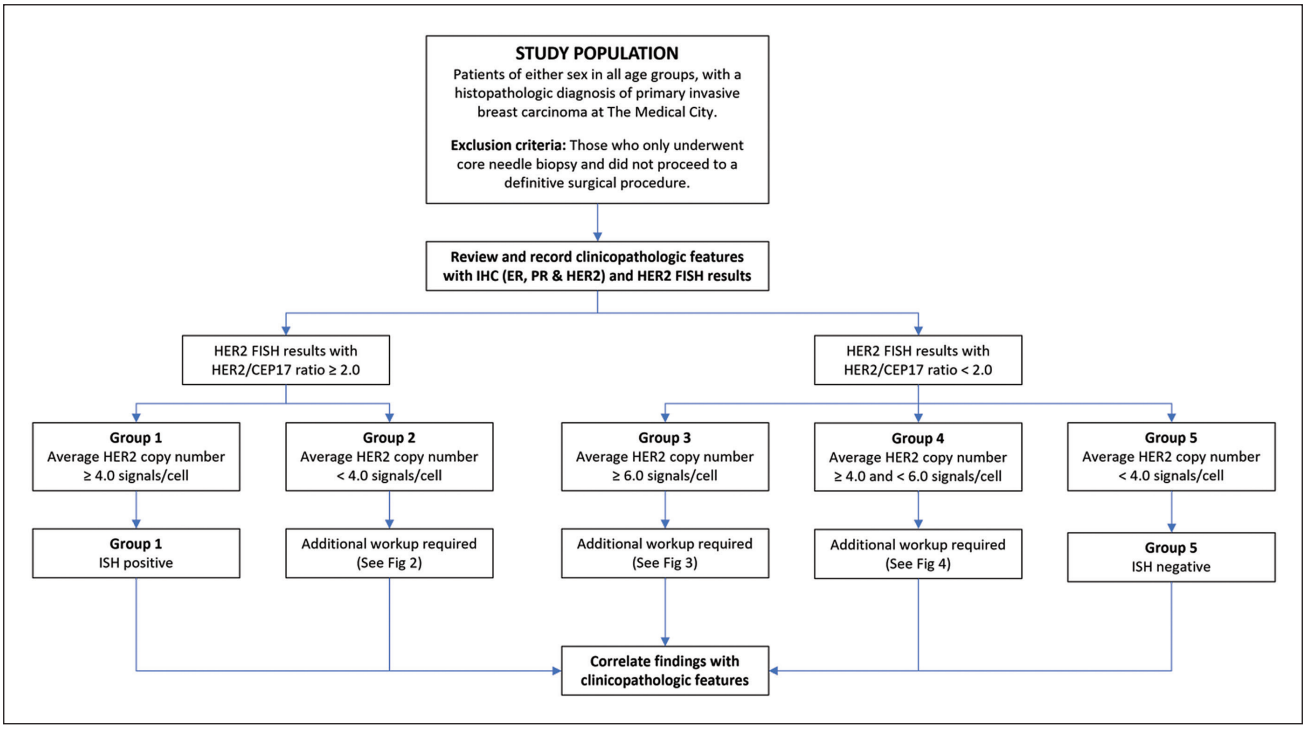

Figure 1. Diagrammatic workflow.

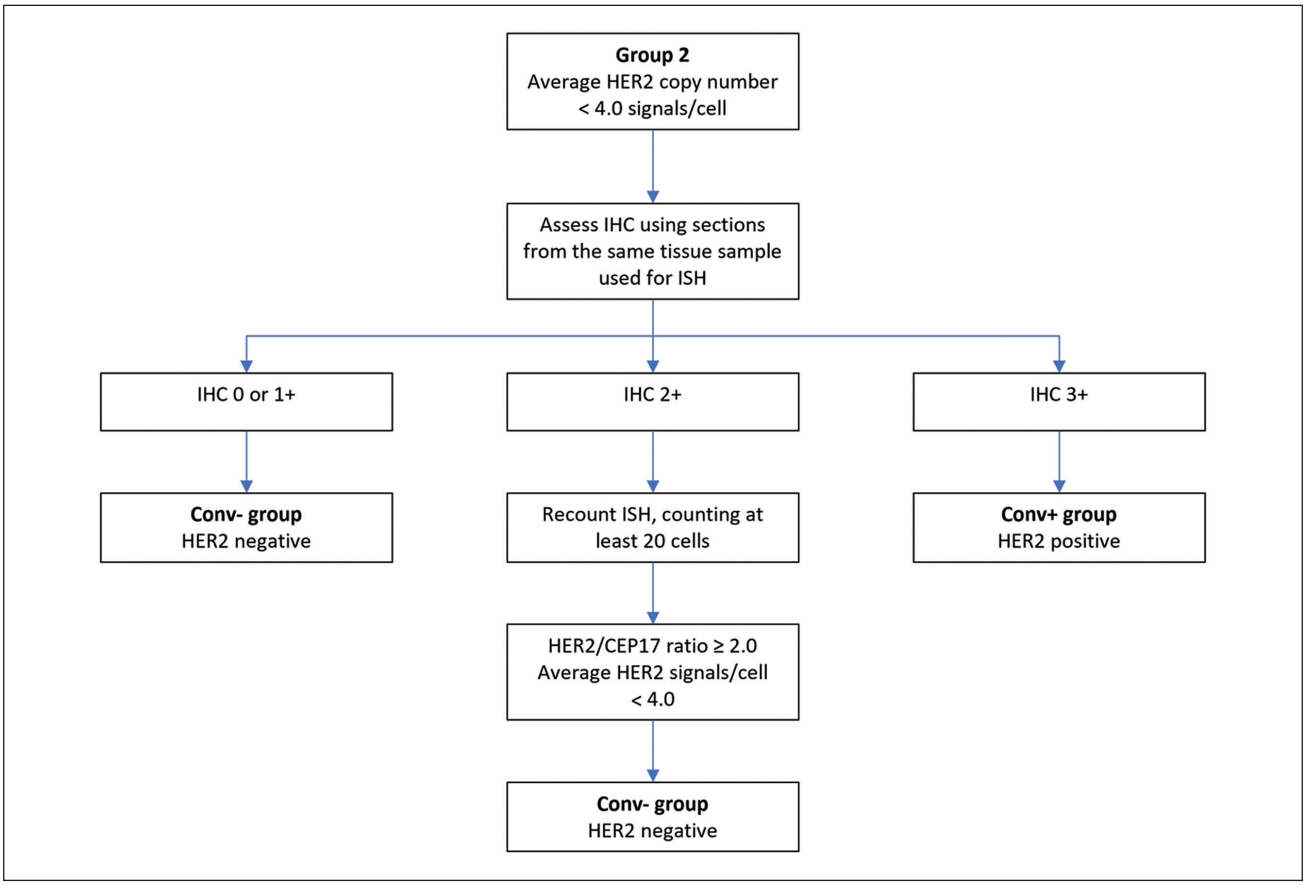

Figure 2. Additional workup to cases classified initially as group 2.

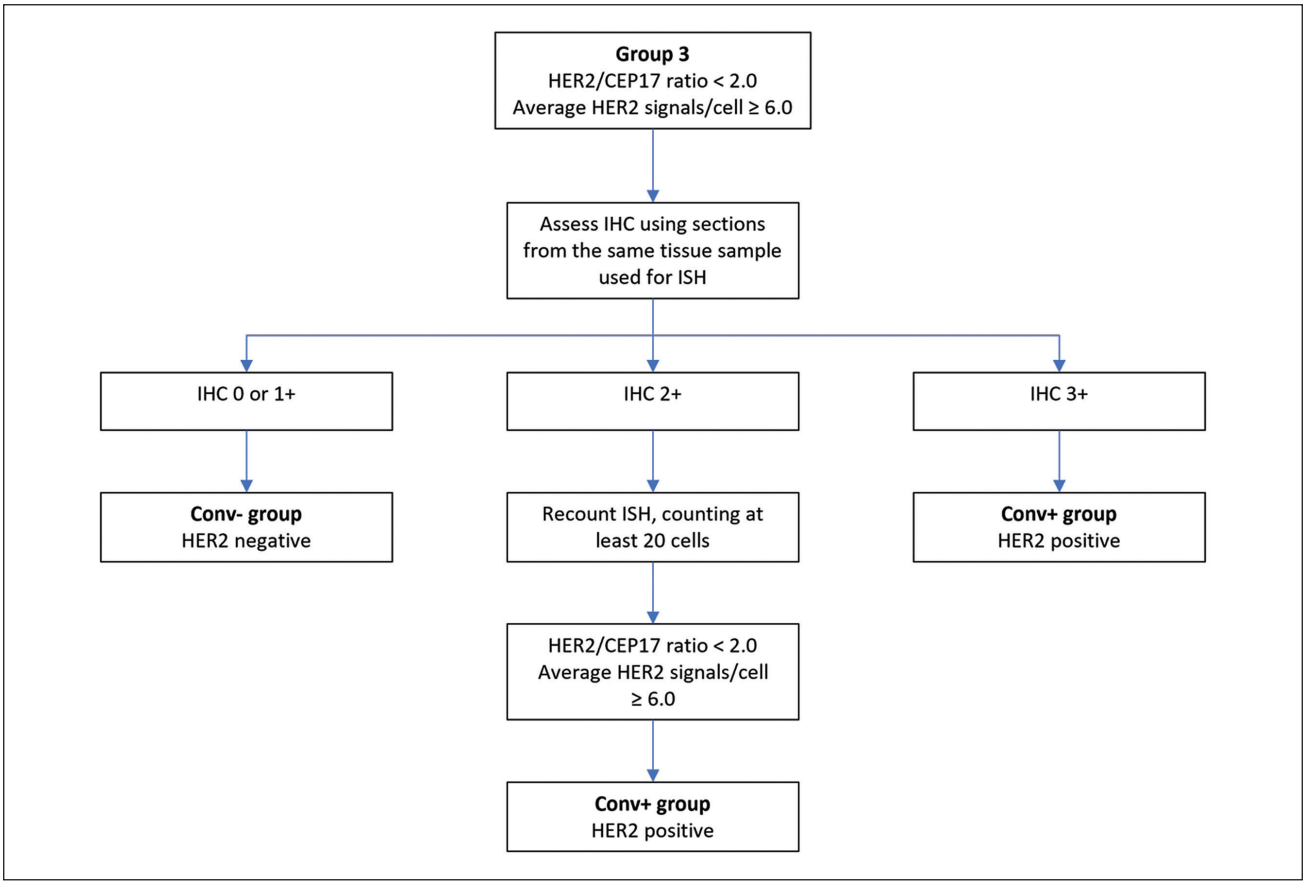

Figure 3. Additional workup to cases classified initially as group 3.

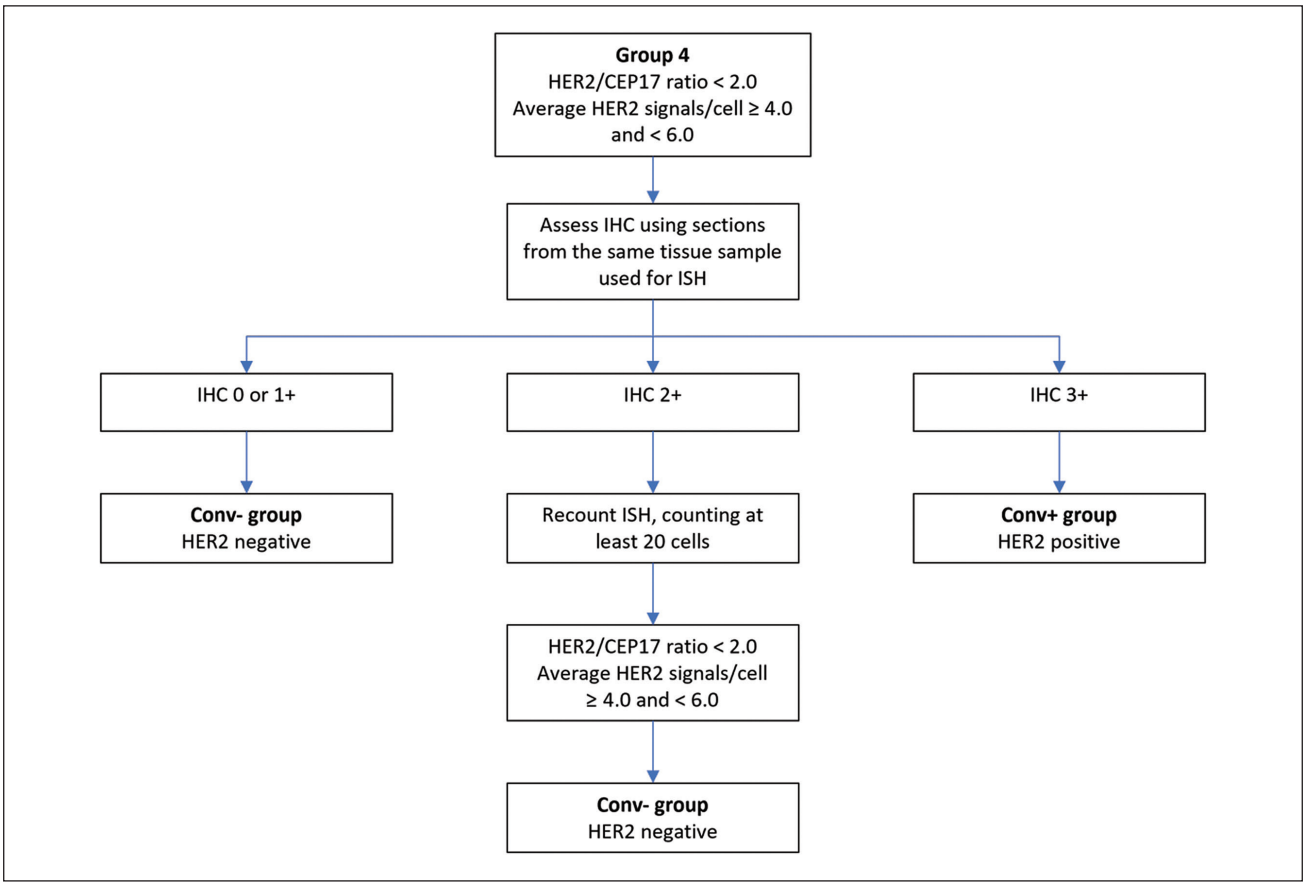

Figure 4. Additional workup to cases classified initially as group 4.

- Conv- group – Tumors with:
  - HER2/CEP17 ratio ≥2.0 and average HER2 copy number <4.0 signals per cell (group 2), concurrent IHC 0, 1+, or 2+ and a final status designation of HER2 negative;
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥6.0 signals per cell (group 3), concurrent IHC 0 or 1+ and a final status designation of HER2 negative; and
  - HER2/CEP17 ratio <2.0 and average HER2 copy number ≥4.0 and <6.0 signals per cell (group 4), concurrent IHC 0, 1+, or 2+, and a final status designation of HER2 negative.
- Group 5 – Tumors with HER2/CEP17 ratio <2.0 and average HER2 copy number <4.0 signals per cell and a final status designation of HER2 negative.

HER2 IHC status reading was done at the Anatomic Pathology section of The Medical City. The recounting of ISH was done at the Institute of Personalized Molecular Medicine (IPMM) of the same institution.

Data analysis

Demographic characteristics and clinical features of patients were collected using the data collection form and summarized using frequencies and percentages. Contingency tables were generated to examine the relationship between clinicopathologic features and HER2 status. The clinicopathologic features include the following: age, sex, histologic type, histologic grade, presence or absence of ductal carcinoma in situ (DCIS), involvement of skin, nipple and/or skeletal muscle, regional lymph node involvement, lymphovascular space invasion, pathologic stage (pT and pN), and breast biomarkers (ER and PR). Associations between categorical variables were tested using the Fisher exact test. All tests were performed at a 5% level of significance.

RESULTS

Between January 2017 and December 2020, 226 patients underwent HER2 FISH testing at The Medical City. After applying inclusion and exclusion criteria, 132 patients ranging from 25 to 86 years of age were selected. Tables 1, 2 and 3 summarize the clinicopathologic characteristics of the breast cancer patients included in the study. Based on the 2018 ASCO/CAP update and reclassification used in this study, there were 28 group 1 cases, 4 conv+ cases, 19 conv- cases, and 86 group 5 cases. Most patients were over 50 years old (64.2%), and almost all were female (99.3%). The most common histological type was invasive carcinoma of no special type (ductal, NOS), with 101 cases (73.7%) and a Nottingham Histologic Grade of 2 (56.2%).

Significant differences were found in histologic type, nuclear pleomorphism, mitotic rate, PR, and regional lymph node involvement. Regarding conv+ samples, no tumor cells were present in the regional lymph nodes, while group 5 showed tumor cell involvement ($p = 0.048$). Conversely, conv- samples showed a significant difference in histologic type ($p = 0.001$), nuclear pleomorphism ($p = 0.025$), mitotic rate (p=0.010), and overall Nottingham Histologic Grade ($p = 0.005$) compared to group 5. The conv- group was more likely to have invasive ductal carcinoma, NOS, while group 5 was associated with invasive carcinoma with lobular and other features (e.g., micropapillary). Group 5 had a lower grade of nuclear pleomorphism (nuclear grade 1) compared to an intermediate grade (nuclear grade 2) in the conv- group. Conv- (score of 2) had a higher mitotic count than group 5 (score of 1). Finally, the overall Nottingham histologic grade was higher for conv- (grade 2) than for group 5 (grade 1).

There was a significant association between progesterone receptors in Group 1 and conv- ($p = 0.003$), with the former showing mostly negative results and the latter showing positive results.

Twenty-three FISH samples were categorized into groups 3 (4.35%) and 4 (95.65%), as shown in Table 4. Following this, the IHC staining degree of the samples was re-evaluated, leading to the classification of the samples as either conv+ or conv-. One sample under group 3 was reclassified to conv-. Out of the remaining twenty-two group 4 samples, four were reclassified to the conv+ group, while the remaining sixteen were classified as conv-.

DISCUSSION

The study reclassified samples in ISH groups 3 and 4 as either ISH-HER2 positive or negative and correlated clinicopathologic features with groups 1 and 5.

Table 1. Comparison of Clinicopathologic Features Across Classified Groups (Group 1, Conv+, Conv-, and Group 5) Based on 2018 ASCO Guidelines

	All (137)	Group1 (28)	Conv+ group (4)	Conv- group (19)	Group 5 (86)	$p^{\#}$			
						Conv+ vs Group 1	Conv+ vs Group 5	Conv- vs Group 1	Conv- vs Group 5
Age, years									
≤50	49 (35.8)	10 (35.7)	2 (50.0)	8 (42.1)	29 (33.7)	0.485	0.427	0.444	0.330
>50	88 (64.2)	18 (64.3)	2 (50.0)	11 (57.9)	57 (66.3)				
Sex									
Female	136 (99.3)	28 (100.0)	4 (100.0)	19 (100.0)	85 (98.8)	1.000	0.956	1.000	0.819
Male	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)				
Surgical procedure done									
Partial mastectomy with axillary contents	15 (10.9)	4 (14.3)	0 (0.0)	4 (21.1)	7 (8.1)				
Partial mastectomy without axillary contents	9 (6.6)	2 (7.1)	1 (25.0)	2 (10.5)	4 (4.7)	0.404	0.354	0.515	**0.025**
Total mastectomy with axillary contents	56 (40.9)	10 (35.7)	2 (50.0)	3 (15.8)	41 (47.7)				
Modified radical mastectomy	57 (41.6)	12 (42.9)	1 (25.0)	10 (52.6)	34 (39.5)				

#Fisher-exact test

Table 2. Comparison of Clinicopathologic Features Across Classified Groups (Group 1, Conv+, Conv-, and Group 5) Based on 2018 ASCO Guidelines *(continued)*

	All (137)	Group1 (28)	Conv+ group (4)	Conv- group (19)	Group 5 (86)	$p^{\#}$			
						Conv+ vs Group 1	Conv+ vs Group 5	Conv- vs Group 1	Conv- vs Group 5
Histologic type									
Ductal, NOS	101 (73.7)	26 (92.9)	4 (100.0)	19 (100.0)	52 (60.5)				
Invasive CA with lobular features/ lobular CA	15 (10.9)	2 (7.1)	0 (0.0)	0 (0.0)	13 (15.1)	1.000	0.608	0.508	**0.001**
Invasive CA with other features/ non-ductal	21 (15.3)	0 (0.0)	0 (0.0)	0 (0.0)	21 (24.4)				
Histologic grade (Nottingham histologic score)									
Glandular differentiation									
1	14 (10.2)	1 (3.6)	0 (0.0)	2 (10.5)	11 (12.8)	0.606	0.746	0.319	0.585
2	96 (70.1)	20 (71.4)	4 (100.0)	15 (78.9)	57 (66.3)				
3	27 (19.7)	7 (25.0)	0 (0.0)	2 (10.5)	18 (20.9)				
Nuclear pleomorphism									
1	22 (16.1)	3 (10.7)	1 (25.0)	0 (0.0)	18 (20.9)	0.540	0.999	0.382	**0.025**
2	90 (65.7)	19 (67.9)	3 (75.0)	13 (68.4)	55 (64.0)				
3	25 (18.2)	6 (21.4)	0 (0.0)	6 (31.6)	13 (15.1)				
Mitotic rate									
1	63 (46.0)	10 (35.7)	1 (25.0)	4 (21.1)	48 (55.8)	0.999	0.327	0.366	**0.010**
2	72 (52.6)	16 (57.1)	3 (75.0)	15 (78.9)	38 (44.2)				
3	2 (1.5)	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)				
Overall grade									
1	51 (37.2)	7 (25.0)	1 (25.0)	2 (10.5)	41 (47.7)	1.000	0.696	0.424	**0.005**
2	77 (56.2)	18 (64.3)	3 (75.0)	16 (84.2)	40 (46.5)				
3	9 (6.6)	3 (10.7)	0 (0.0)	1 (5.3)	5 (5.8)				
Tumor focality									
Single focus	123 (89.8)	27 (96.4)	4 (100.0)	18 (94.7)	74 (86.0)	0.875	0.558	0.650	0.270
Multiple foci	14 (10.2)	1 (3.6)	0 (0.0)	1 (5.3)	12 (14.0)				
Ductal carcinoma in-situ									
Not identified	51 (37.2)	7 (25.0)	3 (75.0)	6 (31.6)	35 (40.7)	0.181	0.516	0.684	0.671
Present: negative for EIC	60 (43.8)	13 (46.4)	1 (25.0)	10 (52.6)	36 (41.9)				
Present: positive for EIC	26 (19.0)	8 (28.6)	0 (0.0)	3 (15.8)	15 (17.4)				
DCIS architectural patterns									
Comedo	56 (40.9)	13 (46.4)	1 (25.0)	9 (47.4)	33 (38.4)				
Cribriform	68 (49.6)	18 (64.3)	1 (25.0)	11 (57.9)	38 (44.2)	0.999	0.999	0.883	0.966
Micropapillary/ Papillary	19 (13.9)	4 (14.3)	0 (0.0)	4 (21.1)	11 (12.8)				
Solid	62 (45.3)	17 (60.7)	1 (25.0)	9 (47.4)	35 (40.7)				
DCIS nuclear grade									
I	9 (6.6)	1 (3.6)	0 (0.0)	3 (15.8)	5 (5.8)	0.999	0.999	0.308	0.333
II	71 (51.8)	18 (64.3)	1 (25.0)	9 (47.4)	43 (50.0)				
III	6 (4.4)	2 (7.1)	0 (0.0)	1 (5.3)	3 (3.5)				
Skin, nipple and/or skeletal muscle involvement									
Not identified	125 (91.2)	26 (92.9)	3 (75.0)	15 (78.9)	81 (94.2)	0.339	0.245	0.169	0.054
Present	12 (8.8)	2 (7.1)	1 (25.0)	4 (21.1)	5 (5.8)				
Regional lymph node involvement									
No lymph nodes submitted or found	6 (4.4)	1 (3.6)	1 (25.0)	1 (5.3)	3 (3.5)	0.084	**0.048**	0.609	0.744
Uninvolved by tumor cells	69 (50.4)	16 (57.1)	3 (75.0)	8 (42.1)	42 (48.8)				
Involved by tumor cells	62 (45.3)	11 (39.3)	0 (0.0)	10 (52.6)	41 (47.7)				
Lymphovascular space invasion									
Not identified	59 (43.1)	13 (46.4)	1 (25.0)	10 (52.6)	35 (40.7)	0.402	0.473	0.452	0.243
Present	78 (56.9)	15 (53.6)	3 (75.0)	9 (47.4)	51 (59.3)				

