



JOURNAL OF THE PHILIPPINE MEDICAL ASSOCIATION

Volume 102, Number 1

June - December 2023

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Drastic Times, Drastic Measures: A Case Report on Massive Transfusion

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Journal of the
PHILIPPINE MEDICAL ASSOCIATION
VOLUME 102, NUMBER 1 ▪ June - December 2023

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(This section is primarily based on the previous and existing JPMA Instructions to Contributors but with some modifications based on the ICMJE recommendations. A completely revised version based on the guidelines of the ICMJE will be published in the next issue.

Accompanied by a cover letter from the principal author, the manuscripts, figures, tables, photographs, and references should be submitted in duplicate (an original and a copy) and typed double-space (including legends and footnotes) on one side of a white bond paper, 8.5 and 11 inches properly numbered consecutively on the upper right-hand corner of each page beginning with the title page. Illustrations must also be in duplicates. An electronic copy of the articles in a CD must be submitted.

The first page should contain the title, subtitle (if any, all authors' full names and highest earned academic degrees, and hospital or institutional affiliations. It must also include disclaimer, if any.

For the original article, an abstract must be type at the beginning of each paper after the title. It must contain, in structured format, the following: background or context of the study, objectives, methods, results and conclusions of the study, as appropriate. It must not be more than 300 words. No footnotes/ references must be in the abstract. For other articles, an unstructured abstract may be preferred. Below the abstract, identify three to ten keywords or short phrases that will assist in indexers in cross-indexing the article.

Abbreviations and nomenclatures: the use of abbreviations should be minimized and preferably confined to tables only; non-standard abbreviations must be accompanied by legends.

Generic names of drugs are preferred. Trade names may be given only once at the end of the paper or in the acknowledgement and should follow the generic name in parenthesis.

References are to be cited consecutively in the text as superscripts numbers. At the end of each article, references should be listed consecutively in the numerical order as they appeared in the text

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Journal of the
PHILIPPINE MEDICAL ASSOCIATION
VOLUME 102, NUMBER 1 ■ June - December 2023

Editor's Note:

Albert Szent-Györgi, a Hungarian Biochemist, a 1937 Nobel Prize winner in Medicine, once said, "Research is to see what everybody else has seen, and to think what nobody else has thought."

This is exactly the idea behind the first medical journals were first published in the 18th century. It provided a place to share important research and studies.

With this idea also in mind, the Philippine Medical Association (PMA) thought to put together various researches and studies done by our fellow doctors and publish them in this very first medical journal of the PMA.

After reading through various articles and studies, we chose a variety of a subjects from this different fields. There is one about Another proves that Yet, there is piece on An interesting brief on concludes that...

With that, we welcome everyone to enjoy our premiere edition of the PMA Medical Journal, which is the first of many.

"Everything is theoretically impossible until it is done." – Robert A Heinlein

MARIANNE L. ORDOÑEZ-DOBLES, MD
PMA Secretary General
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Factors Associated with the Inappropriate Use of Topical Corticosteroids among Out-Patient Dermatology Patients: A Cross-Sectional Study*

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ABSTRACT

Topical corticosteroids (TC) are among the most commonly prescribed topical agents and are used to treat various dermatoses. This study aimed to determine the prevalence, factors associated and reasons patients inappropriately use TC. Incidence of AE and risk of the development of AE due to inappropriate TC. Out-patient dermatology patients in a tertiary hospital in the Philippines were screened for TC use and interviewed using a questionnaire. Descriptive analysis and logistic regression to determine odds ratios were done. Out of 801 patients recruited, 260 (32%) used TC. Among those who used TC, 147 (56.53%) inappropriately used TC. Among the factors associated with inappropriate use of TC were: 1) Diagnosis of dermatitis as primary dermatosis (OR = 2.82, 95% CI 0.497, 1.276), 2) Lack of awareness of the FDA advisory (OR = 2.1, 95% CI 1.245, 3.601), 3) Lack of knowledge that TC cannot be applied for prolonged periods (OR = 5.5, 95% CI 3.201, 9.334), and 4) Lack of knowledge that TC use can result into AE (OR = 4.5, 95% CI 2.637, 7.657). Relatives and friends as source of information (OR=437, 95% CI 25.997, >1000), procurement (OR=60, 95% CI 3.081, >1000) and instruction (OR=337, 95% CI 19.827, >1000) were highly associated with inappropriate use. Twenty-two percent of those who inappropriately used TC self-medicated upon recommendation by

family and friends. Hypopigmentation was the most common AE. There is a 3.8 times (OR= 3.8, 95% CI: 1.918, 7.662) likelihood for a person who has inappropriately used TC to have an AE as compared to a person who has appropriately used TC. There is a need to educate the general public regarding proper TC use. Patient encounters at the clinic may be a good opportunity to reinforce guidelines on the use of TC.

Keywords: adverse effects, corticosteroids, Philippines

INTRODUCTION

Topical corticosteroids (TC) are among the most commonly prescribed topical agents.¹ They are utilized in the treatment of numerous cutaneous pathologies, such as atopic dermatitis, dyshidrotic eczema, nummular eczema, seborrheic dermatitis, irritant contact dermatitis, allergic contact dermatitis (acute phase), lichen simplex chronicus, insect bites, lupus