$^{\#}$Fisher-exact test

Most of the group 4 samples were still classified as HER2 negative status (conv-) (81.82%) than HER2 positive status (conv+) (18.18%), which is consistent with the findings of a similar study by Yang et al. The study included samples with complete records of both IHC and FISH tests between January 2010 and August 2018 at West China Hospital. Of the 401 samples classified under group 4, 94.3% were HER2 negative, and 5.7% were HER2 positive.[14]

The clinicopathologic features of the conv- group are significantly different from those classified as group 5. The present study found that the histologic type, nuclear pleomorphism, mitotic rate, and overall Nottingham Histologic Grade were statistically different from group 5. Other studies by Woo et al.[15] and Yang et al.[14] support these findings, with the conv- group showing more aggressive clinicopathologic features. Woo et al. reported that their samples categorized as HER2 ISH-negative tumors in ISH group 4 showed significant associations with high T stage, lymph node metastasis, high histologic grade, lymphovascular invasion, high Ki-67 proliferation index, equivocal HER2 IHC, and CEP17 copy number gain compared to those in ISH group 5.[15] Yang et al., also reported that their conv- group had a higher histological grade, histological subtype, and Ki67 index than group 5.[14] These findings suggest that HER2-converted negative tumors, especially those classified from ISH group 4, are biologically different from those in group 5, which may be partly explained by a CEP17 copy number gain that reflects chromosomal instability.[16,17]

Table 3. Comparison of Clinicopathologic Features Across Classified Groups (Group 1, Conv+, Conv-, and Group 5) Based on 2018 ASCO Guidelines *(continued)*

	All (137)	Group1 (28)	Conv+ group (4)	Conv- group (19)	Group 5 (86)	p#			
						Conv+ vs Group 1	Conv+ vs Group 5	Conv- vs Group 1	Conv- vs Group 5
Primary tumor (pT)									
pT1	56 (40.9)	8 (28.6)	3 (75.0)	8 (42.1)	37 (43.0)				
pT2	63 (46.0)	18 (64.3)	1 (25.0)	6 (31.6)	38 (44.2)	0.230	0.774	0.067	0.234
PT3	14 (10.2)	2 (7.1)	0 (0.0)	3 (15.8)	9 (10.5)				
PT4	4 (2.9)	0 (0.0)	0 (0.0)	2 (10.5)	2 (2.3)				
Regional lymph nodes (pN)									
pN0	73 (55.3)	17 (60.7)	3 (100.0)	8 (47.1)	45 (53.6)				
pN1	35 (26.5)	6 (21.4)	0 (0.0)	8 (47.1)	21 (25.0)	0.999	0.777	0.280	0.292
pN2	16 (12.1)	3 (10.7)	0 (0.0)	1 (5.9)	12 (14.3)				
pN3	8 (6.1)	2 (7.1)	0 (0.0)	0 (0.0)	6 (7.1)				
Breast biomarkers									
Estrogen receptor (ER)									
Negative	16 (12.0)	4 (14.3)	0 (0.0)	2 (11.1)	10 (12.0)	0.569	0.607	0.563	0.637
Positive	117 (88.0)	24 (85.7)	4 (100.0)	16 (88.9)	73 (88.0)				
Progesterone receptor (PR)									
Negative	31 (23.3)	13 (46.4)	0 (0.0)	1 (5.6)	17 (20.5)	0.108	0.412	**0.003**	0.118
Positive	102 (76.7)	15 (53.6)	4 (100.0)	17 (94.4)	66 (79.5)				

#Fisher-exact test

Table 4. HER2 FISH status according to 2018 guidelines

ISH category (2018 guidelines)	n (%)	Conv- group	Conv+ group
3	1 (4.35)	1 (100)	0 (0)
4	22 (95.65)	18 (81.82)	4 (18.18)

For the present study, samples classified under group 1 or conv- were not statistically different from conv+. One reason for this discordance may be attributed to the small sample size (n = 4, 17.4%). Only metastasis to axillary lymph nodes within the conv+ group significantly differed from cases under group 5. The conv- had more involved nodes. The positive nodal status of conv- corresponded with larger tumor sizes and more ductal tumors.[14]

When comparing ER and PR status, cases classified under conv- showed a statistical difference to those under group 1. Conv- was disposed to a positive PR result than group 1 (PR negative result). Although this is inferred by one study that HER2 converted negative cases were not significantly different from HER2 negative cases (group 5), no study concluded a statistically significant difference with group 1.[14]

Limitations and recommendations

Due to the rarity of cases with unusual ISH classifications, data regarding it are still considered inadequate. Researchers could not meet the minimum sample size, predominantly due to the imposed strict exclusion criteria and the limited study samples in a single institution. This may be the reason for the discordance and ambiguity of the study in most publications. A multi-institutional study may be considered in the future to obtain the most appropriate sample size. Correlation with HER2/CEP17 ratio and CEP17 copy number may also be beneficial as one of the variables for future studies.

CONCLUSION

In conclusion, our study focused on the clinicopathologic characteristics of breast cancer in ISH groups 3 and 4. Although the sample size was limited, the study revealed that Filipino patients with breast cancer who converted to HER2 ISH-negative status had more aggressive clinicopathologic features than the traditional HER2-negative tumors in ISH group 5.

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STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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OPEN ACCESS – ORIGINAL ARTICLE

The Use of Hedge Phrases in Histopathology Reports by Filipino Pathologists and Clinicians' Interpretation of Them

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ABSTRACT

Introduction. When communicating uncertainty in histopathology reports, pathologists often use hedge phrases (HPs) to qualify their diagnoses, assuming that clinicians understand their meaning. However, Western studies have shown that these phrases have remarkable variations in intended and perceived certainty, which may impact the next steps of patient care.

Objectives. For seven commonly used HPs, we aimed to determine: how frequently these are used and encountered in histopathology reports in the Philippine setting; if there are differences in certainty among the phrases as well as between the intended and perceived certainty by pathologists and clinicians, respectively; the frequency of seeking clarification for each phrase, the preferred mode of communication, and the frequency that the next steps of patient management are taken for each phrase.

Methodology. Through snowball sampling, 57 pathologists and 111 clinicians from different geographic regions in the Philippines were recruited for an online survey. For each HP, participants reported the frequency of use of or encounter, rated percentage certainty, and answered questions regarding frequency of clarification, next step of management, and preferred mode of communication. Differences between intended and perceived certainty were determined by the Mann-Whitney U test. Differences in certainty among HPs were determined by the Kruskal-Wallis H test with the post-hoc Dunn test.

Results. The phrases "consistent with" and "diagnostic of" were the most and least frequent HPs, respectively. Certainty was perceived to be lower than intended for the phrase "cannot rule out" and for when no HP is used. Differences in certainty were found among most of the HPs. "Diagnostic of" and "consistent with" showed high certainty, "compatible with" and "favor" showed moderate certainty, "suggestive of" and "suspicious for" showed fair certainty, and "cannot rule out" had low certainty.

Conclusion. The variability of intended and perceived certainty for different HPs may warrant standardization of usage in reporting to prevent potential miscommunication and misinterpretation.

Key words: communication, diagnostic uncertainty, hedge phrases, histopathology reports, pathology reports, uncertainty

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INTRODUCTION

Uncertainty in the practice of medicine is often conveyed using hedge phrases (HPs), defined as "any term or phrase that is ambiguous or lacks clear precision."[1] HPs are also known as qualifying, modifying, waffling, diagnostic, descriptive, and uncertainty phrases.[1-6] Pathologists commonly use HPs in their written histopathology reports to convey varying degrees of certainty in their diagnoses. These HPs may be inserted in the line diagnosis section of the report where the diagnostic summary is written, and in the free-text comment section that often follows it.[3,7,8]

Pathology reports are how pathologic diagnoses are communicated to clinicians, and it is implicitly assumed that if an HP is included, the clinician is aware of the pathologist's intended level of certainty. For a minor subset of pathology reports, such as those using a standardized diagnostic category scheme like the Bethesda System for Reporting Thyroid Cytopathology,[9] this assumption may be valid since HPs are included in some of the

diagnostic categories, with a corresponding established risk of malignancy per category. However, for reports on histopathology (i.e., non-cytopathology), no such standardization yet exists. Therefore, use of HPs in these reports may be subjective. This is supported by many studies that have shown considerable variation in the level of certainty ascribed to different HPs as used by pathologists and as interpreted by clinicians.[3-7]

While these studies have been performed in North American and British settings, similar studies from non-Western countries where English is the main language of medical practice are lacking. Our study aimed to fill this gap by providing baseline information on the prevalence of HP use in histopathology reports in our setting, and document if there are variations and differences in their level of diagnostic certainty.

Specifically, we aimed to determine:

1. The frequency of usage of the different HPs by Filipino pathologists in their histopathology reports.
2. The frequency of HP encounters by Filipino clinicians who read histopathology reports.
3. The mean/median/mean-rank differences in the intended level of certainty among the HPs used by Filipino pathologists.
4. The mean/median/mean-rank differences in the perceived level of certainty among the HPs encountered by Filipino clinicians.
5. Significant mean/median/mean-rank differences between the level of certainty as intended by Filipino pathologists and the level of certainty as perceived by Filipino clinicians for each HP.
6. The frequency of triggering extra communication and clarification of diagnosis by pathologists to clinicians, and vice-versa, for when each HP is used or encountered.
7. The frequency of clinicians proceeding with patient management for each HP encountered.
8. The frequency of preferred mode of communication for extra communication and clarification of diagnosis by pathologists to clinicians, and vice-versa, for when each HP is used or encountered.

Table 1. Hedge phrases of interest

"cannot rule out"
"compatible with"
"consistent with"
"diagnostic of"
"favor"
"suggestive of"
"suspicious for"

METHODOLOGY

Institutional review board approval was obtained from the UP-Manila Research Ethics Board (UPMREB). We used a cross-sectional study design utilizing a self-reported survey administered through the online survey tool, SurveyMonkey.com. Table 1 lists the HPs of interest in the study. The choice of HPs was based on our experience with writing histopathology reports, informal consultation with our pathologist colleagues, and common HPs gleaned from the available literature.

We used snowball sampling to recruit through our personal networks two groups of Filipino doctors practicing in various regions in the Philippines: (A) anatomic pathologists, and (B) clinicians who read histopathology reports which guide the management of their patients. Our personal networks included colleagues known from past medical training (medical school, medical internship, residency and fellowship training) and present working colleagues (medical school networks, different hospital and university affiliations, etc.), as well as secondary referrals thereof. Select regions from Luzon, Visayas, and Mindanao were included. The participants were sent the SurveyMonkey.com link via messaging apps and/or email over a period of ten days. When accessed, the link obtained their consent, collected basic personal and professional information, and asked a set of questions relating to common HPs tailored to pathologists and clinicians, as applicable (Tables 2 and 3).

The responses were exported to an MS Excel file (.xlsx). Respondents who failed to complete the survey were excluded from the data analysis.

Table 2. Survey questions for pathologists

Question	Type of response and/or options
If you write a diagnosis without a hedge/qualifying phrase in your histopathology report, what is your intended level of diagnostic certainty? (For example, the diagnostic line in the report plainly says "ADENOCARCINOMA.")	Sliding scale from 0% to 100%
Hypothetically, what is your intended level of diagnostic certainty if you use the phrase "X"?	Sliding scale from 0% to 100%
How frequently do you use the phrase "X" in your diagnosis when writing your histopathology reports (e.g., "X adenocarcinoma")? (Please do not include cytology reports and synoptic reports in your estimate)	Likert scale from 0 to 4: 0 – never* 1 – rarely 2 – sometimes 3 – often 4 – always or almost always
If you use the phrase "X" in your diagnosis, how frequently do you attempt to contact the clinician to explain or clarify the diagnosis (may be before or after issuing the report, and through any of the following: text, email, phone call, intermediary, in-person meeting, multidisciplinary tumor board)?	Likert scale from 0 to 4
When there is diagnostic uncertainty in your histopathology report as expressed by any use of hedge phrases, which mode/s of communication do you use to clarify your diagnosis? Please check all that apply:	• Text • Email • Phone call (may be audio or video) • Intermediary (e.g., through a secretary, medical technologist, resident, intern, etc.) • In-person visit/meeting • None of the above (I do not try to contact)

*If the respondent chose "0/never," the survey skipped the next question and proceeded to the succeeding HP.

Table 3. Survey questions for clinicians

Question	Type of response and/or options
What do you think is the level of diagnostic certainty if the diagnosis in the histopathology report does not have a hedge/qualifying phrase? (For example, the diagnostic line in the report plainly says "ADENOCARCINOMA.")	Sliding scale from 0% to 100%
Hypothetically, what do you think is the level of diagnostic certainty if the phrase "X" is used in a histopathology report?	Sliding scale from 0% to 100%
How frequently do you encounter the phrase "X" when reading histopathology reports (e.g., "X adenocarcinoma")?	Likert scale from 0 to 4: 0 – never* 1 – rarely 2 – sometimes 3 – often 4 – always or almost always
If you use read the phrase "X" in a histopathology report, how frequently do you attempt to contact the pathologist for clarification? (may be before or after issuing the report, and through any of the following: text, email, phone call, intermediary, in-person meeting, multidisciplinary tumor board)?	Likert scale from 0 to 4
When there is diagnostic uncertainty in your histopathology report as expressed by any use of hedge phrases, which mode/s of communication do you use to clarify your diagnosis? Please check all that apply:	• Text • Email • Phone call (may be audio or video) • Intermediary (e.g., through a secretary, medical technologist, resident, intern etc.) • In-person visit/meeting • None of the above (I do not try to contact)

*If the respondent chose "0/never," the survey skipped the next question and proceeded to the succeeding HP.

The profile of the study participants was described by descriptive statistics. Numerical variables (age, years of practice) were described as median and interquartile range. Categorical variables (medical specialty, and region of practice) were described as frequency and percentages.

For each of the HPs of interest: the frequency of use by the pathologists, frequency of encounters by the clinicians, frequency of triggering extra communication and clarification of diagnosis by clinicians to pathologists and vice-versa, frequency of clinicians proceeding with patient management, and frequency of preferred mode of communication were described as absolute and relative frequencies; the level of certainty intended by pathologists, and perceived by clinicians were described as median and interquartile range (IQR). Differences between the median/mean-rank level of certainty of each HP as intended by pathologists, and likewise, differences between the median/mean-rank level of certainty of each HP as perceived by clinicians were determined by Kruskal-Wallis H test with post-hoc Dunn test. Differences between the median/mean-rank level of certainty of the HPs as intended by pathologists and median/mean-rank level of certainty of the HPs as perceived by clinicians were determined by Mann-Whitney U test.

Data analysis was performed using Stata version 17. Missing values were neither replaced nor imputed. The normality of distribution of the numerical variables was assessed by the Shapiro-Wilk test of normality. All tests of the hypothesis were evaluated with a significance level set at $\alpha = 0.05$.

RESULTS AND DISCUSSION

The online survey was sent to 174 people, comprised of 58 pathologists and 116 clinicians. Of these, 57 pathologists (98.3%) and 111 clinicians (95.7%) consented to participate and complete the survey. The characteristics of these respondents are shown in Table 4.

The reported frequency of usage of the different HPs by pathologists and the reported frequency of encountering them by clinicians are shown in Figure 1. The reported frequency of HP usage by pathologists and the reported HP encounters by clinicians were similar. The phrase "consistent with" was reported as "often" or "always" used and encountered by the highest number of respondents, while the phrase "diagnostic of" had the lowest number of such ratings among respondents. Conversely, the phrase "consistent with" was reported as "never" or "rarely" used and encountered by the lowest number of respondents, while the phrase "diagnostic of" had the highest number of such ratings among respondents. We acknowledge that the actual real-life frequencies may be different because self-reporting may carry inherent recall bias. Only one prior study[4] counted the actual frequency by examining 1500 sequential surgical pathology reports in their institution which also showed that the phrase "consistent with" appeared the greatest number of times. Although the phrase "diagnostic of" was not included in that study, the phrase "cannot rule out" was the least frequently used phrase, which was the second rarest in our survey.

Figure 2 shows the median, IQR, and range of the level of certainty (%) of the different HPs as intended by pathologists

Table 4. Characteristics of the respondents

	Median/Frequency	IQR/%
Age, years	40	5
Specialty		
Pathologists	57	33.93%
Clinicians		
Medical specialties[a]	38	22.62%
General surgery and subspecialties[b]	23	13.69%
OB-GYN and subspecialties[c]	24	14.29%
Other surgical specialties[d]	26	15.48%
Length of practice, years	7	5
Area of practice		
NCR	74	44.05%
Non-NCR Luzon	43	25.60%
Visayas	26	15.48%
Mindanao	25	14.88%

[a] Includes endocrinology, gastroenterology, hematology, medical oncology, nephrology, pediatric hematology-oncology, pulmonology, and radiation oncology.
[b] Includes colorectal surgery, general surgery, hepatobiliary surgery, plastic surgery, pediatric surgery, surgical oncology, thoracic and cardiovascular surgery, and urology.
[c] Includes gynecologic oncology, obstetrics and gynecology, and urogynecology.
[d] Includes neurosurgery, orthopedic surgery, and otorhinolaryngology.

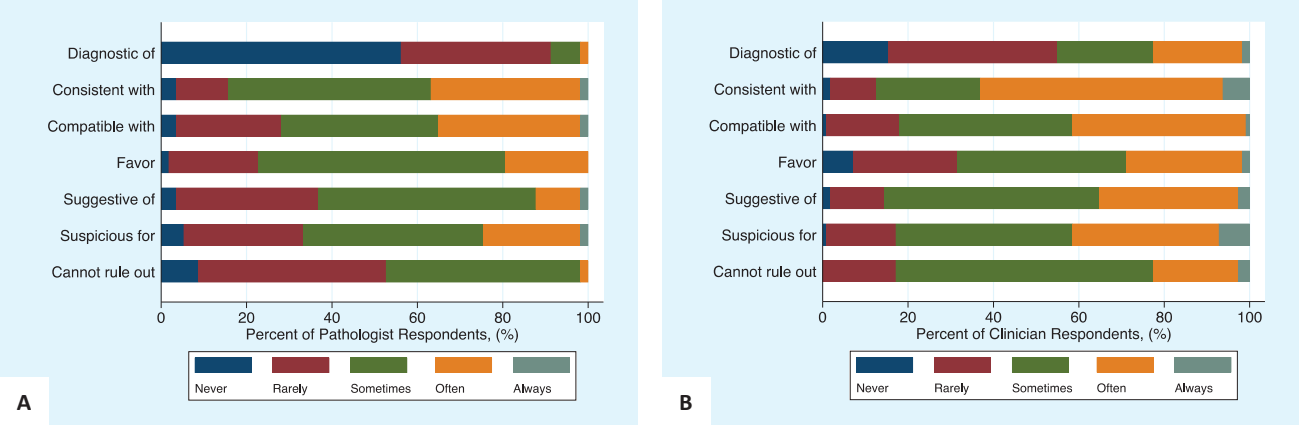

Figure 1. Frequency of hedge phrase usage by pathologists in their histopathology reports **(A)**, and frequency of hedge phrase encounters by clinicians who read histopathology reports **(B)**.

and as perceived by clinicians. For the phrase "cannot rule out," the intended level of certainty by pathologists (median = 50%, IQR = 10%) had a significantly higher mean-rank than the perceived level of certainty by clinicians (median = 50%, IQR = 23%) (p = 0.0087). When no HP was used, the intended level of certainty by pathologists (median = 100%, IQR = 5%) had a significantly higher median than the perceived level of certainty by clinicians (median = 99%, IQR = 20%) (p = 0.0023). There was no sufficient evidence to conclude that there was a difference in the intended level of certainty of pathologists and the perceived level of certainty by clinicians for each of the following HPs: "diagnostic of," "consistent with," "compatible with," "favor," "suggestive of," and "suspicious for" (p = 0.6376, 0.9562, 0.6170, 0.9083, 0.1730, and 0.2120).

The presence of a difference in intended versus perceived level of certainty for the phrase "cannot rule out" is unlike in previous quantitative studies that found no such difference.[2,7,10] For our pathologist respondents, the phrase "cannot rule out" appeared to bear the certainty of a coin toss, while our clinician respondents found its certainty to be even lower than that. Interestingly, this phrase was rated as having a lower level of certainty in prior studies, with means ranging from 20% to 43.75%[2,3,4,7] compared to this study's (with a mean certainty level of 54% for pathologists and 47% for clinicians). Perhaps the fact that these studies were from higher-income countries where further ancillary tests are more accessible and affordable allowed them more diagnostic uncertainty at the onset.

The slightly lower perceived certainty of a diagnosis containing no HP compared to its intended certainty as seen in our study has been suggested in one other prior study[4] but the latter did not test it statistically. Similar to the difference of certainty seen in the phrase "cannot rule out," it appears that clinicians harbored a slightly higher skepticism of pathologists' diagnoses even when no HPs were used.

For pathologists, the phrase "suspicious for" had the highest variability in expressing a level of certainty (IQR = 25%), while the other phrases had less than 20% IQR (Figure 2). For clinicians, the phrase "suspicious for" also had the highest variability in perceived level of certainty (IQR = 25%), followed by "cannot rule out" (IQR = 23%).

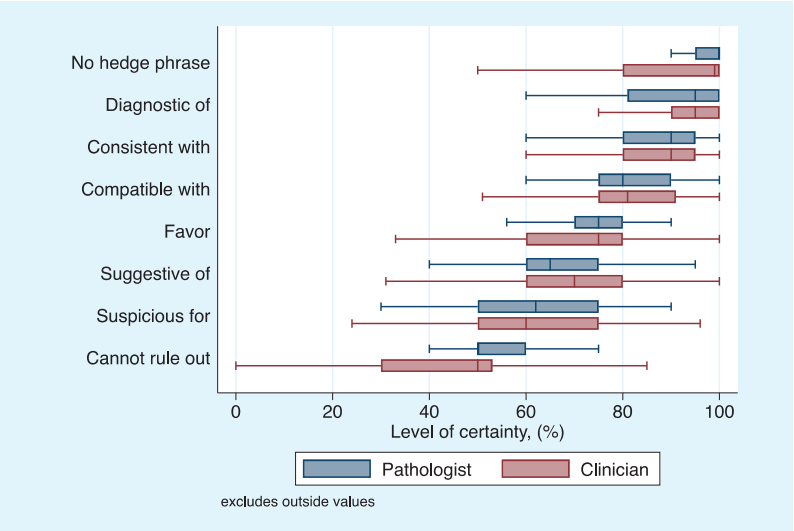

Figure 2. Comparison of the level of certainty intended by the pathologists and perceived by the clinicians among the different hedge phrases used.

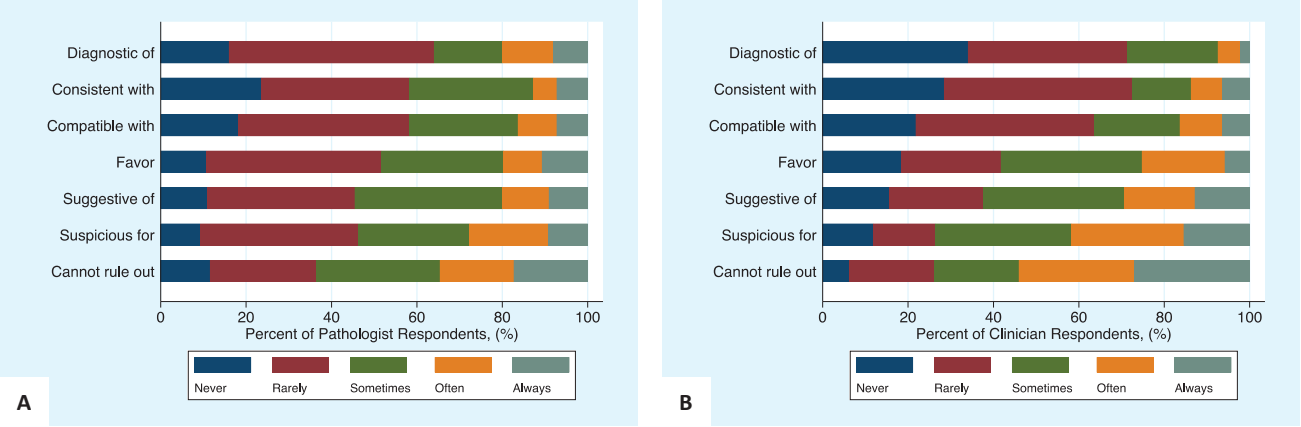

Figure 3. Frequency of triggering extra communication and clarification of diagnosis by pathologists to clinicians for each hedge phrase **(A)**, and frequency of triggering extra communication and clarification of diagnosis by clinicians to pathologists for each hedge phrase **(B)**.

Clinicians also showed high variability (IQR = 20%) in perceived certainty for "favor," "suggestive of," and for diagnoses that did not have HPs. The high variability of intended and perceived certainties for different HPs is consistent with prior studies.[3,4,7] That the phrase "suspicious for" had the highest variability for both pathologist and clinician respondents in our study is unexpected for two reasons: first, other studies did not find it to be the most variable in terms of certainty level; and second, it is a phrase that is already being used in certain systems of pathology reporting, specifically cytopathology of the thyroid[9] and salivary gland,[11] with established risks of malignancy. The expectation that knowledge of its relatively established level of certainty – by pathologists, at least – would be transposed to histopathology reports was unmet. In any case, when phrases such as "suspicious for," "cannot rule out," "favor," and "suggestive of" are encountered by clinicians in histopathology reports, they should be cognizant of the high variability of the certainty associated with such phraseology.

Kruskal-Wallis H test with post hoc Dunn test showed that there were significant differences in the level of certainty among the different HPs. The intended level of certainty according to pathologists was as follows: no HP > "diagnostic of" = "consistent with" > "compatible with" > "favor" > "suggestive of" = "suspicious for" > "cannot rule out." For clinicians, the perceived level of certainty was as follows: no HP = "diagnostic of" = "consistent with" > "compatible with" > "favor" > "suggestive of" > "suspicious for" > "cannot rule out." A hierarchical pattern appears to emerge: "diagnostic of" and "consistent with" have high certainty, "compatible with" and "favor" have moderate certainty, "suggestive of" and "suspicious for" have fair certainty, and "cannot rule out" has low certainty. This pattern is similar to prior studies that included all these phrases.[2,3,7,11] The low certainty of "cannot rule out" is also reflected in the finding that it was the phrase most likely to trigger extra communication and clarification by both pathologists and clinicians (Figure 3), and the phrase most likely to stop clinicians from proceeding with their next step of patient management (Figure 4). Curiously, when examining the low- to moderate-certainty phrases (Figure 2), clinician respondents demonstrated broader ranges of perceived certainty compared to pathologists. Therefore, a small subset of clinicians may be underestimating or overestimating the intended certainties of "favor," "suggestive of," "suspicious for," and "cannot rule out."

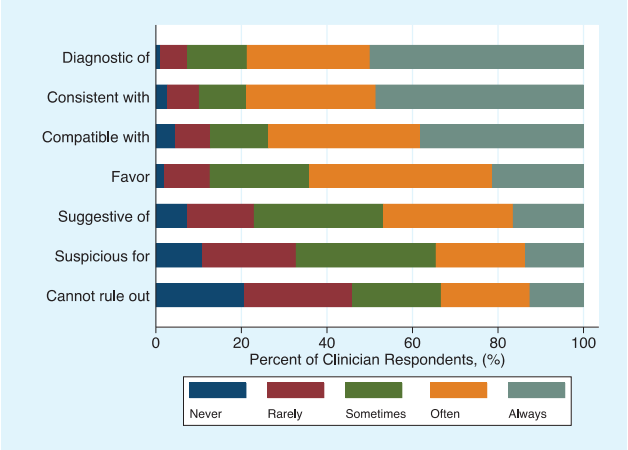

Figure 4. Frequency of clinicians proceeding with patient management for each hedge phrase used by pathologists.

Table 5. Preferred mode/s of communication of pathologists and clinicians when using/encountering hedge phrases

Mode of communication	Pathologists	Clinicians
	Frequency (%)	
Text	42 (73.68%)	74 (66.67%)
Email	3 (5.26%)	19 (17.12%)
Phone call	37 (64.91%)	71 (63.96%)
Intermediary	29 (50.88%)	35 (31.53%)
In-person meeting	18 (31.58%)	31 (27.93%)
Multidisciplinary tumor board	14 (24.56%)	36 (32.43%)
No communication	3 (5.26%)	4 (3.60%)

The preferred mode/s of communication of pathologists and clinicians when encountering HPs are shown in Table 5. For both groups, the most common modes of communication were via text, phone calls and intermediary. Compared to clinician respondents, pathologist respondents appeared to be slightly more inclined to text, use an intermediary, and – perhaps unexpectedly – meet the clinician in person.

Pathologist respondents also seemed less likely to email and attend a multidisciplinary tumor board. One possible explanation for the former may be that some pathologists prefer to provide an explanatory note in the comment section of the histopathology report, as was communicated to us by a few of the pathologist respondents after answering the survey. As for the latter, we surmise that it was the least available resource among the options. The lack of an open-ended response/comment field for each of the questions in our survey was a limitation in gathering more information.

CONCLUSION

The apparent hierarchical consistency in the levels of certainty suggests that for many pathologists and clinicians, there is an intuitive grasp of the levels of certainty for these HPs. The challenge would be for those whose intended and perceived level of certainty fall outside the interquartile ranges reported in our study. Perhaps a move to standardize the usage of these phrases in histopathology reports is warranted in this regard. Such a suggestion is not novel. Investigators from prior studies have proposed schemes such as providing formal training at a local institutional level as well as urging national medical organizations to reach a consensus on the levels of certainty of common HPs.[3,7] One group[2] has even proposed a classification system akin to the Breast Imaging Reporting and Data System (BI-RADS) used by radiologists and the Bethesda System for Reporting Thyroid Cytopathology used by cytopathologists, where the common HPs are categorized into five groups of decreasing certainty levels, along with the recommended steps of patient management per category. Applying a similar scheme in our setting can reduce ambiguity, miscommunication and misinterpretation, and avoid potential delays, errors, and unnecessary costs in patient treatment.

STATEMENT OF AUTHORSHIP

Both authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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OPEN ACCESS – CASE REPORT

Mucosal Melanoma of the Male Urethra: A Case Report

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ABSTRACT

This is a rare case of a mucosal melanoma, located in the urethra of a 59-year-old male. Malignant melanomas of the genitourinary tract are rare, representing <1% of malignancies in the genitourinary tract, and <0.1% of all melanomas. In the male genitourinary tract, the most affected sites are the glans penis and the distal urethra in the fossa navicularis. Urethral melanomas comprise 4% of all urethral cancers.

Key words: mucosal melanoma, urethra, genitourinary, urethral melanoma

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CASE

A 59-year-old Filipino male sought consult with a chief complaint of severe dysuria with accompanying symptoms of gross hematuria and urinary retention. Symptoms started nine (9) months (February 2022) prior to consult, when the patient complained of episodes of gross hematuria with blood clots and slight dysuria. Two (2) months (September 2022) prior to consultation, he was seen at the emergency room (ER) due to severe dysuria, gross hematuria and urinary retention. At the time of the ER consult, he was described to be frail-looking and had difficulty doing daily activities of living. A Foley catheter was inserted and CT urogram was performed which shows a non-enhancing exophytic cortical cystic focus measuring 1.4 x 1.3 cm at the right upper pole cortex. A slight enhancing iso to hypodense solid mass measuring 3.0 x 3.2 x 3.0 cm is seen in the middle pole calyx. Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed an enlarged prostate, under-distended urinary bladder with diffuse wall thickening, irregular mucosal thickening with focal areas of restricted diffusion noted in the superior wall, kidneys with mild to moderately dilated right renal pelvis and mid to lower pole calyces, likely representing hemorrhagic or high proteinaceous content.

Submitted to our institution for slide review and immunohistochemical staining studies was a urethral mass biopsy specimen. Microsections of the mass disclosed atypical round cells arranged in nests and sheets. These atypical cells exhibited hyperchromatic nuclei with scant cytoplasm with inconspicuous nucleoli (Figure 1).

The case was initially signed out as a round-cell malignancy. Primary considerations included poorly differentiated urothelial carcinoma, lymphoma, metastatic prostatic adenocarcinoma, and melanoma. Thus, immunohistochemical staining with Cytokeratin (CK), Leucocyte Common Antigen (LCA), p63, p40, GATA-3, Prostate Specific Antigen (PSA), S100, Melan A, and HMB-45 were requested.

Cytokeratin, LCA, p63, p40, GATA-3 and PSA all stained negative. S100 and HMB-45, stained positive and Melan-A was focally positive (Figures 2-4). The immunohistochemical staining results, in correlation with cytomorphology,

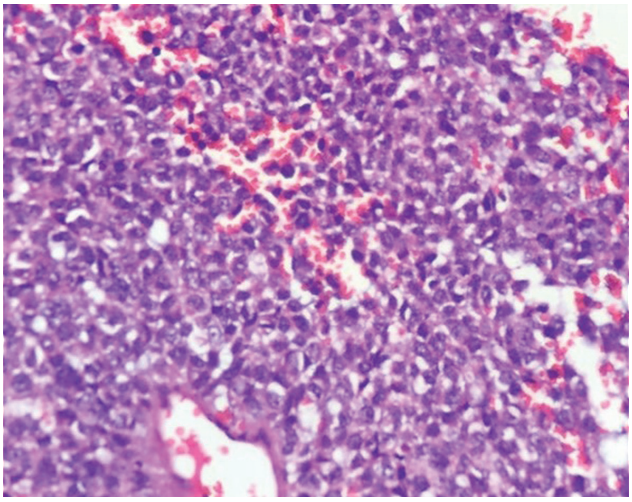

Figure 1. Atypical cells show hyperchromatic nuclei with scant cytoplasm with inconspicuous nucleoli (H&E, 200x).

support the diagnosis of high-grade round cell malignancy. The primary consideration was non-cutaneous / mucosal melanoma. Additional immunohistochemical staining with SOX10, Smooth Muscle Actin (SMA) and Desmin was recommended for a more definitive diagnosis. However, the additional stains requested were no longer performed, and the patient was admitted for urethrectomy with cystoprostatectomy. The urinary bladder, prostate, bilateral ureters, and urethra were submitted for processing. Upon gross inspection, there was a dark brown, soft tissue mass arranged in an excrescence-like pattern, occupying 12.8 cm of the length of the urethra. The mass is seen 1.8 cm and 0.3 cm away from the urethral portion of the prostate and urethral resection margin, respectively. Sections from the specimen were submitted for study.

Microsections from the urethral mass disclose atypical round cells arranged in nests and sheets, like the ones in the initial biopsy specimen, now seen invading but limited

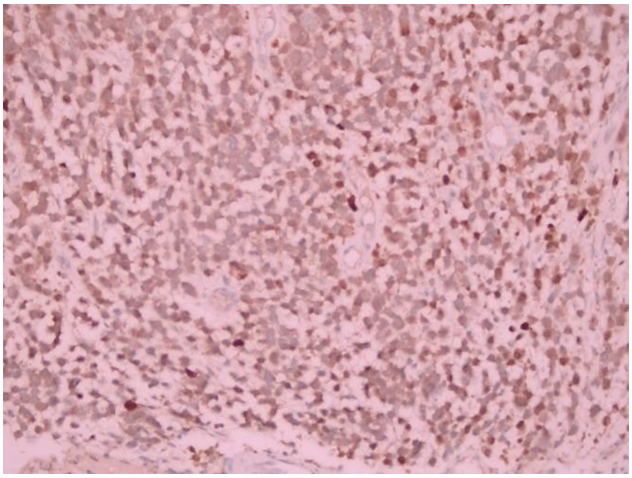

Figure 2. Cytoplasmic and nuclear immunohistochemical staining for S-100 was observed in neoplastic cells (S-100, 200x).

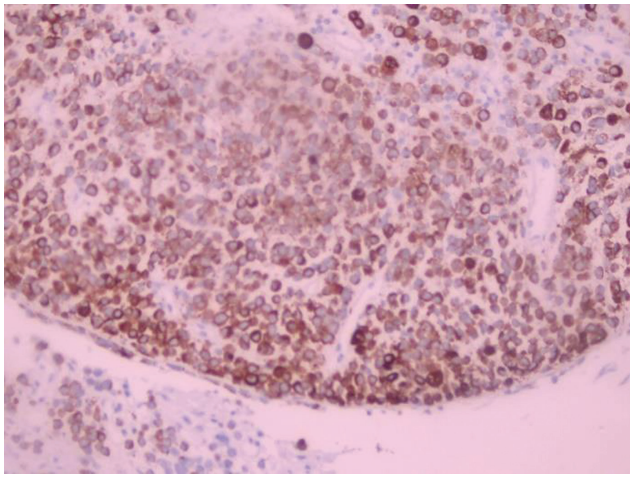

Figure 4. Cytoplasmic immunohistochemical staining for HMB-45 was observed in neoplastic cells (HMB-45, 200x).

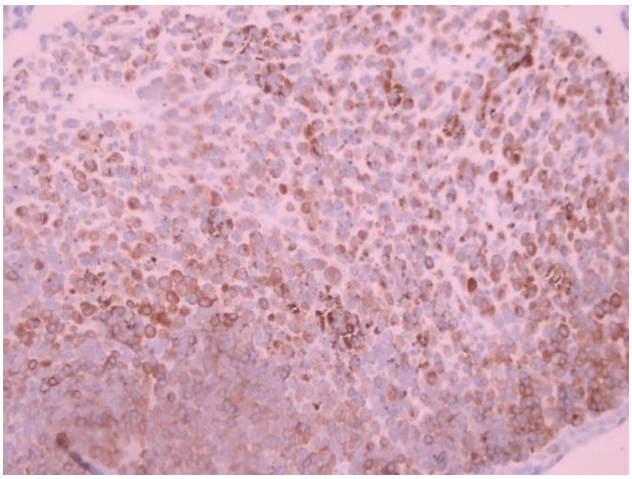

Figure 3. Focal cytoplasmic and nuclear immunohistochemical staining for Melan-A observed in neoplastic cells (Melan-A, 200x).

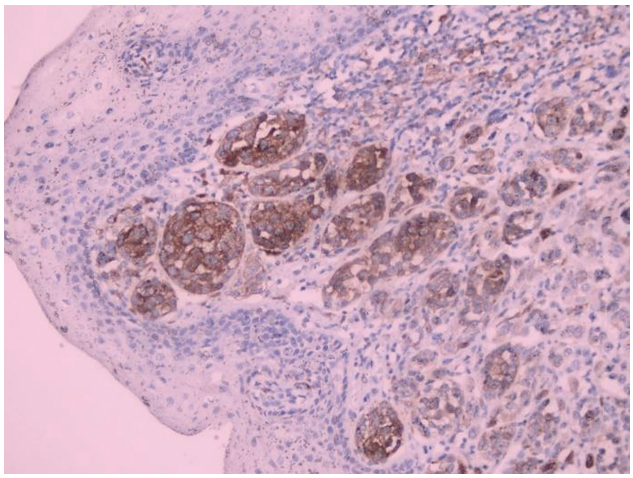

Figure 5. Complete and partial membranous immunohistochemical staining for PDL-1 was observed in 30% of neoplastic cells (PD-L1, 200x).

to the muscularis propria of the urethra. The atypical cells show hyperchromatic nuclei with scant cytoplasm with inconspicuous nucleoli. Additional immunohistochemical staining with PD-L1 and CD 117 (KIT) was requested which showed positivity for 30% (Figure 5) and 40% of the tumor cells, respectively. The case was signed out as mucosal (non-cutaneous) melanoma.

The patient tolerated the procedure well, was discharged stable and was referred to the oncology service for definitive management.

DISCUSSION

Incidence

Malignant melanomas of the genitourinary tract are rare, representing <1% of malignancies in the GU tract[1-4] and <0.1% of all melanomas.[1,5-7] The most common sites being affected are the skin and the eyes.[8] In the male genitourinary tract, the most affected sites are glans penis and the distal urethra in the fossa navicularis.[1,8] Urethral melanomas compromise 4% of all urethral cancers.[7] It is more common in older adults, with the mean age at diagnosis being 65 years.[1,7] There is no gender predilection for urethral melanomas.[1]

In a paper published by Altieri et al., they concluded that "although 1% of melanomas occurring in non-Hispanic whites were mucosal, other racial/ethnic groups have higher proportions of mucosal melanomas (15% for Asian/Pacific Islanders, 9% for non-Hispanic blacks, and 4% for Hispanics)."[3]

Clinical presentation

Signs and symptoms are often non-specific and depend on the anatomical location. In the early stage, patients may be asymptomatic.[9] In the later stages, patients with urethral melanoma may present with hematuria, dysuria, frequency, spraying urinary stream or other symptoms related to urinary obstruction.[1,4,9] Hematuria due to ulceration occurs in cases of urethral melanoma.[5] Ulceration is more common in the urethra compared to the glans penis.[5] Diagnosis of cases is often delayed because of their non-specific signs and symptoms.[5] In men, urethral melanoma can present with symptoms similar to chronic prostatitis or prostatic hyperplasia due to urethral discharge and obstructive symptoms and diagnosis is only achieved after failure of treatment for mimicking diseases.[9] In a systematic review conducted by Safadi et al., urethral mass is the most common presenting symptom.[7]

Imaging

According to Rambhia et al., currently, there are no algorithms for the workup of genitourinary melanomas as patients would present in the late stages of the disease and the prognosis is typically poor for these patients.[8] Primary approach to diagnosis would include a thorough physical exam. For men, this includes inspection of the prepuce, glans, scrotum, frenulum and penile shaft for any lesion, such as ulceration, crusting and irregularity. Excision biopsy is confirmatory for histologic diagnosis and imaging studies such as Positron Emission Tomography (PET), CT, MRI, and chest X-rays are performed to rule out metastases.[9]

Histomorphology and immunohistochemical studies

According to the World Health Organization (WHO), macroscopically, urethral melanomas would present as ulcerated, nodular masses, and associated nevus are rarely present.[1] Microscopically, urethral melanoma would present as "sheets or expansile nodules of large pleomorphic epithelioid or (less commonly) spindle-shaped malignant melanocytic cells. Necrosis is uncommon. The nuclei often have vesicular chromatin and prominent nucleoli. Occasionally, small, or nevoid cells may predominate. Melanin production is variable but usually focally present both within melanoma cells and within macrophages. The junctional component is typically characterized by a lentiginous growth of single atypical melanocytes in the basal epithelial layer, sometimes with nests or confluent growth. A subepithelial lymphocytic infiltrate is common. Immunohistochemically, there is usually reactivity of the tumor cells for S100, SOX10, HMB45, and Melan-A (MART1).[1]

Fine-needle aspiration biopsy is used as a rapid, minimally invasive means of diagnosing metastatic melanoma. The regional lymph nodes would generally be the first ones to be affected.[10] In a paper published by Murali et al., smears of the FNAB specimens would show spindle and/or epithelioid cells with malignant cytologic features.[10] Aside from the previously mentioned findings, according to WHO, the smears would also show, isolated giant cells and intranuclear pseudo-inclusions are often present. Cytoplasmic pigment is usually present in a minority of cells. Pigmented macrophages may be seen in the background.[1]

Molecular studies

Molecular signatures and patterns of chromosomal aberrations in mucosal melanoma have been compared to those in cutaneous melanoma.[9] BRAF mutations in GU melanomas are less common compared to cutaneous melanomas.[9] C-KIT proto-oncogenes receptor tyrosine kinase gene (KIT), which are commonly found in acral melanomas and melanomas arising from chronically sun-exposed skin, have also been described in mucosal melanomas.[9] The downstream targets of KIT include the RAF/MEK/extracellular signal-regulated kinase (ERK) and PI3K/AKT pathways.[9] In a paper published by Omholt et al., there is no association between KIT mutations and a worse prognosis.[11] Activating mutations in the N-ras proto-oncogene (NRAS) are seen in cutaneous melanomas and some cases of mucosal melanoma.[9,12] As reported by Van Engen-van Grunsven et al., NRAS mutations are detected in 20% of urethral melanomas, showing that NRAS mutations are present in significant amounts of GU melanomas but not in the majority.[9,12] Lastly, PD-1, programmed cell death receptor and PD-L1, programmed cell death receptor ligand, have been noted to be expressed in mucosal melanomas in the same amounts as in cutaneous melanomas. Targeted immune checkpoint inhibitors directed against PD-1 receptors were noted to have improved outcomes.[9] Therefore, PD-1 directed immunotherapies in GU melanomas might have a role. In summary, GU melanomas should be tested for BRAF and KIT mutations along with PD-L1 testing if systemic treatment with immunotherapy is being considered.[1]

Staging and prognosis

There are currently no standardized criteria for staging mucosal melanomas of the male GU system.[1,5] Compared to cutaneous melanomas, the prognosis of urothelial primary melanomas is poor with a median survival time being 28 months with a 5-year survival rate of 28%.[1]

Our patient was 58 years old at the time of the presentation of the disease, 7 years younger than the mean age at presentation. He initially presented to his attending physician with the chief complaint of severe dysuria with the accompanying symptoms of gross hematuria and urinary retention, which is a common disease manifestation. However, in our patient's case, the hematuria was not caused by ulceration as gross and microscopic examination of the urethral mass did not show any break in the lining of the epithelium. His imaging studies show no sign of metastasis. A gross examination of the urethral mass showed dark brown, soft tissue mass arranged in an excrescences-like pattern, unlike the usual presentation of ulcerated, nodular masses. Microsections of the urethral mass disclosed atypical round cells arranged in nests and sheets, which is similar to how mucosal melanomas are commonly described (i.e., "sheets or expansile nodules of large pleomorphic epithelioid or [less commonly] spindle-shaped malignant melanocytic cells"). Immunohistochemical staining results were positive for S100 and HMB-45 and Melan A which is compatible with the usual picture. For our patient, PD-L1 and KIT testing expressed positivity for 30% and 40% of the tumor cells, respectively. As such, our patient is considered for targeted immunotherapy with pembrolizumab or kinase inhibitors as options for treatment.

FOLLOW-UP AND OUTCOMES

A few months after the initial diagnosis and surgery of the patient, a Computed tomography (CT) scan of the whole abdomen and chest was performed on two (2) separate occasions. CT scan of the whole abdomen (status post cystoprostatectomy and ileal conduit formation/construction) revealed non-specific punctate pancreatic tail calcification, likely post-inflammatory; splenomegaly; swollen left kidney with decreased nephrogram enhancement and moderate hydronephroureter which may be related to obstructive nephropathy; dilated distal left ureter with lobulated border and surrounding fat stranding densities; bilateral renal cortical cysts with suggestive parapelvic cyst in the right; prominent retroperitoneal lymph nodes; and minimal ascites. The possibility of tumor recurrence was not ruled out. CT scan of the chest revealed fibrotic changes, in both upper lobes; subsegmental atelectasis, right lower lobe; minimal bilateral pleural effusion with passive atelectasis; atherosclerosis, thoracic aorta and coronary arteries; dorsal spondylosis; and vertebral hemangioma, T8.

Unfortunately, no further testing has been performed on the patient as he was reported to have passed away last April 2023, fourteen (14) months after the initial onset of symptoms, shorter than the reported median survival period of patients with urothelial melanoma.

CONCLUSION

We have reported a case of a urethral mucosal melanoma in a 59-year-old male. Malignant melanomas of the genitourinary tract are rare, representing <1% of malignancies in the genitourinary tract, and <0.1% of all melanomas. Survival remains dismal for patients with this disease, underscoring the need for its recognition and diagnosis in the appropriate clinical context, aided by appropriate imaging, histopathological, and immunohistochemical studies.

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ETHICAL CONSIDERATION

Patient consent was obtained before submission of the manuscript.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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OPEN ACCESS – CASE REPORT

An Incidental Finding of Leydig Cell Tumor in a 36-year-old Southeast Asian Male who presents with Infertility: A Case Report and Literature Review

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ABSTRACT

Leydig cell tumor is a rare testicular neoplasm that can present as a non-palpable small testicular nodule. Here we present a case of a 36-year-old Filipino male who initially came in for fertility work-up. Semen analysis showed azoospermia. However, an incidental finding on ultrasound showed a well-circumscribed round tumor. The patient underwent radical orchiectomy. On histopathologic examination, a Leydig cell tumor was identified and supported by immunohistochemical staining. We discuss the clinical features pathogenesis, treatment, diagnosis and prognosis of this uncommon entity.

Key words: Leydig cell, testis, orchiectomy, infertility

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INTRODUCTION

Leydig cell tumor (LCT) is a rare neoplasm representing 1% to 3% of testicular tumors and is the most common sex cord-stromal tumor in all ages.[1] The tumor can be seen at any age but is most common in prepubertal boys (5-10 years old) and young adults (30-60 years old).[2,3] Patients are usually asymptomatic except for the finding of a testicular mass.[4] Furthermore, the tumor can produce endocrine changes because of increased production of androgens and/or estrogens such as precocious puberty, breast tenderness, or gynecomastia.[4] However, in this case, the patient had no overt signs and symptoms.

LCT's are generally benign tumors with only 5% to 10% being considered malignant.[3,5] While surgical resection is currently the mainstay effective treatment,[6] some cases require adjuvant medication for fertility.[7] According to the GLOBOCAN 2020 database, 2,858 testicular cancer cases have been reported in Southeast Asia, 358 of which are registered in the Philippines. This database is limited in that it does not specify the histologic type of testicular tumor. To the best of our knowledge, there is no definite number of cases reported in the Philippines. Currently, there is still a lack of data as to the relationship of testicular LTC with male infertility.

CASE

We present a case of a 36-year-old married Filipino male who originally sought consultation for an infertility work-up after trying to conceive with his wife for one year. Physical examination revealed that the left testis was smaller than the right testis and the patient denied claims of any palpable scrotal mass or pain. Testicular sperm extraction was done and revealed no spermatozoa seen in both left and right testicular tissues. Hormone studies revealed the following results: Follicle Stimulating Hormone (FSH): 13.10 mIU/mL (Normal value: 1.55-9.74), Luteinizing Hormone (LH): 5.12 mIU/mL, Testosterone (TT): 356 ng/mL (Normal value for ages 20-49: 132-813 ng/mL),

Estradiol (E2): 21.8 pg/mL (Normal value: 5.37-65.9 pg/mL), and Prolactin: 12.8 ng/mL (Normal value: 3.7-17.9 ng/mL). Only FSH was noted to be elevated. Scrotal ultrasound was done which revealed a hypoechoic nodular focus with minimal to absent vascularity in the left testicle (Figure 1). Also seen in the epididymal head is a cyst measuring 0.2 x 0.1 cm.

The patient underwent radical orchiectomy of the left testis with an uneventful postoperative course. Onco-testicular sperm extraction was done on both testes which yielded no sperm cells. The specimen was submitted for histopathologic examination. Gross examination revealed an unremarkable testis, epididymis and attached spermatic cord. Serial sectioning of the testis revealed brown tan, soft to spongy cut surfaces with no areas of hemorrhage or necrosis. There were no grossly identifiable lesions or masses as well. The entire testis was submitted for processing.

Microscopic examination revealed a tumor in small solid nests separated by delicate fibrovascular septae, composed of tumor cells with round to ovoid nuclei, some with prominent nucleoli, and eosinophilic, granular cytoplasm (Figures 2 and 3). Immunohistochemical studies showed positive staining with Inhibin, Melan-A, Calretinin, and AR (Figure 4). Hence, a diagnosis of Leydig Cell Tumor was made.

Unfortunately, there was no post-surgical update as the patient was lost to follow-up.

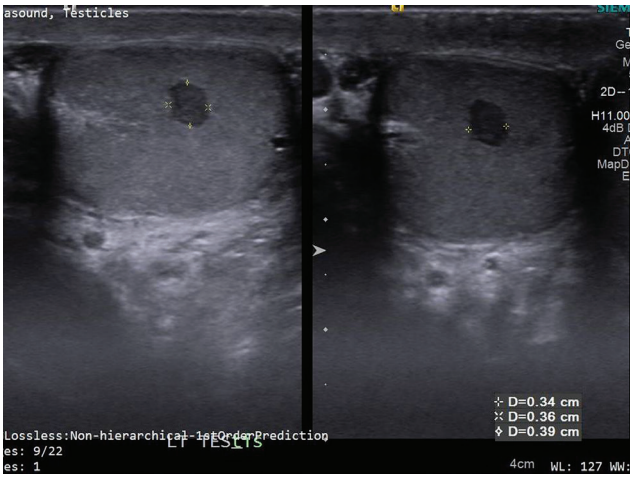

Figure 1. A well-circumscribed round hypoechoic focus with minimal to absent vascularity on scrotal ultrasound measuring 0.34 x 0.36 x 0.39 cm.

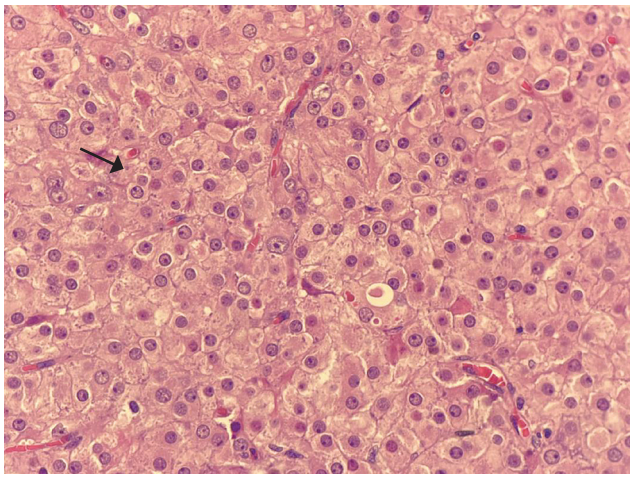

Figure 3. Polygonal cells with uniform round nuclei and eosinophilic granular cytoplasm (H&E, 400x).

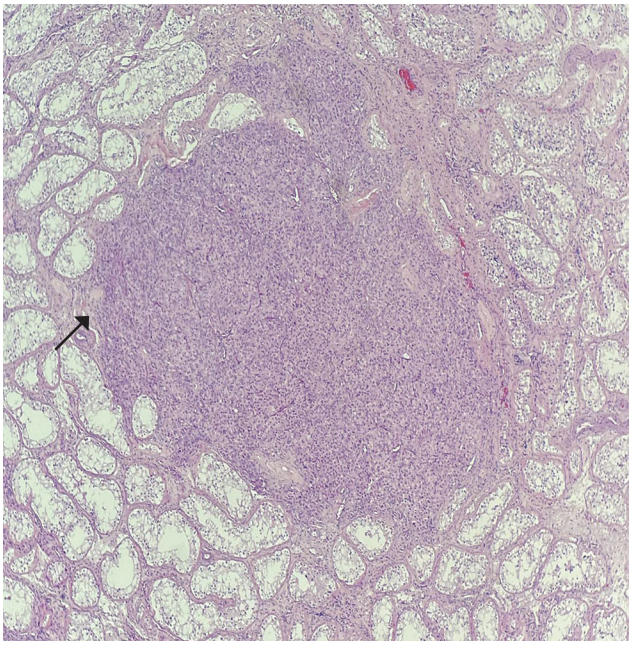

Figure 2. Tumor is composed of nests separated by delicate fibrous septa. The tumor is surrounded by seminiferous tubules showing severe hypospermatogenesis (H&E, 100x).

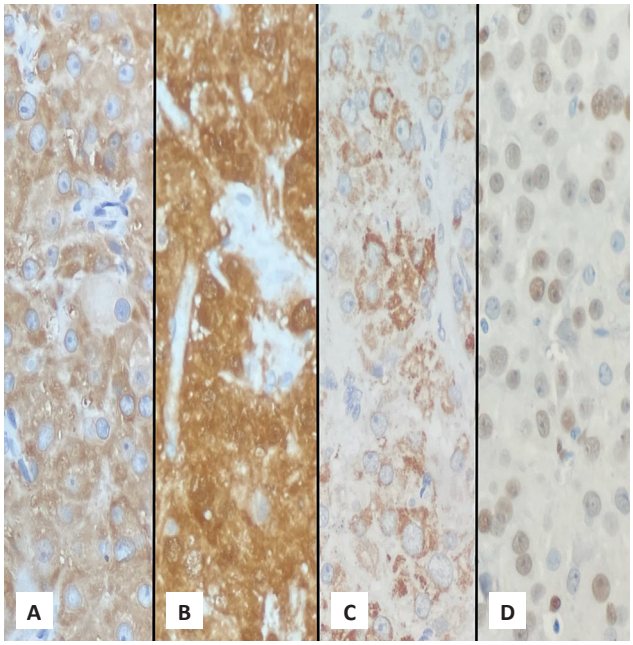

Figure 4. Positive immunohistochemical staining for Inhibin **(A)**, Calretinin **(B)**, Melan-A **(C)**, and AR **(D)**, 1000x.

DISCUSSION

Testicular tumors can be grouped into five (5) general categories: germ cell tumors arising from the germinal epithelium of seminiferous tubules; sex-cord stromal tumors; mixed germ cell-sex cord-stromal tumors; primary tumors not specific to the testis; and metastatic tumors.[4] Sex cord–stromal tumors are derived from 2 types of somatic cells: the Leydig cells, and the Sertoli cells. LCTs are derived from Leydig cells, which are interstitial cells located between the seminiferous tubules and they produce androgens, mainly testosterone when stimulated by luteinizing hormone.[5,7] They are thus involved in the development of secondary male characteristics and maintenance of spermatogenesis. A hormonal imbalance with increased production of estradiol instead of testosterone in adults can then lead to disruption of spermatogenesis, although with regards to our case, the patient had normal estradiol levels.[5,8] In our case, the patient sought consultation for a fertility work-up after trying to conceive with his wife for a year.

The exact pathogenesis underlying the development of these tumors are still unknown. However, it was suggested that activating mutations of the G protein genes, specifically *gsp*, may play a significant role in the pathogenesis of these neoplasms.[9]

Although scrotal ultrasound is not routinely requested in the initial evaluation of male infertility cases, its widespread use has led to a marked increase in the number of incidentally detected small testicular nodules, described by Fabiani et al. 2014 as a non-palpable (<10 mm), asymptomatic solid lesion with normal levels of oncological testicular markers.[10] Most of these lesions are hypoechoic and vascularity is variable but usually increased.[11] Up to 6% have a final histopathologic finding of LCT.[6] It was found that a considerable number of patients who were diagnosed with LCT initially sought consultation for infertility work-up.[6,12] Other common referrals were for general andrologic screening and varicocele.[12] This is similar to our patient who initially sought consultation for an infertility work-up and tried to conceive with his wife for a year.

The tumor is typically well-circumscribed, often lobulated by fibrous septa and is generally uniformly solid. It is generally yellow, yellow-tan, brown or red-brown.[2] Microscopically, tumor cells have well-defined borders, eosinophilic, occasionally clear cytoplasm and a round or oval nucleus. Marked variation in the size and shape of cells can occur. It generally presents as solid but other patterns of growth such as trabecular, myxoid, pseudofollicular and microcystic formation can occur.[4] In the case of our patient, a solid growth pattern was appreciated with tumor cells predominantly in nests separated by delicate fibrous septa. These tumor cells have fairly uniform round nuclei and ample eosinophilic, granular cytoplasm. A differential diagnosis would be Leydig cell hyperplasia which represents an overgrowth of normal Leydig cells. However, this would usually present multifocally. Another differential would be Granular cell tumors. These tend to have nesting or diffuse growth patterns and the cells are organized in a swirl pattern, giving a distinct appearance.[4] A combination of clinical, imaging, and histological evaluation is crucial for accurate diagnosis and appropriate management.

LCT's are generally benign and an estimated 10% are malignant. Diagnostic criteria for malignancy have not been established except for metastasis.[3,13] However, features that are suggestive of aggressive behavior have been described such as large tumor size (greater than 5 cm.,), increased mitotic figures (>3 mitotic figures per 10 high power fields), overt cytologic atypia, vascular or capsular invasion, infiltrative borders and tumor necrosis.[1-3] Age was also found to be significantly associated with malignancy in several reports.[14,15] At least 2 of the features mentioned above are required to assume malignancy.[14] As there is limited data on having proper identification for malignant LCTs, we can only rely on current literature and available data in describing these tumors. In the study by Benarji et al., a combined census of 79,120 cases of testicular cancer between 1998 and 2011 was assessed. 250 of which were malignant Leydig cell tumors and races that were not African American or White comprised 48 out of the 250 cases (19%). In another case series from Fankhauser et al., a total of 101 out of 1,040 (10%) patients developed metastases at any point in time, 65 of which developed during follow-up and 82% of all metastases were diagnosed during the first 5 years. The diagnosis was primarily made clinically by the detection of metastases at the initial presentation or during follow-up.[14]

The immunohistochemical markers utilized for evaluating these tumors are Inhibin, Calretinin, Melan-A, and AR.

- **Inhibin alpha subunit protein (INHA)** is a member of the TGF-beta (transforming growth factor-beta) superfamily encoded by a gene located at 2q35.[16] It is currently used as an immunohistochemical marker for adrenocortical tumors and sex cord-stromal tumors of the testis and the ovary and is generally considered an important diagnostic feature for sex cord-stromal tumors of the testis. In a study by Iczkowski, it was shown that Inhibin was a sensitive marker showing 100% expression in LCTs. It is also the recommended stain to use to differentiate from germ cell tumors.[16]
- **Melan-A/MART-1** is a melanocytic differentiation marker, which is recognized as an antigen on melanoma cells by cytotoxic T-lymphocytes. One monoclonal antibody available against Melan-A is A103 which was made by the Ludwig Institute by Chen et al.[17] A103 has the unique property of staining many steroid hormone-producing cells, and immunoreactivity can be detected in Leydig cells of the testis and in tumors derived from.[17] This clonal antibody is specific for sex-cord stromal tumors. Thus, it is a good marker for steroid-secreting tumors, including LCT.
- **AR** expression has been described previously in reproductive tissues in the second trimester of human fetal development. It is specifically located in the nuclei of Sertoli cells and Leydig cells and is seen to be strongly positive.[18]
- **Calretinin,** also called calcium retinal protein 2 (calb2), is a hexa-EF-hand Ca^{2+} binding protein.[19] It participates in a variety of physiological functions, such as regulation of synthesis of sex hormones, cell proliferation and apoptosis. Calretinin was recently found to be expressed in steroidogenic cells, such

as adrenal cells and Leydig cells and expression was detected in many tumors derived from these cells (such as seminomas, Leydig cell tumors and Sertoli cell tumors).[19]

The management of benign LCT is primarily surgical with simple orchiectomy historically being the standard of care in these patients. If features suggestive of malignant behavior are present, a retroperitoneal lymph node dissection should be considered (as these tumors are chemo and radioresistant).[1] After surgery, hormone replacement treatment can be done in an attempt to establish spermatogenesis.[20] However, there have been several reports on testicular sparing surgery in conjunction with an intraoperative frozen section showing promising results especially those in small lesions (<2.8 cm^3) with normal tumor markers.[21,22] The advantages of which can include preservation of fertility and endocrine function, avoiding the risk of late-onset hypogonadism and preservation of male body image as well.[23] This was implemented to reduce the risk of overtreatment with radical orchiectomy.[23] Outcomes of *Testis Sparing Surgery* (TSS) can be comparable to that of radical orchiectomy in managing benign LCTs where there was an excellent prognosis as well as no tumor recurrence on follow-up.[8,22,23]

CONCLUSION

LCT is a rare, testicular neoplasm that can present clinically occult findings. Scrotal ultrasound evaluation can help detect scrotal pathologies especially when they are non-palpable. Immunohistochemical studies may be used to confirm the diagnosis. Treatment options include radical orchiectomy, testicular sparing surgery, excisional biopsy and active surveillance. Although no ultrasound appearances are entirely diagnostic, it is best to correlate clinical, imaging studies as well as histopathologic findings for the appropriate management.

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ETHICAL CONSIDERATION

Informed consent was not obtained despite all efforts and due diligence exerted to contact the patient. Efforts were undertaken to ensure that no personal identifying patient information was shared.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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OPEN ACCESS – CASE REPORT

A Case Report of Extensive Facial Primitive Myxoid Mesenchymal Tumor of Infancy: An Approach to Diagnosis and Review of Literature

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ABSTRACT

We report a case of a 14-month-old female presenting with a one-year history of rapidly enlarging left hemifacial mass with recurrence despite excision. The tumor consists of bland round to short spindle cells in a myxoid stroma with positive expression to vimentin, CD99, SATB2, cyclin D1 and BCOR, compatible with a sarcoma with BCOR genetic alteration. Next-generation sequencing was performed that detected a BCOR internal tandem duplication, confirming the diagnosis of a primitive myxoid mesenchymal tumor of infancy (PMMTI). This report highlights the importance of attention to histopathologic characteristics, prudent application of immunohistochemical stains and molecular studies in differentiating PMMTI from other soft tissue sarcomas.

Key words: primitive myxoid mesenchymal tumor of infancy, BCL6 co-repressor gene internal tandem duplication, soft tissue sarcoma

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INTRODUCTION

Primitive myxoid mesenchymal tumor of infancy (PMMTI) is a rare soft tissue malignancy and newly recognized distinct entity under undifferentiated small round cell sarcomas in the most recent World Health Organization classification of soft tissue and bone tumors. It is characterized by BCL6 co-repressor (BCOR) gene internal tandem duplication (ITD).[1] Since its initial description by Alaggio et al., in 2006, only a few cases have been reported worldwide, hence extensive information is still needed to understand further its biologic and clinical behavior that is fundamental to its successful management, particularly in cases with unresectable conditions. To our knowledge, this report is the first to describe a PMMTI with extensive involvement of the left hemifacial structures in a 14-month-old female. The clinical, radiologic, histologic, immunohistochemical, and molecular features are discussed.

CASE

Clinical history and imaging

A 14-month-old female with unremarkable prenatal and family history was evaluated for a one-year history of left hemifacial mass that was rapidly enlarging, firm, painless, non-movable, and initially measuring 3 x 3 cm on the left zygomaticus at three months of age. Surgical excision was done at seven months and an initial histopathologic diagnosis of lipoblastoma was made in another institution. Postoperatively, recurrence was noticed on the same site that grew rapidly in a span of five months. It was non-erythematous, firm, multinodular, and measured 6 x 8 x 10 cm. extensively involving the periorbital, temporal, zygomatic, maxilla and mandibular area (Figure 1A). A computer tomography scan revealed a large, lobulated heterogeneously enhancing mass in the left zygomatico-maxillary region, which deforms and erodes the bones in the left side of the skull base, left zygomatic bone, left paranasal sinus walls, septa, left orbit, and a portion of

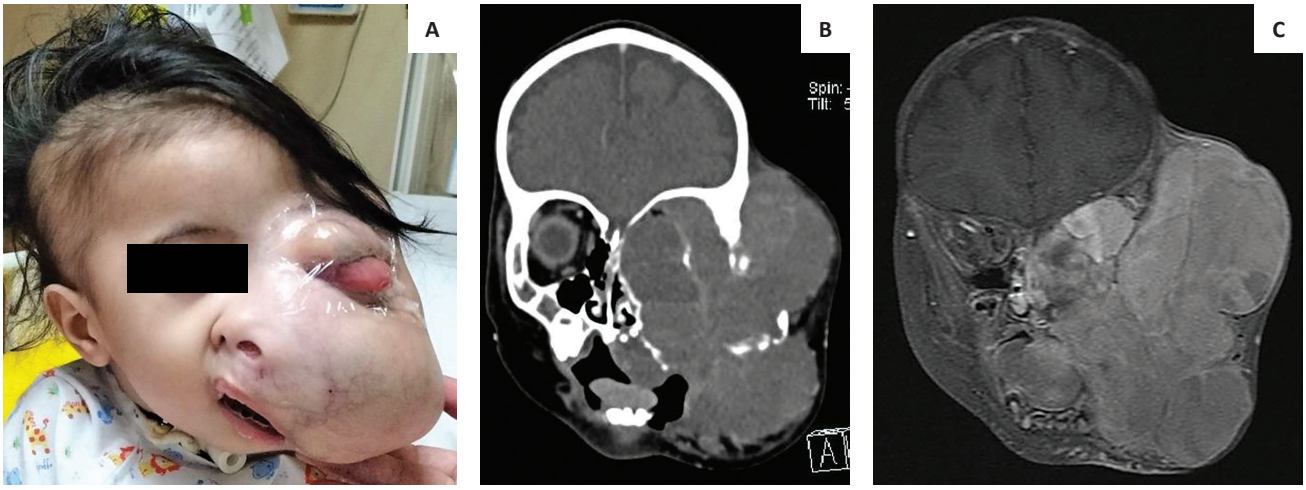

Figure 1. ***Clinical findings and imaging, recurrent lesion.*** **(A)** Gross structure of tumor at 14 months of age; **(B)** Cranial C scan; and **(C)** MRI showing the invasion of tumor to adjacent bone and soft tissue structures.

the body of the left mandible. The adjacent soft tissue structures are poorly defined, the left globe is displaced, and the extraocular muscles and optic nerve cannot be distinguished, indicating potential severe compression or infiltration of these tissues (Figures 1A and 1B). Magnetic resonance imaging showed invasion of the left cavernous sinus and effacement of the anterior aspect of the left middle cranial fossa. Brain parenchymal volume loss is also noted, with no abnormal intracranial parenchymal or meningeal enhancement identified (Figure 1C).

Microscopic findings

Histologic examination of the initial excision biopsy of the lesion disclosed a neoplasm composed of monomorphic, round to slight spindle cells haphazardly arranged in myxoid stroma with prominent, thin-walled blood vessels (Figure 2A). The cells are bland appearing and have ovoid and vesicular nuclei, absent to small nucleoli, and delicate to indistinct, pale, eosinophilic cytoplasm (Figure 2B). The myxoid nodules blend into more fibrous areas composed of vague fascicles of bland short spindle to ovoid cells

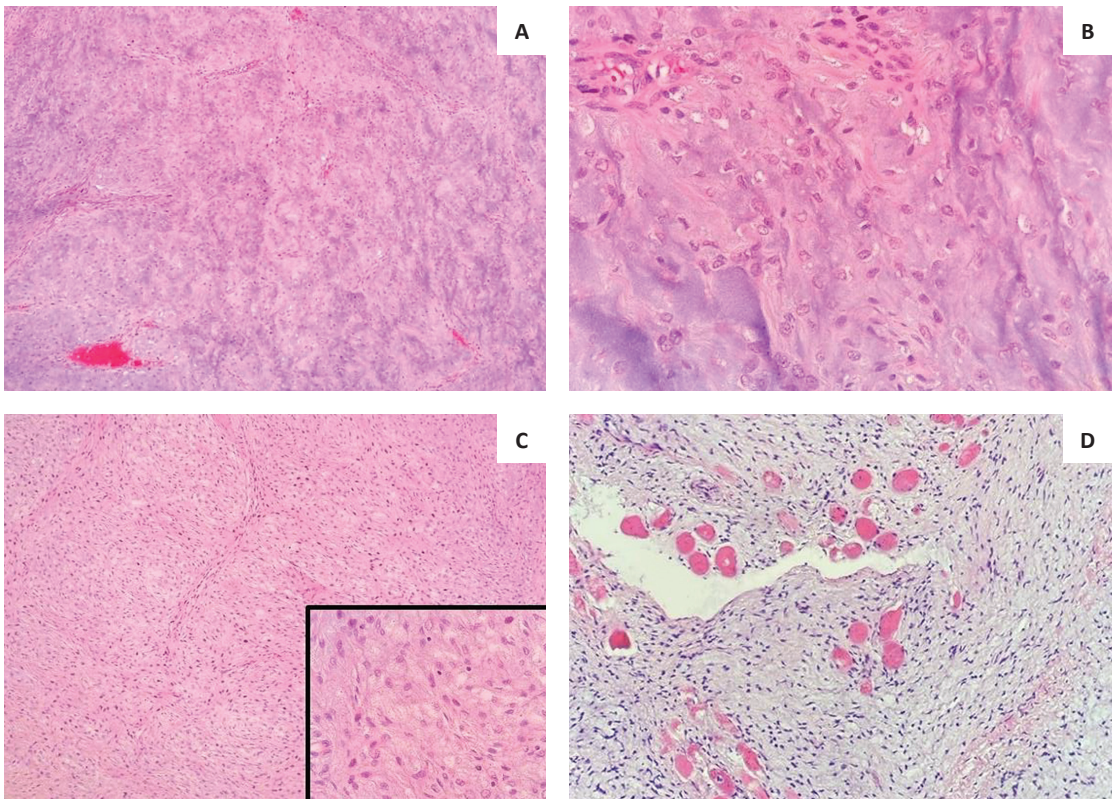

Figure 2. ***Histopathologic findings, initial excision*** *(hematoxylin and eosin stain).* **(A)** Bland round to short spindle cells in myxoid stroma with prominent, thin-walled blood vessels (40x). **(B)** Neoplastic cells with ovoid, vesicular nuclei, absent to small nucleoli, and delicate to indistinct cytoplasm (400x). **(C)** More fibrous areas with vague fascicles of short spindle to ovoid cells (40x, 400x). **(D)** Infiltration of skeletal muscle (200x).

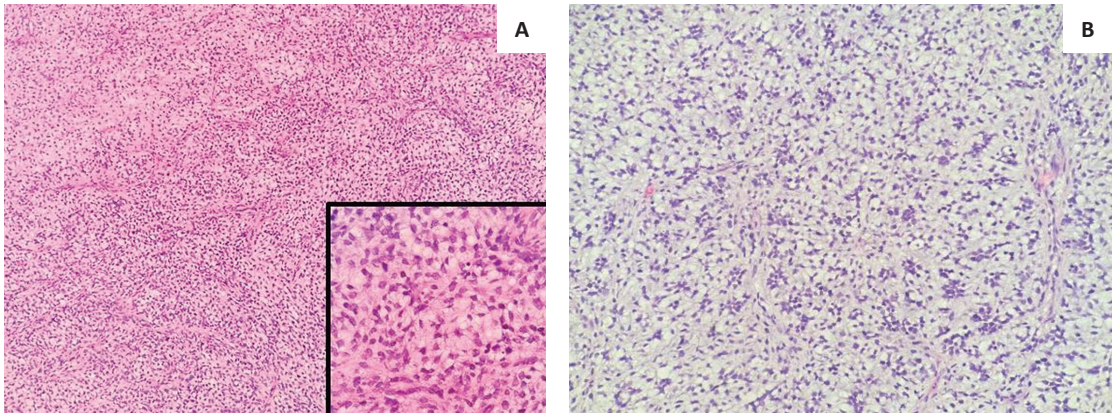

Figure 3. ***Histopathologic findings, recurrence.*** **(A)** Repeat biopsy showed slightly increased cellularity (40x, 400x), and **(B)** focal clustering of cells in myxoid stroma (200x).

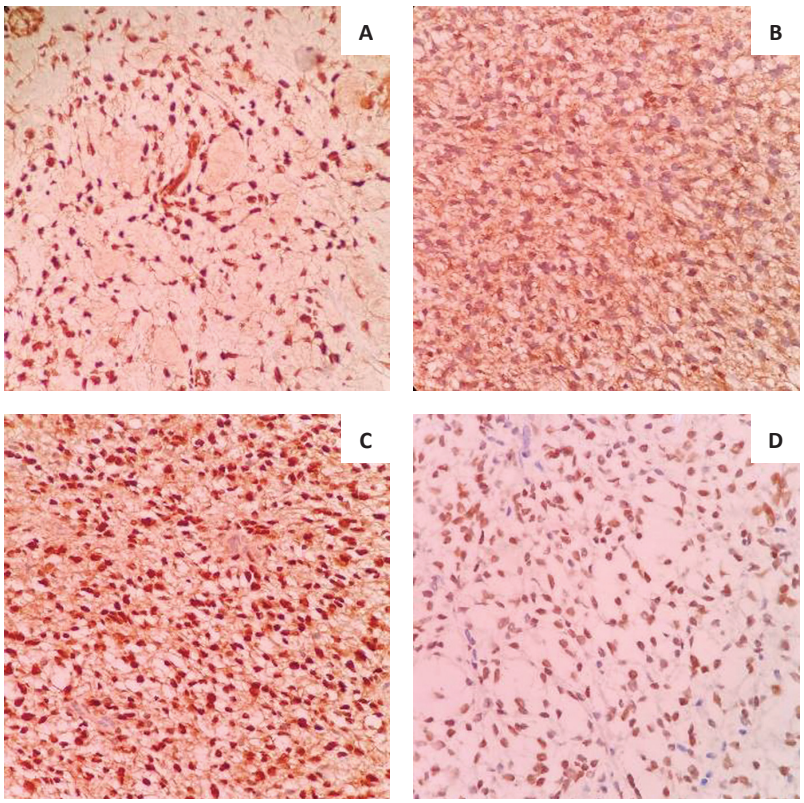

Figure 4. ***Immunohistochemistry (200x)***. **(A)** Retained nuclear staining for INI-1; **(B)** Diffuse, cytoplasmic staining for CD99; **(C)** Diffuse, nuclear staining for Cyclin D1; **(D)** Diffuse, nuclear staining for SATB2.

(Figure 2C). Skeletal muscle invasion was present (Figure 2D). Mitosis is noted at 0 to 4 per 10 high power fields. There were no atypical forms and necrosis was not identified.

An incision biopsy done on the recurrent lesion predominantly displayed similar microscopic features but with increased cellularity and nuclear chromasia (Figure 3A), focal clustering of neoplastic cells (Figure 3B), and slightly increased mitotic activity at 6/10 high power fields.

Immunohistochemical studies

The neoplastic cells showed diffuse immunoreactivity to vimentin, negative staining for cytokeratin, SMA, S100, CD34, ERG, desmin, myogenin, and BCL6, and retained nuclear expression for INI-1 (Figure 4A). Diffuse positivity with CD99, SATB2, cyclin D1 and BCOR immunohistochemistry was noted (Figure 4B, 4C, and 4D; photomicrograph for BCOR immunohistochemistry not available).

Molecular study

Although the immunohistochemical profile and histomorphology were highly suggestive of a sarcoma with BCOR genetic alteration, next-generation sequencing using Archer FusionPlex Pan-Solid Tumor Assay was performed. It detected a BCOR (exon 15) – BCOR (exon 15) breakpoint, indicating the presence of BCOR internal

tandem duplication, and confirming the diagnosis of primitive myxoid mesenchymal tumor of infancy.

Clinical management

With the continuous enlargement of the mass and impending airway/esophageal obstruction, the patient underwent tracheostomy, gastrostomy tube insertion, and porta catheter insertion. The large size and extent of the neoplasm precluded surgical management. Chemotherapy with vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide was initiated. The patient received a total of four cycles of chemotherapy over five months, after which repeat imaging was performed.

Post-treatment reassessment

There appeared to be no changes to the size of the mass on physical examination. Contrast-enhanced craniofacial MRI showed an increase in the size of the mass to 10.3 x 8.1 x 11.6 cm. There was still associated cortical destruction of the adjacent osseous structures and left mastication space, extension to the left orbital space with exophthalmos and superomedial displacement of the conal structures, and extension to the nasal septum. There was progression in the extent of the mass with involvement of the inferomedial aspect of the oral cavity and indentation of the tongue. Abnormal signals with post-contrast enhancement are also seen within the sphenoid sinuses. With this outcome after treatment, chemotherapy was stopped, and the patient was advised palliative care.

DISCUSSION

Primitive myxoid mesenchymal tumor of infancy (PMMTI) is a new category of undifferentiated round cell sarcoma (URCS) that has been proven to be distinct based on histopathology, immunohistochemical markers, and on the nature of the tumor.[1] The molecular hallmark of PMMTI has been recently identified by Kao et al in BCL6 co-repressor (BCOR) gene internal tandem duplication (ITD), the same genetic alteration detected in infantile undifferentiated round cell sarcoma (URCS), clear cell sarcoma of the kidney, group of central nervous system primitive neuroectodermal tumors (CNS-PNET), as well as in certain high-grade endometrial sarcomas, hence suggesting shared pathogenesis.[2,3]

PMMTI typically occurs within the first year of life or may be present at birth, frequently presenting with painless mass ranging from 0.9 cm to 15 cm (mean 6.18 cm). While there is a wide anatomic distribution, the most common sites of occurrence are the deep tissues of the trunk, extremities, and neck. Among the truncal tumors, the paravertebral region is mostly affected.[1,2,4] In the head and neck, cases have been reported around the optic nerve, nasal cavity, throat and scalp.[5-7] In the case presented, the neoplasm arose in an infant at three months of age in the left zygomatic area to subsequently involve the left hemifacial structures extensively. Incompletely resected tumors tend to recur,[5,6] with two cases involving the optic nerve recurring after 8 and 12 months.[5,7] This may be in part due to the difficulty of wide resection in the head and neck region. In the case presented, there was a recurrence five months post-resection with positive margins.

Histologically, PMMTI is characterized by the multinodular appearance and variable cellularity ranging from hypocellular myxoid areas to sheets of primitive spindle and round cells in a myxoid background with delicate vasculature.[1-3,8] In a recent study by Antonescu et al, most of the cases diagnosed as PMMTI displayed predominantly low cellularity, with the myxoid component often in the range of >80-90% of the 13 cases reviewed.[9] Tumor cells have round to ovoid nuclei, with mild to moderate atypia and diffuse hyperchromasia. Necrosis is rarely observed. The mean mitotic rate was 4.1 mitoses (range: 1 to 20 mitoses) per 10 high-power fields. In cases of recurrence and progression, cellularity and cellular atypia were higher. These features were seen in the case presented. The primary neoplasm displayed predominantly mildly cellular myxoid nodules with modest mitotic activity (0 to 4 mitoses per 10 high power fields). The recurrent lesion showed increased cellularity and cytologic atypia, and focal clustering of cells. One case of transformation into an aggressive, undifferentiated sarcoma after chemotherapy and radiation therapy was also reported. Due to its rare incidence, further studies are needed to evaluate the impact of various histologic subtypes and their myxoid component on survival.[4,9,10]

The main differential diagnoses based on histology and age include infantile fibrosarcoma, lipoblastoma, lipofibromatosis, low-grade fibromyxoid sarcoma, embryonal rhabdomyosarcoma, and malignant extrarenal rhabdoid tumor.[8]

Infantile fibrosarcoma (IF) presents as a rapidly enlarging, painless mass and affects children less than 4 years of age with more than 75% diagnosed in the first year of life. It may sometimes arise in the head and neck and has a broad morphological spectrum. It occasionally exhibits monomorphic ovoid to spindle cells in myxoid stroma that resembles PMMTI but is often seen with a hemangiopericytoma-like vascular pattern and a mixed chronic inflammatory infiltrate. The immunohistochemical profile is nonspecific with variable expressions of CD34, S100, SMA and desmin. Pan-TRK antibody may aid in the differential diagnosis as IFs with NTRK rearrangement are immunoreactive, however, this test was not locally available. This lack of characteristic staining pattern in IF and morphologic overlap with PMMTI requires molecular testing to differentiate it from PMMTI. The presence of recurrent ETV6-NTRK3 fusion that confirms its diagnosis[1] was not noted in the NGS testing for this case.

Lipoblastoma is a benign neoplasm of embryonal white fat that similarly occurs in newborns and infants. It occurs in a wide variety of anatomic sites that includes the head and neck and consists of cells with a wide range of maturation states from primitive mesenchymal cells, lipoblasts to mature adipocytes, often with a myxoid background. The presence of primitive mesenchymal cells and myxoid stroma overlaps with PMMTI and it may be difficult to distinguish the two entities in small biopsies as exemplified in this case report. However, the presence of other features (i.e., lipoblasts, mature adipocytes) should aid in the diagnosis. Immunohistochemical studies, which are nonspecific, play a limited role in differentiating lipoblastoma from PMMTI. Lipoblastoma demonstrates

positivity for S100, CD56, and CD34 while the primitive mesenchymal component is often reactive for desmin. The demonstration of rearrangements or amplification of the PLAG1 gene is a characteristic feature.[1] PLAG1 gene aberrations were not noted in the NGS testing for this case.

Lipofibromatosis occurs in children from birth to the second decade of life with a predilection for the hands and feet. The presence of small haphazardly arranged round or oval cells in a myxoid background that is notable in newborn patients may mimic PMMTI. However, it can be easily differentiated due to the presence of interspersed mature adipose cells, capillary-sized vessels, a distinct bundled and fascicular fibroblastic component, and a typical site of predilection. Immunohistochemistry is non-specific with variable expression of CD34 and SMA.[1]

Low-grade fibromyxoid sarcoma (LGFMS) is characterized by collagenous hypocellular areas and cellular myxoid nodules that can histologically imitate PMMTI. However, it can be readily distinguished by its characteristic alternating collagenous and myxoid areas with either an abrupt or gradual transition. It also has a predilection for the proximal extremities and trunk of young adults. Diffuse strong MUC4 reaction and identification of FUS-CREB3L2 fusion confirm the diagnosis.[1] The NGS testing for this case was negative for FUS translocation, dissuading from LGFMS.

Other likely considerations that may occur in the same site and age group, may show round cell morphology and fibromyxoid background including embryonal rhabdomyosarcoma, peripheral nerve sheath tumor, vascular neoplasm, myoepithelial lesions, and malignant extrarenal rhabdoid tumor, but can be readily ruled out based on negative immunohistochemical staining in desmin, myogenin, S100, ERG, CD34, SMA, cytokeratin and retained INI1 expression. In addition, aberrations in CAMTA, EWSR1, and FUS genes were not detected in the NGS testing of this case, which do not support epithelioid hemangioendothelioma, myoepithelial neoplasms, and other undifferentiated round cell sarcomas, respectively.

As with other tumors harboring BCOR gene alterations, PMMTI shows strong and diffuse nuclear positivity for both BCOR and BCL6 as well as in most cases also expresses SATB2, TLE1, and cyclin D1. However, for this case, BCL6 was negative suggesting a variable expression. Moreover, it is positive for vimentin and approximately 50% of cases is reactive for CD99. Even though these immunohistochemical stain markers are nonspecific, they still appear to be very useful in differentiating PMMTI from other tumors, particularly when molecular testing for BCOR internal tandem duplication is not available.[1-3]

The continuous advancement in molecular characterization of human tumors has elucidated the role of the BCOR gene in a variety of mesenchymal neoplasms and more recently in a central nervous system high-grade neuroepithelial tumor. This gene is situated at Xp11.4 and codes for a protein that participates in transcriptional repression by interacting with BCL-6 and promoting epigenetic silencing via polycomb repressive complex 1 (PRC1). Two major genetic alterations have been described namely gene fusions (mainly BCOR-CCNB3, BCOR-MAML3, and ZC3H7B-BCOR) and internal tandem duplications (ITD) of the polycomb-group RING finger homolog (PCGF) ubiquitin-like fold discriminator (PUFD) domain (BCOR-ITD). The presence of the latter distinguishes PMMTI from its histological differential diagnoses. These ITDs were in frame and located in the last exon of BCOR but the nucleotide number and genomic positions were variable.[11] The clinicopathologic importance of the insert size and/or length of the homologous region in positive internal tandem duplication is still unknown due to a limited number of reported cases which restricts a larger multi-institutional investigation.[9]

PMMTI must be differentiated from various analogous pathologies encompassing both benign and malignant conditions due to its different management approach. Available data imply that it has an intermediate biological behavior because it can be locally invasive and infrequently metastasizes.[10] Currently, complete surgical excision with the establishment of negative margins is the gold standard treatment in this pathology. However, consensus treatment protocols for unresectable tumors are still lacking. Based on published cases, chemotherapy resistance is common; however, doxorubicin-containing and ifosfamide-containing regimens seem to be the most effective.[12] Recently, Yang et al., reported a case of a 38-day-old female with right shoulder PMMTI who received an intratumoral injection of bleomycin leading to a distinct boundary between the tumor and adjacent tissue, facilitating its successful resection.[13] The four cycles of doxorubicin and ifosfamide-containing chemotherapy given to the patient, in this case, did not appear to reduce the size and extent of the tumor, and the patient was advised palliative care.

The outcome and long-term survival of patients with PMMTI is mostly unknown.[4, 14] To date, there is only one study published that evaluated the prognosis of 33 BCOR ITD-positive URCS/PMMTI cases which revealed an overall survival of 42% (at 3 years) and 36% (at 5 years). It also found that there was no statistically significant survival difference between cases diagnosed as URCS and PMMTI as well as between those with BCOR ITD and YWHAE fusions.[9]

CONCLUSION

This report emphasizes the importance of cautious attention to histopathologic characteristics, prudent application of immunohistochemical stains together with molecular analysis in differentiating PMMTI from other soft tissue sarcomas. Larger studies are also required to investigate its biologic and clinical behavior and to determine appropriate treatment modalities particularly in unresectable cases.

ETHICAL CONSIDERATIONS

Patient consent was obtained prior to submission.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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Ileo-Ileal Intussusception with Meckel Diverticulum in a Filipino Adolescent

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Key words: ileo-ileal intussusception, Meckel's diverticulum, heterotropia, adolescent, Filipino

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INTRODUCTION

Intussusception refers to the invagination (telescoping) of a part of the intestine into itself. Intussusception occurs primarily in infants and toddlers.[1] The peak incidence is between 4 and 36 months of age, and it is the most common cause of intestinal obstruction in this age group.[2] Approximately 1 percent of cases are in infants younger than three months, 30 percent between 3 and 12 months, 20 percent between one and two years, 25 percent between two and three years, and 10 percent between three and four years.[3] Although intussusception is most common in infants and young children, it is important to consider this diagnosis in children outside this age range. Approximately 10 percent of cases are in children over five years, and 3 to 4 percent in those over 10 years.[3,4] We share here images from an actual case of a 15-year-old Filipino male with an ileo-ileal intussusception that is beyond the typical age range, with an incidental finding of an intraluminal mass that was histomorphologically diagnosed as Meckel's diverticulum (MD). The diagnosis of intussusception is relatively rare in the patient's age and the diagnosis of MD in the presence of intussusception is sparsely reported in the Philippines.

Briefly, a previously well 15-year-old male presented with epigastric discomfort for one week prior to admission. This was associated with abdominal distention, vomiting and hematochezia. The patient was subjected to CT Whole Abdomen with IV Contrast revealing: ileo-ileal intussusception causing small bowel obstruction, minimal ascites, and hiatal hernia (Figure 1).

The patient underwent surgical resection and the resected portion was then submitted for histopathologic evaluation (Figure 2A). The specimen consisted of a light gray to dark brown, partially-opened bowel segment measuring 50.8 cm in length by 5.2 cm in diameter in one line of resection (inked blue) and 1.5 cm in diameter in the other line of resection (inked black), and a segment of intussuscepted bowel measuring 19.6 cm in length, with adherent fibrinopurulent material, is noted 13.0 cm from one line of resection. Opening of the bowel segment shows a dark red-brown mucosa with hemorrhagic areas. A constricted segment measuring 3.0 cm x 0.8 cm (inked red) is noted to telescope into the adjacent bowel lumen. An area of ulceration measuring 1.5 x 1.0 cm, is noted 7.0 cm from one line of resection. The rest of the bowel has a well-folded, tan brown mucosa (Figure 2B).

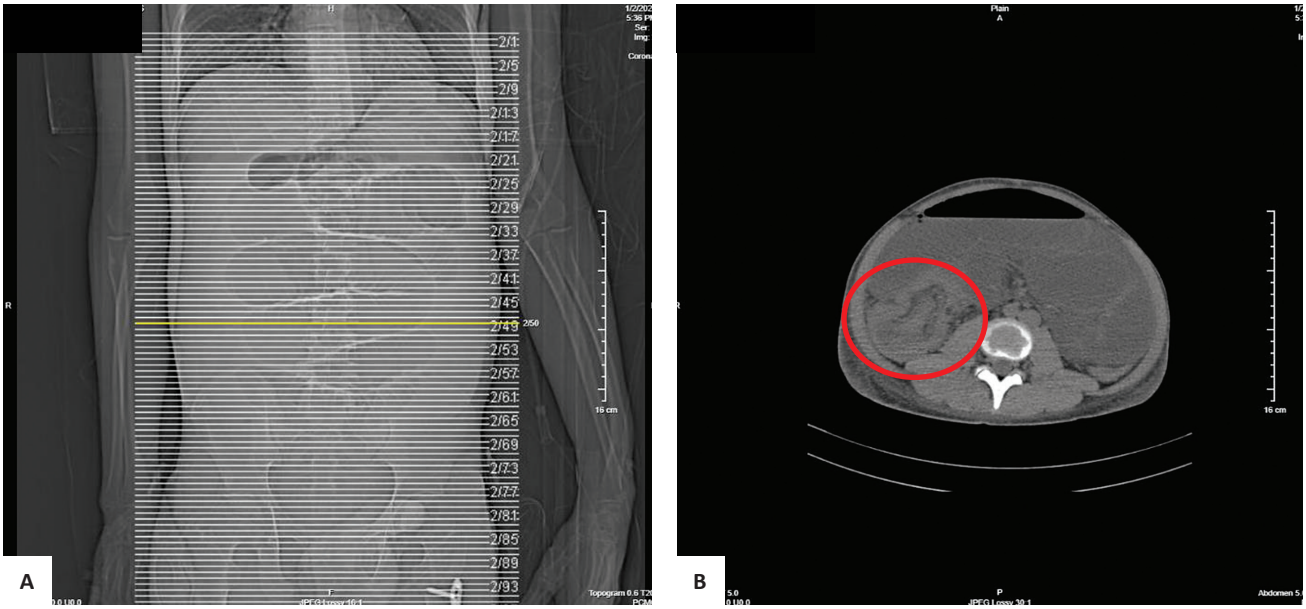

Figure 1. **(A)** CT Whole Abdomen with IV contrast (Coronal Plane) showing a bowel-within-bowel configuration; **(B)** CT Whole Abdomen with IV Contrast (Transverse Plane) showing a bowel-within-bowel configuration *(red circle)*.

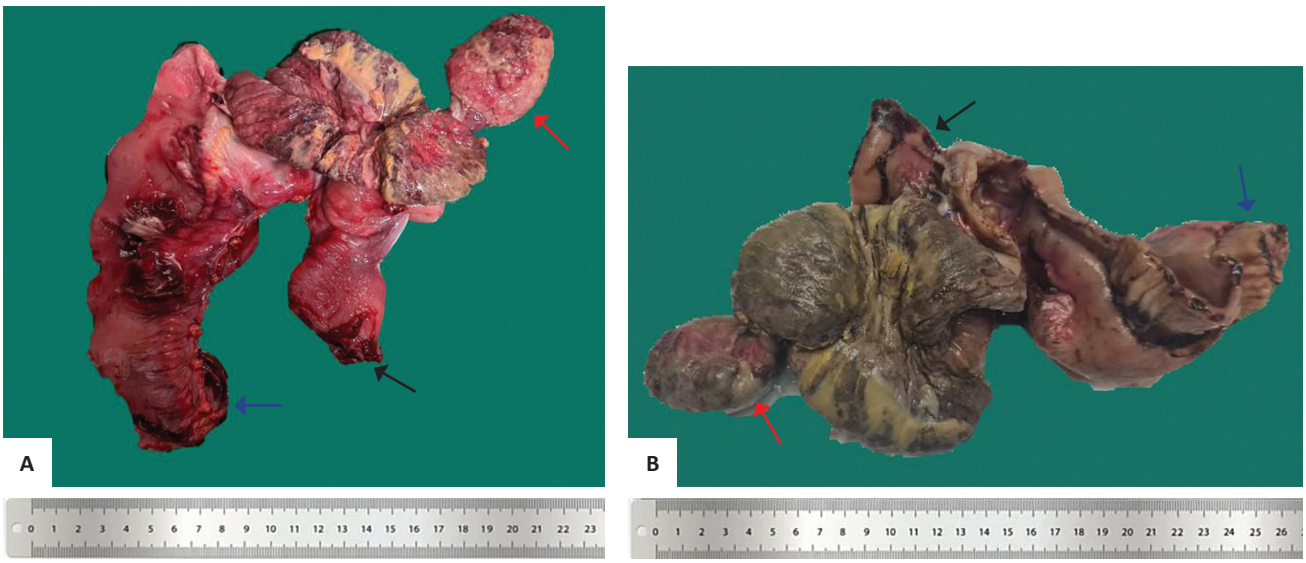

Figure 2. **(A)** Gross figure of Ileo-ileal resection specimen; *(red arrow)* intussusceptum; *(blue arrow)* one (1) line of resection; *(black arrow)* other line of resection. **(B)** Gross figure of fixed Ileo-ileal resection specimen; *(red arrow)* intussusceptum; *(blue arrow)* one (1) line of resection; *(black arrow)* other line of resection.

Microscopic examination shomws benign intestinal tissue with large areas of transmural infarction, hemorrhage and foci of necrosis of the area of intussusception (Figure 3A). There are submucosal and myenteric plexi with Schwann cells and ganglion cells identified throughout the intestinal segment (Figure 3B). Benign pancreatic tissue (Figure 3C) and gastric mucosa (Figure 3D) are seen interspersed within the stroma. No atypical or malignant cells were noted.

The most common congenital abnormality in the gastrointestinal tract is MD. It occurs in 1% to 2% of the population. MD is more often asymptomatic, and when complications develop it becomes apparent. MD is the most common clinical presentation of MD is intestinal obstruction in adults and second most common in children. In pediatric presentation of intussusception, there may be acute onset of abdominal pain, vomiting or painless red currant stools. Both abdominal pain and vomiting are present in the case presented. Rarely, inversion of MD into the lumen of the bowel can cause intussusception, ischemia and infarction. The incidence of intussusception attributed to an inversion of MD accounts for 4% of all cases presenting with intestinal obstruction due to intussusception. is an outpouching of all three layers of the enteric mucosa characterized by a persistent remnant of the vitellointestinal duct. MD droops into the bowel lumen and then initiates as a lead point to allow telescoping of the

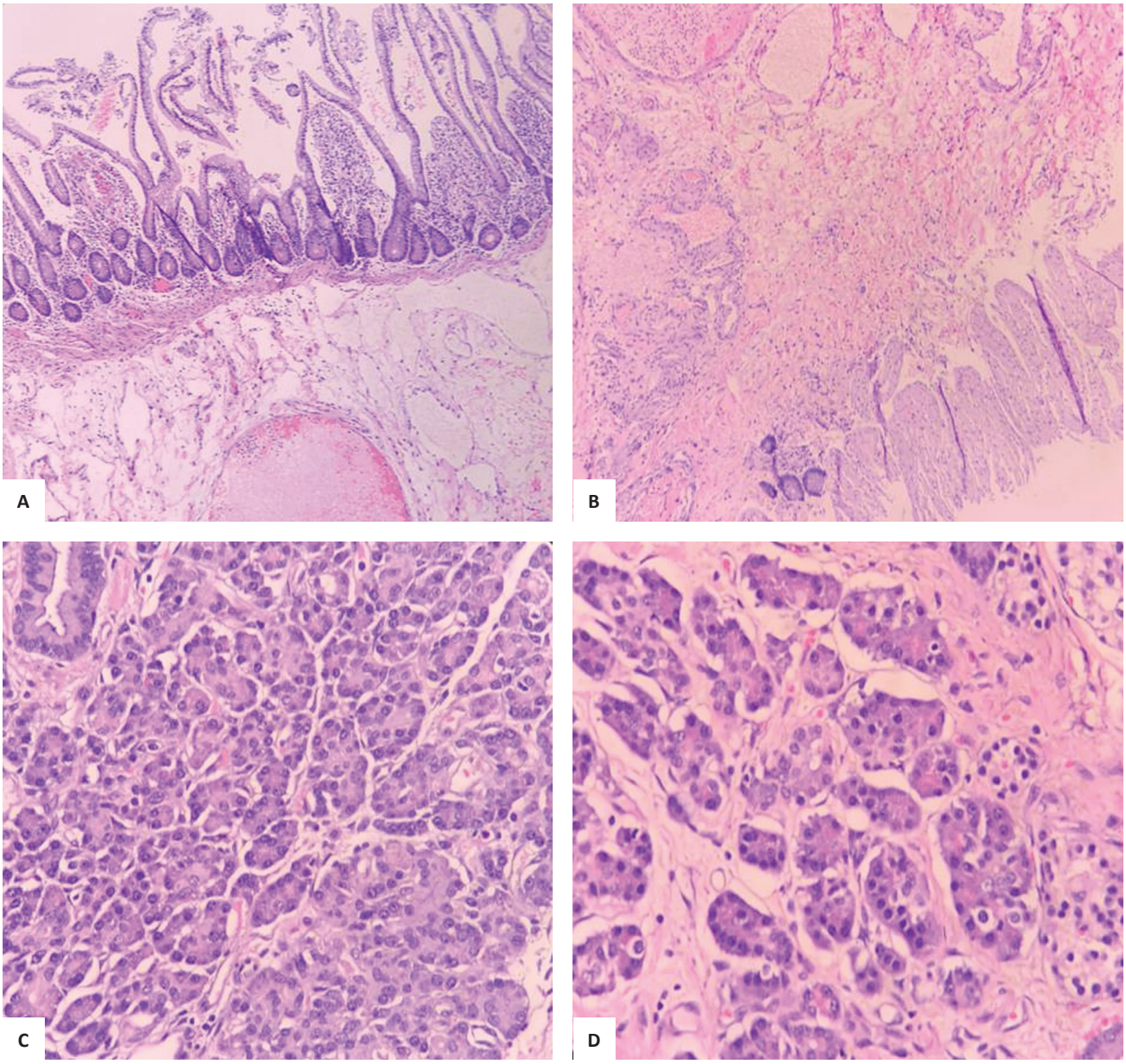

Figure 3. **(A)** Intestinal tissue with areas of hemorrhage and necrosis *(H&E 100x)*; **(B)** Intestinal mucosa with transmural infarction, hemorrhage and necrosis. There are submucosal plexi with Schwann cells and ganglion cells *(H&E 100x)*; **(C)** Pancreatic tissue *(H&E 400x)*; and **(D)** Gastric mucosa *(H&E 400x)*.

intestinal segment, first into the distal ileum and then into the large intestine, causing ileo-ileal and ileocolic type of intussusceptions. [5-8] In a retrospective study that involves 100 children with diagnosed cases of symptomatic MD. Seventeen cases are associated with intussusception having a mean age of 4.55 ± 3.76 with male predominance.[9] Histologically, MD is composed of intestinal villi, crypts, Paneth cells and abundant goblet cells with gastric mucosa and or pancreatic acini. In this case, it is worth noting that both gastric mucosa and pancreatic acini are present.

ETHICAL CONSIDERATION

Patient consent was obtained before submission of the manuscript.

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- **For manuscripts under the "Feature Article," "Review Article," "Case Report," "Brief Communications," and "Autopsy Vault" sections:** the abstract should be no more than 200 words and need not be structured.
- Letters to the Editor and editorials do not require an abstract.

Keywords

At least three (3) keywords but no more than six (6), preferably using terms from the **Medical Subject Headings (MeSH) list of Index Medicus,** should be listed horizontally under the abstract for cross-indexing of the article.

Text

- The text should be organized consecutively as follows: **Introduction, Methodology, Results and Discussion, Conclusion** (IMRaD format), followed by **Disclosures, Acknowledgments** and **References.**
- All references, tables, figures and illustrations should be cited in the text, in numerical order.
- All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the full names.
- All measurements and weights should be in System International (SI) units.
- Under **Methodology**, information should be provided on institutional review board/ethics committee approval or informed consent taking (if appropriate).
- **Acknowledgements** to individuals/groups of persons, or institution/s who have contributed to the manuscript but *did not qualify as authors* based on the ICMJE criteria, should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

References

- References in the text should be identified by Hindu-Arabic Numerals in superscript on the same line as the preceding sentence.
- References should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
- All references should provide inclusive page numbers.
- Journal abbreviations should conform to those used in PubMed.
- A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
- The style/punctuation approved by PJP conforms to that recommended by the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org. Examples are shown below:

One to Six Authors

Krause RM. The origin of plagues: old and new. *Science*. 1992;257:1073-1078.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the US. JAMA. 2001;286(10):1195-1200.

More than Six Authors

Rhynes VK, McDonald JC, Gelder FB, et al. Soluble HLA class I in the serum of transplant recipients. Ann Surg. 1993; 217 (5): 485–9.

Authors Representing a Group

Moher D, Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-1991.

Book

Byrne, DW. Publishing your medical research paper: What they don't teach in medical school. Baltimore: Williams & Wilkins, 1998.

World Wide Web

Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. JTranslational Med. January 20, 2004;2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

Tables

- Cite all tables consecutively in the text and number them accordingly.
- Create tables preferably using Microsoft Excel with one table per worksheet.
- Tables should not be saved as image files.
- The content of tables should include a table number (Hindu-Arabic) and title in capital letters above the table.
- Place explanatory notes and legends, as well as definitions of abbreviations used below the table. For legends, use small letters (i.e., a, b, c, d).
- Each table must be self-explanatory, being a supplement rather than a duplicate of information in the text.
- Up to a maximum of five (5) tables are allowed.

Figures and Graphs

- Figures or graphs should be identified by Hindu-Arabic Numeral/s with titles and explanations underneath.
- The numbers should correspond to the order in which the figures/graphs occur in the text.
- Figures & graphs should not be saved as image files. For illustrations and photographs, see next section.
- Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
- All identifying data of the subject/s or patient/s under study such as name or case numbers, should be removed.
- Up to a maximum of five (5) figures and graphs are allowed.

Illustrations and Photographs

- Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as .png, .jpeg, .tif, .psd or .pdf files).
- For photomicrographs, the stain used (e.g. H & E) and magnification (e.g. 400X) should be included in the description.
- Computer-generated illustrations which are not suited for reproduction should be professionally redrawn or printed on good quality laser printers. Photocopies are not acceptable.
- All letterings for illustration should be of adequate size to be readable even after size reduction.
- Place explanatory notes and legends, as well as definitions of abbreviations used below the illustration/photograph.
- Up to a maximum of five (5) illustrations/ photographs are allowed.

N.B.: For tables, figures, graphs, illustrations and photographs that have been previously published in another journal or book, a note must be placed under the specific item stating that such has been adapted or lifted from the original publication. This should also be referenced in the **References** portion.

EDITORIAL PROCESS (Figure 1)

- The Editorial Coordinator shall review each submission to check if it has met aforementioned criteria and provide feedback to the author within 24 hours.
- Once complete submission is acknowledged, the manuscript undergoes Editorial Board Deliberation to decide whether it shall be considered or not for publication in the journal. Within five (5) working days, authors shall be notified through e-mail that their manuscript either (a) has been sent to referees for peer-review or (b) has been declined without review.
- The PJP implements a strict double blind peer review policy. For manuscripts that are reviewed, authors can expect a decision within ten (10) working days from editorial deliberation. There may be instances when decisions can take longer: in such cases, the Editorial Coordinator shall inform the authors.
- The editorial decision for manuscripts shall be one of the following: (a) acceptance without further revision, (b) acceptance with minor revisions, (c) major manuscript revision and resubmission, or (d) non-acceptance.
- Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal. Copyediting and layout shall take five (5) working days, after which the manuscript is published online.
- All online articles from the last six (6) months shall be collated and published in print as a full issue.

EDITORIAL OFFICE CONTACT INFORMATION:

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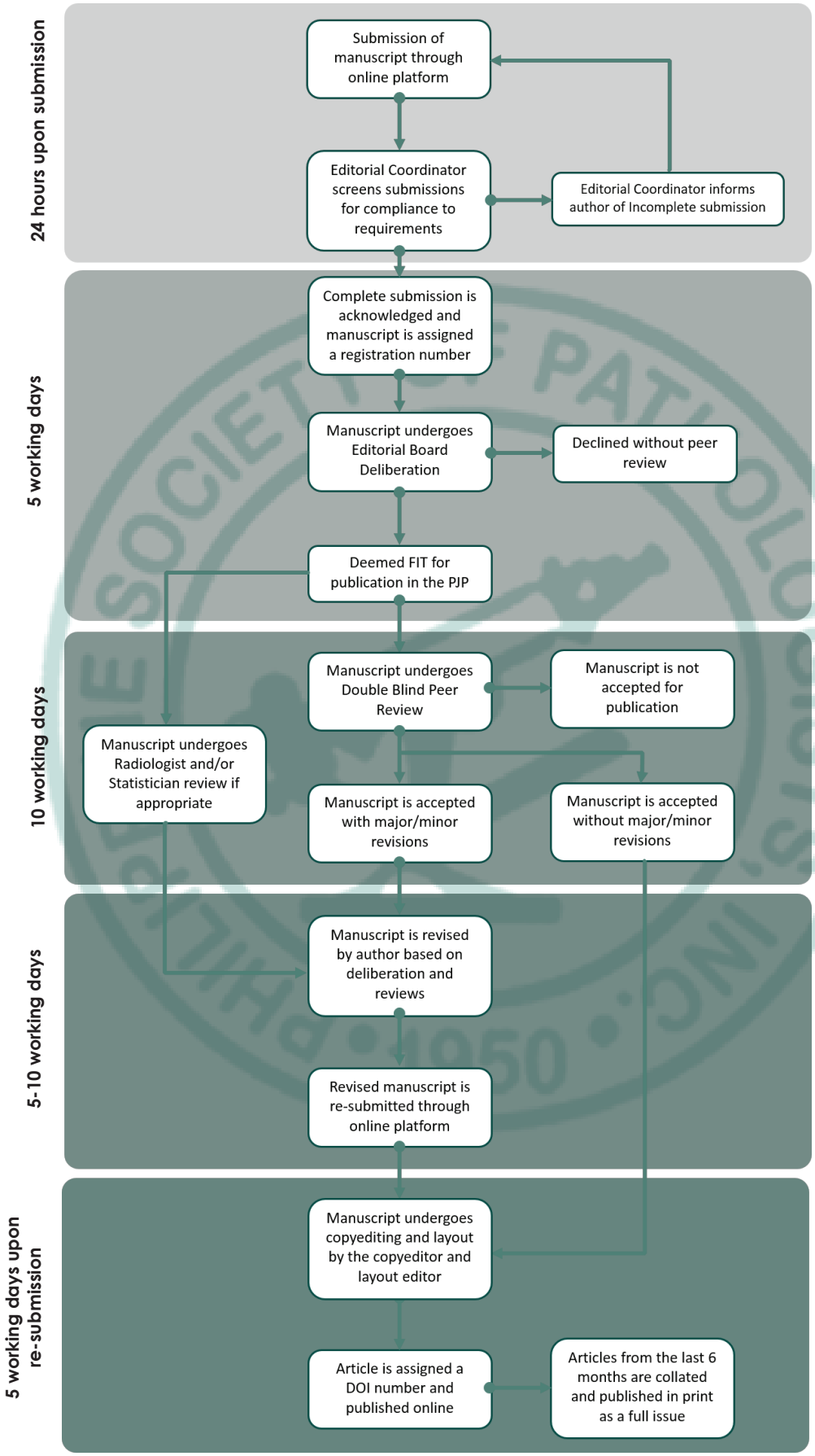

Figure 1. Editorial Process Flow.

PHILIPPINE JOURNAL OF PATHOLOGY
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PJP AUTHOR FORM

For submissions to the PJP to be accepted, all authors must read and sign this PJP Author Form consisting of: (1) the Authorship Certification, (2) the Author Declaration, (3) the Statement of Copyright Transfer, and (4) the Statement of Disclosure of Conflicts of Interest. The completely accomplished PJP Author Form shall be scanned and submitted along with the manuscript. No manuscript shall be received without the PJP Author Form.

COMPLETE TITLE OF MANUSCRIPT

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AUTHORSHIP CERTIFICATION

☐ In consideration of our submission to the Philippine Journal of Pathology (PJP), the undersigned author(s) of the manuscript hereby certify, that all of us have actively and sufficiently participated in (1) the conception or design of the work, the acquisition, analysis and interpretation of data for the work; AND (2)drafting the work, revising it critically for important intellectual content; AND (3) that we are all responsible for the final approval of the version to be published; AND (4) we all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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☐ The undersigned author(s) of the manuscript hereby certify, that the submitted manuscript represents original, exclusive and unpublished material. It is not under simultaneous consideration for publication elsewhere. Furthermore, it will not be submitted for publication in another journal, until a decision is conveyed regarding its acceptability for publication in the PJP.

☐ The undersigned hereby certify, that the study on which the manuscript is based had conformed to ethical standards and/or had been reviewed by the appropriate ethics committee.

☐ The undersigned likewise hereby certify that the article had written/informed consent for publication from involved subjects (for case report/series only) and that in case the involved subject/s can no longer be contacted (i.e., retrospective studies, no contact information, et cetera), all means have been undertaken by the author(s) to obtain the consent.

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AUTHOR DISCLOSURE OF CONFLICTS OF INTEREST

In order to ensure scientific objectivity and independence, the PJP requires all authors to make a full disclosure of areas of potential conflict of interest. Such disclosure will indicate whether the person and/or his/her immediate family has any financial relationship with pharmaceutical companies, medical equipment manufacturers, biomedical device manufacturers, or any companies with significant involvement in the field of health care. Place all disclosures in the table below. An extra form may be used if needed.

Examples of disclosures include but not limited to: ownership, employment, research support (including provision of equipment or materials), involvement as speaker, consultant, or any other financial relationship or arrangement with manufacturers, companies or suppliers. With respect to any relationships identified, author(s) must provide sufficiently detailed information to permit assessment of the significance of the potential conflict of interest (for example, the amount of money involved and/or the identification of any value of goods and services).

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All disclosures shall remain confidential during the review process and the nature of any final printed disclosure will be determined by the PJP. If there are no conflicts of interest to disclose, the author(s) should check the box below.

☐ I/We do not have any conflicts of interest to disclose.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals

Updated May 2022

I. About the Recommendations

A. Purpose of the Recommendations

ICMJE developed these recommendations to review best practice and ethical standards in the conduct and reporting of research and other material published in medical journals, and to help authors, editors, and others involved in peer review and biomedical publishing create and distribute accurate, clear, reproducible, unbiased medical journal articles. The recommendations may also provide useful insights into the medical editing and publishing process for the media, patients and their families, and general readers.

B. Who Should Use the Recommendations?

These recommendations are intended primarily for use by authors who might submit their work for publication to ICMJE member journals. Many non-ICMJE journals voluntarily use these recommendations (see www.icmje.org/journals-following-the-icmje-recommendations/). The ICMJE encourages that use but has no authority to monitor or

enforce it. In all cases, authors should use these recommendations along with individual journals' instructions to authors. Authors should also consult guidelines for the reporting of specific study types (e.g., the CONSORT guidelines for the reporting of randomized trials); see www.equator-network.org.

Journals that follow these recommendations are encouraged to incorporate them into their instructions to authors and to make explicit in those instructions that they follow ICMJE recommendations. Journals that wish to be identified on the ICMJE website as following these recommendations should notify the ICMJE secretariat at www.icmje.org/journals-following-the-icmje-recommendations/journal-listing-request-form/. Journals that in the past have requested such identification but who no longer follow ICMJE recommendations should use the same means to request removal from this list.

The ICMJE encourages wide dissemination of these recommendations and reproduction of this document in its entirety for educational, not-for-profit purposes without regard for copyright, but all uses of the recommendations and document should direct readers to www.icmje.org for the official, most recent version, as the ICMJE updates the recommendations periodically when new issues arise.

C. History of the Recommendations

The ICMJE has produced multiple editions of this document, previously known as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). The URM was first published in 1978 as a way of standardizing manuscript format and preparation across journals. Over the years, issues in publishing that went well beyond manuscript preparation arose, resulting in the development of separate statements, updates to the document, and its renaming as "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" to reflect its broader scope. Previous versions of the document may be found in the "Archives" section of www.icmje.org.

II. Roles and Responsibilities of Authors, Contributors, Reviewers, Editors, Publishers, and Owners

A. Defining the Role of Authors and Contributors

1. Why Authorship Matters

Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work. The following recommendations are intended to ensure that contributors who have made substantive intellectual contributions to a paper are given credit as authors, but also that contributors credited as authors understand their role in taking responsibility and being accountable for what is published.

Because authorship does not communicate what contributions qualified an individual to be an author, some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy. Such policies remove much of the ambiguity surrounding contributions, but leave unresolved the question of the quantity and quality of contribution that qualify an individual for authorship. The ICMJE has thus developed criteria for authorship that can be used by all journals, including those that distinguish authors from other contributors.

2. Who Is an Author?

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged–see Section II. A.3 below. These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion #s 2 or 3. Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript.

The individuals who conduct the work are responsible for identifying who meets these criteria and ideally should do so when planning the work, making modifications as appropriate as the work progresses. We encourage collaboration and co-authorship with colleagues in the locations where the research is conducted. It is the collective responsibility of the authors, not the journal to which the work is submitted, to determine that all people named as authors meet all four criteria; it is not the role of journal editors to determine who qualifies or does not qualify for authorship or to arbitrate authorship conflicts. If agreement cannot be reached about who qualifies for authorship, the institution(s) where the work was performed, not the journal editor, should be asked to investigate. The criteria used to determine the order in which authors are listed on the byline may vary, and are to be decided collectively by the author group and not by

editors. If authors request removal or addition of an author after manuscript submission or publication, journal editors should seek an explanation and signed statement of agreement for the requested change from all listed authors and from the author to be removed or added.

The corresponding author is the one individual who takes primary responsibility for communication with the journal during the manuscript submission, peer-review, and publication process. The corresponding author typically ensures that all the journal's administrative requirements, such as providing details of authorship, ethics committee approval, clinical trial registration documentation, and disclosures of relationships and activities, are properly completed and reported, although these duties may be delegated to one or more co-authors. The corresponding author should be available throughout the submission and peer-review process to respond to editorial queries in a timely way, and should be available after publication to respond to critiques of the work and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication. Although the corresponding author has primary responsibility for correspondence with the journal, the ICMJE recommends that editors send copies of all correspondence to all listed authors.

When a large multi-author group has conducted the work, the group ideally should decide who will be an author before the work is started and confirm who is an author before submitting the manuscript for publication. All members of the group named as authors should meet all four criteria for authorship, including approval of the final manuscript, and they should be able to take public responsibility for the work and should have full confidence in the accuracy and integrity of the work of other group authors. They will also be expected as individuals to complete disclosure forms.

Some large multi-author groups designate authorship by a group name, with or without the names of individuals. When submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists, and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript, and MEDLINE lists as authors whichever names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.

3. Non-Author Contributors

Contributors who meet fewer than all 4 of the above criteria for authorship should not be listed as authors, but they should be acknowledged. Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading. Those whose contributions do not justify authorship may be acknowledged individually or together as a group under a single heading (e.g., "Clinical Investigators" or "Participating Investigators"), and their contributions should be specified (e.g., "served as scientific advisors," "critically reviewed the study proposal," "collected data," "provided and cared for study patients," "participated in writing or technical editing of the manuscript").

Because acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, editors are advised to require that the corresponding author obtain written permission to be acknowledged from all acknowledged individuals.

B. Disclosure of Financial and Non-Financial Relationships and Activities, and Conflicts of Interest

Public trust in the scientific process and the credibility of published articles depend in part on how transparently an author's relationships and activities, directly or topically related to a work, are handled during the planning, implementation, writing, peer review, editing, and publication of scientific work.

The potential for conflict of interest and bias exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest.

Individuals may disagree on whether an author's relationships or activities represent conflicts. Although the presence of a relationship or activity does not always indicate a problematic influence on a paper's content, perceptions of conflict may erode trust in science as much as actual conflicts of interest. Ultimately, readers must be able to make their own judgments regarding whether an author's relationships and activities are pertinent to a paper's content. These judgments require transparent disclosures. An author's complete disclosure demonstrates a commitment to transparency and helps to maintain trust in the scientific process.

Financial relationships (such as employment, consultancies, stock ownership or options, honoraria, patents, and paid expert testimony) are the most easily identifiable, the ones most often judged to represent potential conflicts of interest and thus the most likely to undermine the credibility of the journal, the authors, and science itself. Other interests may also represent or be perceived as conflicts, such as personal relationships or rivalries, academic competition, and intellectual beliefs.

Authors should avoid entering into agreements with study sponsors, both for-profit and nonprofit, that interfere with authors' access to all of the study's data or that interfere with their ability to analyze and interpret the data and to prepare and publish manuscripts independently when and where they choose. Policies that dictate where authors may publish their work violate this

principle of academic freedom. Authors may be required to provide the journal with the agreements in confidence.

Purposeful failure to report those relationships or activities specified on the journal's disclosure form is a form of misconduct, as is discussed in Section III.B.

1. Participants

All participants in the peer-review and publication process—not only authors but also peer reviewers, editors, and editorial board members of journals—must consider and disclose their relationships and activities when fulfilling their roles in the process of article review and publication.

a. Authors

When authors submit a manuscript of any type or format they are responsible for disclosing all relationships and activities that might bias or be seen to bias their work. The ICMJE has developed a Disclosure Form to facilitate and standardize authors' disclosures. ICMJE member journals require that authors use this form, and ICMJE encourages other journals to adopt it.

b. Peer Reviewers

Reviewers should be asked at the time they are asked to critique a manuscript if they have relationships or activities that could complicate their review. Reviewers must disclose to editors any relationships or activities that could bias their opinions of the manuscript, and should recuse themselves from reviewing specific manuscripts if the potential for bias exists. Reviewers must not use knowledge of the work they're reviewing before its publication to further their own interests.

c. Editors and Journal Staff

Editors who make final decisions about manuscripts should recuse themselves from editorial decisions if they have relationships or activities that pose potential conflicts related to articles under consideration. Other editorial staff members who participate in editorial decisions must provide editors with a current description of their relationships and activities (as they might relate to editorial judgments) and recuse themselves from any decisions in which an interest that poses a potential conflict exists. Editorial staff must not use information gained through working with manuscripts for private gain. Editors should regularly publish their own disclosure statements and those of their journal staff. Guest editors should follow these same procedures.

Journals should take extra precautions and have a stated policy for evaluation of manuscripts submitted by individuals involved in editorial decisions. Further guidance is available from COPE (https://publicationethics.org/files/A_Short_Guide_to_Ethical_Editing.pdf) and WAME (http://wame.org/conflict-of-interest-in-peer-reviewed-medical-journals).

2. Reporting Relationships and Activities

Articles should be published with statements or supporting documents, such as the ICMJE Disclosure Form, declaring:

- Authors' relationships and activities; and
- Sources of support for the work, including sponsor names along with explanations of the role of those sources if any in study design; collection, analysis, and interpretation of data; writing of the report; any restrictions regarding the submission of the report for publication; or a statement declaring that the supporting source had no such involvement or restrictions regarding publication; and
- Whether the authors had access to the study data, with an explanation of the nature and extent of access, including whether access is ongoing.

To support the above statements, editors may request that authors of a study sponsored by a funder with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

C. Responsibilities in the Submission and Peer-Review Process

1. Authors

Authors should abide by all principles of authorship and declaration of relationships and activities detailed in Sections II.A and II.B of this document.

a. Predatory or Pseudo-Journals

A growing number of entities are advertising themselves as "scholarly medical journals" yet do not function as such. These journals ("predatory" or "pseudo-journals") accept and publish almost all submissions and charge article processing (or publication) fees, often informing authors about this after a paper's acceptance for publication. They often claim to perform peer review but do not and may purposefully use names similar to well-established journals. They may state that they are members of ICMJE but are not (see www.icmje.org for current members of the ICMJE) and that they follow the recommendations of organizations such as the ICMJE, COPE, and WAME. Researchers must be aware of the existence of such entities and avoid submitting research to them for publication. Authors have a responsibility to evaluate the integrity, history, practices, and reputation of the journals to which they submit manuscripts. Guidance from various organizations is available to help identify the characteristics of reputable peer-reviewed journals (www.wame.org/identifying-predatory-or-pseudo-journals and www.wame.org/principles-of-transparency-and-best-practice-in-scholarly-publishing).

Seeking the assistance of scientific mentors, senior colleagues, and others with many years of scholarly publishing experience may also be helpful.

Authors should avoid citing articles in predatory or pseudo-journals.

2. Journals

a. Confidentiality

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Editors therefore must not share information about manuscripts, including whether they have been received and are under review, their content and status in the review process, criticism by reviewers, and their ultimate fate, to anyone other than the authors and reviewers. Requests from third parties to use manuscripts and reviews for legal proceedings should be politely refused, and editors should do their best not to provide such confidential material should it be subpoenaed.

Editors must also make clear that reviewers should keep manuscripts, associated material, and the information they contain strictly confidential. Reviewers and editorial staff members must not publicly discuss the authors' work, and reviewers must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy paper copies of manuscripts and delete electronic copies after submitting their reviews.

When a manuscript is rejected, it is best practice for journals to delete copies of it from their editorial systems unless retention is required by local regulations. Journals that retain copies of rejected manuscripts should disclose this practice in their Information for Authors.

When a manuscript is published, journals should keep copies of the original submission, reviews, revisions, and correspondence for at least three years and possibly in perpetuity, depending on local regulations, to help answer future questions about the work should they arise.

Editors should not publish or publicize peer reviewers' comments without permission of the reviewer and author. If journal policy is to blind authors to reviewer identity and comments are not signed, that identity must not be revealed to the author or anyone else without the reviewers' expressed written permission.

Confidentiality may have to be breached if dishonesty or fraud is alleged, but editors should notify authors or reviewers if they intend to do so and confidentiality must otherwise be honored.

b. Timeliness

Editors should do all they can to ensure timely processing of manuscripts with the resources available to them. If editors intend to publish a manuscript, they should attempt to do so in a timely manner and any planned delays should be negotiated with the authors. If a journal has no intention of proceeding with a manuscript, editors should endeavor to reject the manuscript as soon as possible to allow authors to submit to a different journal.

c. Peer Review

Peer review is the critical assessment of manuscripts submitted to journals by experts who are usually not part of the editorial staff. Because unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including scientific research, peer review is an important extension of the scientific process.

The actual value of peer review is widely debated, but the process facilitates a fair hearing for a manuscript among members of the scientific community. More practically, it helps editors decide which manuscripts are suitable for their journals. Peer review often helps authors and editors improve the quality of reporting.

It is the responsibility of the journal to ensure that systems are in place for selection of appropriate reviewers. It is the responsibility of the editor to ensure that reviewers have access to all materials that may be relevant to the evaluation of the manuscript, including supplementary material for e-only publication, and to ensure that reviewer comments are properly assessed and interpreted in the context of their declared relationships and activities.

A peer-reviewed journal is under no obligation to send submitted manuscripts for review, and under no obligation to follow reviewer recommendations, favorable or negative. The editor of a journal is ultimately responsible for the selection of all its content, and editorial decisions may be informed by issues unrelated to the quality of a manuscript, such as suitability for the journal. An editor can reject any article at any time before publication, including after acceptance if concerns arise about the integrity of the work.

Journals may differ in the number and kinds of manuscripts they send for review, the number and types of reviewers they seek for each manuscript, whether the review process is open or blinded, and other aspects of the review process. For this reason and as a service to authors, journals should publish a clear, transparent description of their peer-review process for all types of manuscripts.

Journals should notify reviewers of the ultimate decision to accept or reject a paper, and should acknowledge the contribution of peer reviewers to their journal. Editors are encouraged to share reviewers' comments with co-reviewers of the same paper, so reviewers can learn from each other in the review process.

As part of peer review, editors are encouraged to review research protocols, plans for statistical analysis if separate from the protocol, and/or contracts associated with project-specific studies. Editors should encourage authors to make such documents publicly available at the time of or after publication, before accepting such studies for publication. Some journals may require public posting of these documents as a condition of acceptance for publication.

Journal requirements for independent data analysis and for public data availability are in flux at the time of this revision, reflecting evolving views of the importance of data availability for pre- and post-publication peer review. Some journal editors currently request a statistical analysis of trial data by an independent biostatistician before accepting studies for publication. Others ask authors to say whether the study data are available to third parties to view and/or use/reanalyze, while still others encourage or require authors to share their data with others for review or reanalysis. Each journal should establish and publish their specific requirements for data analysis and post in a place that potential authors can easily access.

Some people believe that true scientific peer review begins only on the date a paper is published. In that spirit, medical journals should have a mechanism for readers to submit comments, questions, or criticisms about published articles, and authors have a responsibility to respond appropriately and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication (see Section III).

ICMJE believes investigators have a duty to maintain the primary data and analytic procedures underpinning the published results for at least 10 years. The ICMJE encourages the preservation of these data in a data repository to ensure their longer-term availability.

d. Integrity

Editorial decisions should be based on the relevance of a manuscript to the journal and on the manuscript's originality, quality, and contribution to evidence about important questions. Those decisions should not be influenced by commercial interests, personal relationships or agendas, or findings that are negative or that credibly challenge accepted wisdom. In addition, authors should submit for publication or otherwise make publicly available, and editors should not exclude from consideration for publication, studies with findings that are not statistically significant or that have inconclusive findings. Such studies may provide evidence that, combined with that from other studies through meta-analysis, might still help answer important questions, and a public record of such negative or inconclusive findings may prevent unwarranted replication of effort or otherwise be valuable for other researchers considering similar work.

Journals should clearly state their appeals process and should have a system for responding to appeals and complaints.

e. Diversity and Inclusion

To improve academic culture, editors should seek to engage a broad and diverse array of authors, reviewers, editorial staff, editorial board members, and readers.

f. Journal Metrics

The journal impact factor is widely misused as a proxy for research and journal quality and as a measure of the importance of specific research projects or the merits of individual researchers, including their suitability for hiring, promotion, tenure, prizes, or research funding. ICMJE recommends that journals reduce the emphasis on impact factor as a single measure, but rather provide a range of article and journal metrics relevant to their readers and authors.

3. Peer Reviewers

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Reviewers therefore should keep manuscripts and the information they contain strictly confidential. Reviewers must not publicly discuss authors' work and must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy copies of manuscripts after submitting their reviews.

Reviewers who seek assistance from a trainee or colleague in the performance of a review should acknowledge these individuals' contributions in the written comments submitted to the editor. These individuals must maintain the confidentiality of the manuscript as outlined above.

Reviewers are expected to respond promptly to requests to review and to submit reviews within the time agreed. Reviewers' comments should be constructive, honest, and polite.

Reviewers should declare their relationships and activities that might bias their evaluation of a manuscript and recuse themselves from the peer-review process if a conflict exists.

D. Journal Owners and Editorial Freedom

1. Journal Owners

Owners and editors of medical journals share a common purpose, but they have different responsibilities, and sometimes those differences lead to conflicts.

It is the responsibility of medical journal owners to appoint and dismiss editors. Owners should provide editors at the time of their appointment with a contract that clearly states their rights and duties, authority, the general terms of their appointment, and mechanisms for resolving conflict. The editor's performance may be assessed using mutually agreed-upon measures, including but not necessarily limited to readership, manuscript submissions and handling times, and various journal metrics.

Owners should only dismiss editors for substantial reasons, such as scientific misconduct, disagreement with the long-term editorial direction of the journal, inadequate performance by agreed-upon performance metrics, or inappropriate behavior that is incompatible with a position of trust.

Appointments and dismissals should be based on evaluations by a panel of independent experts, rather than by a small number of executives of the owning organization. This is especially necessary in the case of dismissals because of the high value society places on freedom of speech within science and because it is often the responsibility of editors to challenge the status quo in ways that may conflict with the interests of the journal's owners.

A medical journal should explicitly state its governance and relationship to a journal owner (e.g., a sponsoring society).

2. Editorial Freedom

The ICMJE adopts the World Association of Medical Editors' definition of editorial freedom (http://wame.org/editorial-independence), which holds that editors-in-chief have full authority over the entire editorial content of their journal and the timing of publication of that content. Journal owners should not interfere in the evaluation, selection, scheduling, or editing of individual articles either directly or by creating an environment that

strongly influences decisions. Editors should base editorial decisions on the validity of the work and its importance to the journal's readers, not on the commercial implications for the journal, and editors should be free to express critical but responsible views about all aspects of medicine without fear of retribution, even if these views conflict with the commercial goals of the publisher.

Editors-in-chief should also have the final say in decisions about which advertisements or sponsored content, including supplements, the journal will and will not carry, and they should have final say in use of the journal brand and in overall policy regarding commercial use of journal content.

Journals are encouraged to establish an independent and diverse editorial advisory board to help the editor establish and maintain editorial policy. To support editorial decisions and potentially controversial expressions of opinion, owners should ensure that appropriate insurance is obtained in the event of legal action against the editors, and should ensure that legal advice is available when necessary. If legal problems arise, the editor should inform their legal adviser and their owner and/or publisher as soon as possible. Editors should defend the confidentiality of authors and peer reviewers (names and reviewer comments) in accordance with ICMJE policy (see Section II.C.2.a). Editors should take all reasonable steps to check the facts in journal commentary, including that in news sections and social media postings, and should ensure that staff working for the journal adhere to best journalistic practices including contemporaneous note-taking and seeking a response from all parties when possible before publication. Such practices in support of truth and public interest may be particularly relevant in defense against legal allegations of libel.

To secure editorial freedom in practice, the editor should have direct access to the highest level of ownership, not to a delegated manager or administrative officer.

Editors and editors' organizations are obliged to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical, academic, and lay communities.

E. Protection of Research Participants

All investigators should ensure that the planning, conduct, and reporting of human research are in accordance with the Helsinki Declaration as revised in 2013 (www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). All authors should seek approval to conduct research from an independent local, regional, or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional, or national review body explicitly approved the doubtful aspects of the study. Approval by a responsible review body does not preclude editors from forming their own judgment whether the conduct of the research was appropriate.

Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that an identifiable patient be shown the manuscript to be published. Authors should disclose to these patients whether any potential identifiable material might be available via the Internet as well as in print after publication. Patient consent should be written and archived with the journal, the authors, or both, as dictated by local regulations or laws. Applicable laws vary from locale to locale, and journals should establish their own policies with legal guidance. Since a journal that archives the consent will be aware of patient identity, some journals may decide that patient confidentiality is better guarded by having the author archive the consent and instead providing the journal with a written statement that attests that they have received and archived written patient consent.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are deidentified, authors should provide assurance, and editors should so note, that such changes do not distort scientific meaning.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained, it should be indicated in the published article.

When reporting experiments on animals, authors should indicate whether institutional and national standards for the care and use of laboratory animals were followed.

III. Publishing and Editorial Issues Related to Publication in Medical Journals

A. Corrections, Retractions, Republications, and Version Control

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum. Updates of previous publications (e.g., an updated systematic review or clinical guideline) are considered a new publication rather than a version of a previously published article.

If a correction is needed, journals should follow these minimum standards:

- The journal should publish a correction notice as soon as possible detailing changes from and citing the original publication; the correction should be on an electronic or numbered print page that is

included in an electronic or a print Table of Contents to ensure proper indexing.
- The journal should also post a new article version with details of the changes from the original version and the date(s) on which the changes were made.
- The journal should archive all prior versions of the article. This archive can be either directly accessible to readers or can be made available to the reader on request.
- Previous electronic versions should prominently note that there are more recent versions of the article.
- The citation should be to the most recent version.

Pervasive errors can result from a coding problem or a miscalculation and may result in extensive inaccuracies throughout an article. If such errors do not change the direction or significance of the results, interpretations, and conclusions of the article, a correction should be published that follows the minimum standards noted above.

Errors serious enough to invalidate a paper's results and conclusions may require retraction. However, retraction with republication (also referred to as "replacement") can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then retraction with republication of the changed paper, with an explanation, allows full correction of the scientific literature. In such cases, it is helpful to show the extent of the changes in supplementary material or in an appendix, for complete transparency.

B. Scientific Misconduct, Expressions of Concern, and Retraction

Scientific misconduct in research and non-research publications includes but is not necessarily limited to data fabrication; data falsification, including deceptive manipulation of images; purposeful failure to disclose relationships and activities; and plagiarism. Some people consider failure to publish the results of clinical trials and other human studies a form of scientific misconduct. While each of these practices is problematic, they are not equivalent. Each situation requires individual assessment by relevant stakeholders. When scientific misconduct is alleged, or concerns are otherwise raised about the conduct or integrity of work described in submitted or published papers, the editor should initiate appropriate procedures detailed by such committees as the Committee on Publication Ethics (COPE) (http://publicationethics.org/resources/flowcharts), consider informing the institutions and funders, and may choose to publish an expression of concern pending the outcomes of those procedures. If the procedures involve an investigation at the authors' institution, the editor should seek to discover the outcome of that investigation; notify readers of the outcome if appropriate; and if the investigation proves scientific misconduct, publish a retraction of the article. There may be circumstances in which no misconduct is proven, but an exchange of letters to the editor could be published to highlight matters of debate to readers.

Expressions of concern and retractions should not simply be a letter to the editor. Rather, they should be prominently labelled, appear on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing, and include in their heading the title of the original article. Online, the retraction and original article should be linked in both directions and the retracted article should be clearly labelled as retracted in all its forms (abstract, full text, PDF). Ideally, the authors of the retraction should be the same as those of the article, but if they are unwilling or unable the editor may under certain circumstances accept retractions by other responsible persons, or the editor may be the sole author of the retraction or expression of concern. The text of the retraction should explain why the article is being retracted and include a complete citation reference to that article.

Retracted articles should remain in the public domain and be clearly labelled as retracted.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of other work published in their journals, or they may retract it. If this is not done, editors may choose to publish an announcement expressing concern that the validity of previously published work is uncertain.

The integrity of research may also be compromised by inappropriate methodology that could lead to retraction.

See COPE flowcharts for further guidance on retractions and expressions of concern. See Section IV.A.1.g.i for guidance about avoiding referencing retracted articles.

C. Copyright

Journals should make clear the type of copyright under which work will be published, and if the journal retains copyright, should detail the journal's position on the transfer of copyright for all types of content, including audio, video, protocols, and data sets. Medical journals may ask authors to transfer copyright to the journal. Some journals require transfer of a publication license. Some journals do not require transfer of copyright and rely on such vehicles as Creative Commons licenses. The copyright status of articles in a given journal can vary: Some content cannot be copyrighted (e.g., articles written by employees of some governments in the course of their work). Editors may waive copyright on other content, and some content may be protected under other agreements.

D. Overlapping Publications

1. Duplicate Submission

Authors should not submit the same manuscript, in the same or different languages, simultaneously to more than one journal. The rationale for this standard is the potential for disagreement when two (or more) journals claim the right to publish a manuscript that has been submitted simultaneously to more than one journal, and the possibility that two or more journals will unknowingly and unnecessarily undertake the work of peer review, edit the same manuscript, and publish the same article.

2. Duplicate and Prior Publication

Duplicate publication is publication of a paper that overlaps substantially with one already published, without clear, visible reference to the previous publication. Prior publication may include release of information in the public domain.

Readers of medical journals deserve to be able to trust that what they are reading is original unless there is a clear statement that the author and editor are intentionally republishing an article (which might be considered for historic or landmark papers, for example). The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic because it can result in inadvertent double-counting of data or inappropriate weighting of the results of a single study, which distorts the available evidence.

When authors submit a manuscript reporting work that has already been reported in large part in a published article or is contained in or closely related to another paper that has been submitted or accepted for publication elsewhere, the letter of submission should clearly say so and the authors should provide copies of the related material to help the editor decide how to handle the submission. See also Section IV.B.

This recommendation does not prevent a journal from considering a complete report that follows publication of a preliminary report, such as a letter to the editor, a preprint, or an abstract or poster displayed at a scientific meeting. The ICMJE does not consider results or data contained in assessment reports published by health technology assessment agencies, medical regulators, medical device regulators, or other regulatory agencies to be duplicate publication. It also does not prevent journals from considering a paper that has been presented at a scientific meeting but was not published in full, or that is being considered for publication in proceedings or similar format. Press reports of scheduled meetings are not usually regarded as breaches of this rule, but they may be if additional data tables or figures enrich such reports. Authors should also consider how dissemination of their findings outside of scientific presentations at meetings may diminish the priority journal editors assign to their work.

Authors who choose to post their work on a preprint server should choose one that clearly identifies preprints as not peer-reviewed work and includes disclosures of authors' relationships and activities. It is the author's responsibility to inform a journal if the work has been previously posted on a preprint server. In addition, it is the author's (and not the journal editors') responsibility to ensure that preprints are amended to point readers to subsequent versions, including the final published article. See Section III.D.3.

In the event of a public health emergency (as defined by public health officials), information with immediate implications for public health should be disseminated without concern that this will preclude subsequent consideration for publication in a journal. We encourage editors to give priority to authors who have made crucial data publicly available without delay.

Sharing with public media, government agencies, or manufacturers the scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances; reportable diseases; or public health hazards, such as serious adverse effects of drugs, vaccines, other biological products, medical devices. This reporting, whether in print or online, should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance when possible.

The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the criteria noted in Section III.L if results are limited to a brief (500 word) structured abstract or tables (to include participants enrolled, key outcomes, and adverse events). The ICMJE encourages authors to include a statement with the registration that indicates that the results have not yet been published in a peer-reviewed journal, and to update the results registry with the full journal citation when the results are published.

Editors of different journals may together decide to simultaneously or jointly publish an article if they believe that doing so would be in the best interest of public health. However, the National Library of Medicine (NLM) indexes all such simultaneously published joint publications separately, so editors should include a statement making the simultaneous publication clear to readers.

Authors who attempt duplicate publication without such notification should expect at least prompt rejection of the submitted manuscript. If the editor was not aware of the violations and the article has already been published, then the article might warrant retraction with or without the author's explanation or approval.

See COPE flowcharts for further guidance on handling duplicate publication.

3. Preprints

Posting of work as a preprint may influence a journal's interest in or priority for peer review and publication of that work. Journals should clearly describe their policies related to the posting and citing of preprints in their Information for Authors. Authors should become familiar with the policies of journals they wish to submit their work to prior to posting work on a preprint server.

a. Choosing a Preprint Archive

There has been an increase in preprint archives in biomedicine. There are both benefits and harms in dissemination of scientific findings prior to peer review. To maximize potential benefits and minimize potential harms, authors who wish to make preprints of non–peer-reviewed work publicly available should choose preprint archives that have the following characteristics:

- Clearly identify preprints as work that is not peer reviewed;
- Require authors to document disclosures of interest;
- Require authors to indicate funding source(s);

- Have a clear process for preprint archive users to notify archive administrators about concerns related to posted preprints—a public commenting feature is desirable for this purpose;
- Maintain metadata for preprints that are withdrawn from posting and post withdrawal notices indicating the timing and reason for withdrawal of a preprint; and
- Have a mechanism for authors to indicate when the preprint article has been subsequently published in a peer-reviewed journal.

b. Submitting Manuscripts That Are in Preprint Archives to a Peer-Reviewed Journal

Authors should inform a journal if the work submitted to the journal has been posted on a preprint server and provide a link to the preprint, whether the posting occurs prior to submission or during the peer-review process. It is also helpful to indicate in the text of the manuscript, perhaps in the introduction, that a preprint is available and how reviewers can access that preprint. In addition, it is the authors' (and not the journal editors') responsibility to ensure that preprints are amended to point readers to subsequent versions of the work, including the published article. Authors should not post in the preprint archive the published article nor interim versions that are produced during the peer-review process that incorporate revisions based on journal feedback.

c. Referencing Preprints in Submitted Manuscripts

When preprints are cited in submitted manuscripts or published articles, the citation should clearly indicate that the reference is a preprint. When a preprint article has been subsequently published in a peer-reviewed journal, authors should cite the subsequent published article rather than the preprint article whenever appropriate. Journals should include the word "preprint" following the citation information in the reference list and consider indicating that the cited material is a preprint in the text. The citation should include the link to the preprint and DOI if the preprint archive issues DOIs. Authors should be cautious about referencing preprints that were posted and never subsequently published in a peer-reviewed journal, but the time interval of concern will vary depending on the topic and specific reasons for citation.

4. Acceptable Secondary Publication

Secondary publication of material published in other journals or online may be justifiable and beneficial, especially when intended to disseminate important information to the widest possible audience (e.g., guidelines produced by government agencies and professional organizations in the same or a different language). Secondary publication for various other reasons may also be justifiable provided the following conditions are met:

1. The authors have received approval from the editors of both journals (the editor concerned with secondary publication must have access to the primary version).
2. The priority of the primary publication is respected by a publication interval negotiated by both editors with the authors.
3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
4. The secondary version faithfully reflects the authors, data, and interpretations of the primary version.
5. The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the [journal title, with full reference]"—and the secondary version cites the primary reference.
6. The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the NLM does not consider translations to be "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

When the same journal simultaneously publishes an article in multiple languages, the MEDLINE citation will note the multiple languages (e.g., Angelo M. Journal networking in nursing: a challenge to be shared. Rev Esc Enferm USP. 2011 Dec 45[6]:1281-2,1279-80,1283-4. Article in English, Portuguese, and Spanish. No abstract available. PMID: 22241182).

5. Manuscripts Based on the Same Database

If editors receive manuscripts from separate research groups or from the same group analyzing the same data set (e.g., from a public database, or systematic reviews or meta-analyses of the same evidence), the manuscripts should be considered independently because they may differ in their analytic methods, conclusions, or both. If the data interpretation and conclusions are similar, it may be reasonable although not mandatory for editors to give preference to the manuscript submitted first. Editors might consider publishing more than one manuscript that overlap in this way because different analytical approaches may be complementary and equally valid, but manuscripts based upon the same data set should add substantially to each other to warrant consideration for publication as separate papers, with appropriate citation of previous publications from the same data set to allow for transparency.

Secondary analyses of clinical trial data should cite any primary publication, clearly state that it contains secondary analyses/results, and use the same identifying trial registration number as the primary trial and unique, persistent data set identifier.

Sometimes for large trials it is planned from the beginning to produce numerous separate publications regarding separate research questions but using the same original participant sample. In this case authors may use the original single trial registration number, if all the outcome parameters were defined in the original registration. If the authors registered several substudies as separate entries in, for example, ClinicalTrials.gov,

then the unique trial identifier should be given for the study in question. The main issue is transparency, so no matter what model is used it should be obvious for the reader.

E. Correspondence

Medical journals should provide readers with a mechanism for submitting comments, questions, or criticisms about published articles, usually but not necessarily always through a correspondence section or online forum. The authors of articles discussed in correspondence or an online forum have a responsibility to respond to substantial criticisms of their work using those same mechanisms and should be asked by editors to respond. Authors of correspondence should be asked to declare any competing relationships or activities.

Correspondence may be edited for length, grammatical correctness, and journal style. Alternatively, editors may choose to make available to readers unedited correspondence, for example, via an online commenting system. Such commenting is not indexed in MEDLINE unless it is subsequently published on a numbered electronic or print page. However the journal handles correspondence, it should make known its practice. In all instances, editors must make an effort to screen discourteous, inaccurate, or libellous comments.

Responsible debate, critique, and disagreement are important features of science, and journal editors should encourage such discourse ideally within their own journals about the material they have published. Editors, however, have the prerogative to reject correspondence that is irrelevant, uninteresting, or lacking cogency, but they also have a responsibility to allow a range of opinions to be expressed and to promote debate.

In the interests of fairness and to keep correspondence within manageable proportions, journals may want to set time limits for responding to published material and for debate on a given topic.

F. Fees

Journals should be transparent about their types of revenue streams. Any fees or charges that are required for manuscript processing and/or publishing materials in the journal shall be clearly stated in a place that is easy for potential authors to find prior to submitting their manuscripts for review or explained to authors before they begin preparing their manuscript for submission (http://publicationethics.org/files/u7140/Principles_of_Transparency_and_Best_Practice_in_Scholarly_Publishing.pdf).

G. Supplements, Theme Issues, and Special Series

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and may be funded by sources other than the journal's publisher. Because funding sources can bias the content of supplements through the choice of topics and viewpoints, journals should adopt the following principles, which also apply to theme issues or special series that have external funding and/or guest editors:

1. The journal editor must be given and must take full responsibility for the policies, practices, and content of supplements, including complete control of the decision to select authors, peer reviewers, and content for the supplement. Editing by the funding organization should not be permitted.
2. The journal editor has the right to appoint one or more external editors of the supplement and must take responsibility for the work of those editors.
3. The journal editor must retain the authority to send supplement manuscripts for external peer review and to reject manuscripts submitted for the supplement with or without external review. These conditions should be made known to authors and any external editors of the supplement before beginning editorial work on it.
4. The source of the idea for the supplement, sources of funding for the supplement's research and publication, and products of the funding source related to content considered in the supplement should be clearly stated in the introductory material.
5. Advertising in supplements should follow the same policies as those of the primary journal.
6. Journal editors must enable readers to distinguish readily between ordinary editorial pages and supplement pages.
7. Journal and supplement editors must not accept personal favors or direct remuneration from sponsors of supplements.
8. Secondary publication in supplements (republication of papers published elsewhere) should be clearly identified by the citation of the original paper and by the title.
9. The same principles of authorship and disclosure of relationships and activities discussed elsewhere in this document should be applied to supplements.

H. Sponsorship or Partnership

Various entities may seek interactions with journals or editors in the form of sponsorships, partnerships, meetings, or other types of activities. To preserve editorial independence, these interactions should be governed by the same principles outlined above for Supplements, Theme Issues, and Special Series (Section III.G).

I. Electronic Publishing

Most medical journals are now published in electronic as well as print versions, and some are published only in electronic form. Principles of print and electronic publishing are identical, and the recommendations of this document apply equally to both. However, electronic publishing provides opportunities for versioning and raises issues about link stability and content preservation that are addressed here.

Recommendations for corrections and versioning are detailed in Section III.A.

Electronic publishing allows linking to sites and resources beyond journals over which journal editors have no editorial control. For this reason, and because links to external sites could be perceived as implying

endorsement of those sites, journals should be cautious about external linking. When a journal does link to an external site, it should state that it does not endorse or take responsibility or liability for any content, advertising, products, or other materials on the linked sites, and does not take responsibility for the sites' availability.

Permanent preservation of journal articles on a journal's website, or in an independent archive or a credible repository, is essential for the historical record. Removing an article from a journal's website in its entirety is almost never justified as copies of the article may have been downloaded even if its online posting was brief. Such archives should be freely accessible or accessible to archive members. Deposition in multiple archives is encouraged. However, if necessary for legal reasons (e.g., libel action), the URL for the removed article must contain a detailed reason for the removal, and the article must be retained in the journal's internal archive.

Permanent preservation of a journal's total content is the responsibility of the journal publisher, who in the event of journal termination should be certain the journal files are transferred to a responsible third party who can make the content available.

Journal websites should post the date that nonarticle web pages, such as those listing journal staff, editorial board members, and instructions for authors, were last updated.

J. Advertising

Most medical journals carry advertising, which generates income for their publishers, but journals should not be dominated by advertisements, and advertising must not be allowed to influence editorial decisions.

Journals should have formal, explicit, written policies for advertising in both print and electronic versions. Best practice prohibits selling advertisements intended to be juxtaposed with editorial content on the same product. Advertisements should be clearly identifiable as advertisements. Editors should have full and final authority for approving print and online advertisements and for enforcing advertising policy.

Journals should not carry advertisements for products proven to be seriously harmful to health. Editors should ensure that existing regulatory or industry standards for advertisements specific to their country are enforced, or develop their own standards. The interests of organizations or agencies should not control classified and other nondisplay advertising, except where required by law. Editors should consider all criticisms of advertisements for publication.

K. Journals and the Media

Journals' interactions with media should balance competing priorities. The general public has a legitimate interest in all journal content and is entitled to important information within a reasonable amount of time, and editors have a responsibility to facilitate that. However, media reports of scientific research before it has been peer-reviewed and fully vetted may lead to dissemination of inaccurate or premature conclusions, and doctors in practice need to have research reports available in full detail before they can advise patients about the reports' conclusions.

An embargo system has been established in some countries and by some journals to assist this balance, and to prevent publication of stories in the general media before publication of the original research in the journal. For the media, the embargo creates a "level playing field," which most reporters and writers appreciate since it minimizes the pressure on them to publish stories before competitors when they have not had time to prepare carefully. Consistency in the timing of public release of biomedical information is also important in minimizing economic chaos, since some articles contain information that has potential to influence financial markets. The ICMJE acknowledges criticisms of embargo systems as being self-serving of journals' interests and an impediment to rapid dissemination of scientific information, but believes the benefits of the systems outweigh their harms.

The following principles apply equally to print and electronic publishing and may be useful to editors as they seek to establish policies on interactions with the media:

- Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication of the original research in the journal, in return for which the journal will cooperate with them in preparing accurate stories by issuing, for example, a press release.
- Editors need to keep in mind that an embargo system works on the honor system—no formal enforcement or policing mechanism exists. The decision of a significant number of media outlets or biomedical journals not to respect the embargo system would lead to its rapid dissolution.
- Notwithstanding authors' belief in their work, very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. When such exceptional circumstances occur, the appropriate authorities responsible for public health should decide whether to disseminate information to physicians and the media in advance and should be responsible for this decision. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors acknowledge the need for immediate release, they should waive their policies limiting prepublication publicity.
- Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from

these meetings (see Duplicate Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters but should be discouraged from offering more detail about their study than was presented in the talk, or should consider how giving such detail might diminish the priority journal editors assign to their work (see Duplicate Publication).
- When an article is close to being published, editors or journal staff should help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the article, or referring reporters to appropriate experts. This assistance should be contingent on the media's cooperation in timing the release of a story to coincide with publication of the article.

L. Clinical Trials

1. Registration

The ICMJE's clinical trial registration policy is detailed in a series of editorials (see News and Editorials [www.icmje.org/news-and-editorials/] and FAQs [www.icmje.org/about-icmje/faqs/]).

Briefly, the ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance (www.icmje.org/journals.html) should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy.

ICMJE uses the date trial registration materials were first submitted to a registry as the date of registration. When there is a substantial delay between the submission of registration materials and their posting at the trial registry, editors may inquire about the circumstances that led to the delay.

The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE does not define the timing of first participant enrollment, but best practice dictates registration by the time of first participant consent.

The ICMJE accepts publicly accessible registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/clinical-trials-registry-platform/network/who-data-set) that includes the minimum acceptable 24-item trial registration data set or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP. The ICMJE endorses these registries because they meet several criteria. They are accessible to the public at no charge, open to all prospective registrants, managed by a not-for-profit organization, have a mechanism to ensure the validity of the registration data, and are electronically searchable. An acceptable registry must include the minimum 24-item trial registration data set (http://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf or www.who.int/clinical-trials-registry-platform) at the time of registration and before enrollment of the first participant.

The ICMJE considers inadequate trial registrations missing any of the 24 data fields, those that have fields that contain uninformative information, or registrations that are not made publicly accessible such as phase I trials submitted to the EU-CTR and trials of devices for which the information is placed in a "lock box." In order to comply with ICMJE policy, investigators registering trials of devices at ClinicalTrials.gov must "opt out" of the lock box by electing public posting prior to device approval. Approval to conduct a study from an independent local, regional, or national review body (e.g., ethics committee, institutional review board) does not fulfill the ICMJE requirement for prospective clinical trial registration. Although not a required item, the ICMJE encourages authors to include a statement that indicates that the results have not yet been published in a peer-reviewed journal, and to update the registration with the full journal citation when the results are published.

The purpose of clinical trial registration is to prevent selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enroll, and to help give ethics review boards considering approval of new studies a view of similar work and data relevant to the research they are considering. Retrospective registration, for example at the time of manuscript submission, meets none of these purposes. Those purposes apply also to research with alternative designs, for example observational studies. For that reason, the ICMJE encourages registration of research with non-trial designs, but because the exposure or intervention in non-trial research is not dictated by the researchers, the ICMJE does not require it.

Secondary data analyses of primary (parent) clinical trials should not be registered as separate clinical trials, but instead should reference the trial registration number of the primary trial.

The ICMJE expects authors to ensure that they have met the requirements of their funding and regulatory agencies regarding aggregate clinical trial results reporting in clinical trial registries. It is the authors', and not the journal editors', responsibility to explain any discrepancies between results reported in registries and journal publications. The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the above criteria if results are limited to a brief (500 word) structured abstract or tables (to include trial

participants enrolled, baseline characteristics, primary and secondary outcomes, and adverse events).

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer either to the trial they are reporting or to other trials that they mention in the manuscript.

Editors may consider whether the circumstances involved in a failure to appropriately register a clinical trial were likely to have been intended to or resulted in biased reporting. Because of the importance of prospective trial registration, if an exception to this policy is made, trials must be registered and the authors should indicate in the publication when registration was completed and why it was delayed. Editors should publish a statement indicating why an exception was allowed. The ICMJE emphasizes that such exceptions should be rare, and that authors failing to prospectively register a trial risk its inadmissibililty to our journals.

2. Data Sharing

The ICMJE's data sharing statement policy is detailed in an editorial (see Updates and Editorials [www.icmje.org/update.html]).

1. As of 1 July 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement as described below.
2. Clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.

Data sharing statements must indicate the following: whether individual deidentified participant data (including data dictionaries) will be shared ("undecided" is not an acceptable answer); what data in particular will be shared; whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Illustrative examples of data sharing statements that would meet these requirements are provided in Table 1.

Authors of secondary analyses using shared data must attest that their use was in accordance with the terms (if any) agreed to upon their receipt. They must also reference the source of the data using its unique, persistent identifier to provide appropriate credit to those who generated it and allow searching for the studies it has supported. Authors of secondary analyses must explain completely how theirs differ from previous analyses. In addition, those who generate and then share clinical trial data sets deserve substantial credit for their efforts. Those using data collected by others should seek collaboration with those who collected the data. As collaboration will not always be possible, practical, or desired, the efforts of those who generated the data must be recognized.

IV. Manuscript Preparation and Submission

A. Preparing a Manuscript for Submission to a Medical Journal

1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT (www.consort-statement.org) for randomized trials, STROBE for observational studies (http://strobe-statement.org/), PRISMA for systematic reviews and meta-analyses (http://prisma-statement.org/), and STARD for studies of diagnostic accuracy (http://www.equator-network.org/reporting-guidelines/stard/). Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, selecting, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network (www.equator-network.org/home/) and the NLM's Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Table 1. Examples of Data Sharing Statements That Fulfill These ICMJE Requirements*

	Example 1	Example 2	Example 3	Example 4
Will individual participant data be available (including data dictionaries)?	Yes	Yes	Yes	No
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification.	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Not available
What other documents will be available?	Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code	Study Protocol, Statistical Analysis Plan, Analytic Code	Study Protocol	Not available
When will data be available (start and end dates)?	Immediately following publication. No end date.	Beginning 3 months and ending 5 years following article publication.	Beginning 9 months and ending 36 months following article publication.	Not applicable
With whom?	Anyone who wishes to access the data.	Researchers who provide a methodologically sound proposal.	Investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.	Not applicable
For what types of analyses?	Any purpose.	To achieve aims in the approved proposal.	For individual participant data meta-analysis.	Not applicable
By what mechanism will data be made available?	Data are available indefinitely at (*Link to be included).*	Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third-party website (*Link to be included).*	Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (*Link to be provided*).	Not applicable

*These examples are meant to illustrate a range of, but not all, data sharing options.

Article title. The title provides a distilled description of the complete article and should include information that, along with the abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

Author information. Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself. Inappropriate attribution of funding sources and affiliations are misleading and should be avoided.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of figures and tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because tables and figures occupy space, to assess if the information provided by the figures and

tables warrants the paper's length and if the manuscript fits within the journal's space limits.

Disclosure of relationships and activities. Disclosure information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform Disclosure Form for use by ICMJE member journals (www.icmje.org/coi_disclosure.pdf), and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require disclosure of relationships and activities on the manuscript title page or other Disclosure section in the manuscript to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential (www.consort-statement.org/resources/downloads/extensions/consort-extension-for-abstracts-2008pdf/). Funding sources should be listed separately after the abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository and/or are being used in a secondary analysis, authors should state at the end of the abstract the unique, persistent data set identifier; repository name; and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. The Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved by an independent local, regional or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional or national review body explicitly approved the doubtful aspects of the study. See Section II.E.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. Comment on how representative the study sample is of the larger population of interest.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance. In the case where race or ethnicity was not collected, explain why it was not collected. Race and ethnicity are social and not biological constructs; authors should interpret results associated with race and ethnicity in that context. Authors should use neutral, precise, and respectful language to describe study participants and avoid the use of terminology that might stigmatize participants.

ii. Technical Information

Specify the study's main and secondary objectives—usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including

statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (e.g., percentages) but also as the absolute numbers from which the derivatives were calculated. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Authors should avoid citing articles from predatory or pseudo-journals. When preprints are cited, the citation should clearly indicate that the reference is a preprint (also see Section III.D.3). Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Published articles should reference the unique, persistent identifiers of the data sets employed.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching

PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to the PubMed's list of retracted publications (https://www.ncbi.nlm.nih.gov/pubmed/?term=retracted+publication+[pt]).

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Style and Format

References should follow the standards summarized in the NLM's Sample References (www.nlm.nih.gov/bsd/uniform_requirements.html) webpage and detailed in the NLM's *Citing Medicine, 2nd edition* (www.ncbi.nlm.nih.gov/books/NBK7256/). These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

i. Illustrations (Figures)

Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For radiological and other clinical and diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Before-and-after images should be taken with the same intensity, direction, and color of light. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the

particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parentheses should be used on first mention unless the abbreviation is a standard unit of measurement.

B. Sending the Manuscript to the Journal

Manuscripts should be accompanied by a cover letter or a completed journal submission form, which should include the following information:

A full statement to the editor about all submissions and previous reports that might be regarded as redundant publication of the same or very similar work. Any such work should be referred to specifically and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor address the situation. See also Section III.D.2.

A statement of financial or other relationships and activities that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form. See also Section II.B.

A statement on authorship. Journals that do not use contribution declarations for all authors may require that the submission letter includes a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work if that information is not provided in another form. See also Section II.A.

Contact information for the author responsible for communicating with other authors about revisions and final approval of the proofs, if that information is not included in the manuscript itself.

The letter or form should inform editors if concerns have been raised (e.g., via institutional and/or regulatory bodies) regarding the conduct of the research or if corrective action has been recommended. The letter or form should give any additional information that may be helpful to the editor, such as the type or format of article in the particular journal that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Editors encourage authors to submit these previous communications. Doing so may expedite the review process and encourages transparency and sharing of expertise.

Many journals provide a presubmission checklist to help the author ensure that all the components of the submission have been included. Some journals also require that authors complete checklists for reports of certain study types (e.g., the CONSORT checklist for reports of randomized controlled trials). Authors should look to see if the journal uses such checklists, and send them with the manuscript if they are requested.

The manuscript must be accompanied by permission to reproduce previously published material, use previously published illustrations, report information about identifiable persons, or to acknowledge people for their contributions.

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Date: _____

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In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the **current manuscript only.**

The author's relationships/activities/interests should be **defined broadly.** For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	____None	
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4	Consulting fees	____None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	____None	
6	Payment for expert testimony	____None	
7	Support for attending meetings and/or travel	____None	
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9	Participation on a Data Safety Monitoring Board or Advisory Board	____None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	____None	
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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	____None	
13	Other financial or non-financial interests	____None	

Please place an "X" next to the following statement to indicate your agreement:

____ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

PHILIPPINE JOURNAL OF PATHOLOGY
PJP

PATIENT CONSENT FORM

For case report and image submissions to the PJP to be accepted, the author/s must ensure that patients or patients' legal guardian/relative have provided informed consent to publish information about them in the journal. The completely accomplished PJP Patient Consent Form shall be scanned and submitted along with the manuscript. No case report and image shall be received without the PJP Consent Form.

Name of person described in article or shown in photograph:_____

_____

Subject matter of photograph or article (brief description):

_____

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(The Subject matter of the photograph or article is hereafter termed as the "INFORMATION.")

Title of article:

_____

_____

I, _____ , give my consent for this information
[please insert your full name]

about MYSELF/MY CHILD OR WARD/MY RELATIVE relating to the subject matter
[please underline correct description]

above to appear in the Philippine Journal of Pathology (PJP) subject to its publication policies and ethical standards.

I have seen and read the material to be submitted to the PJP and thoroughly understand the following:

- The Information will be published in the PJP without my name. It is the obligation of the PJP to make all attempts, within its reasonable jurisdiction and authority, to ensure my anonymity.
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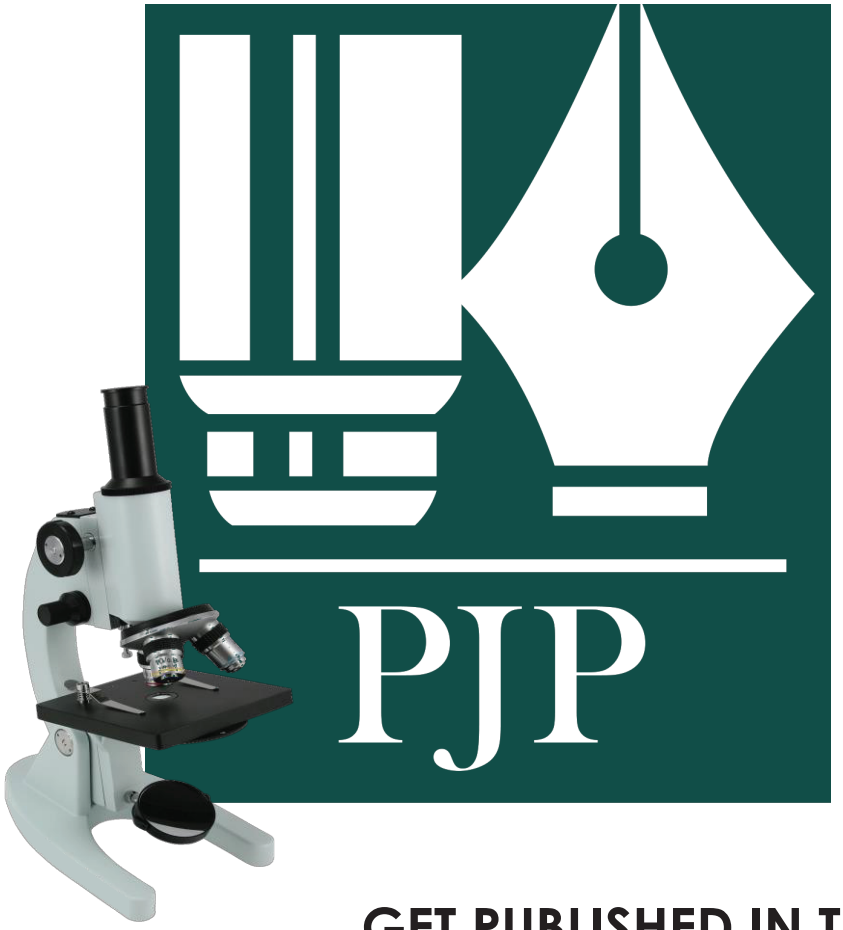

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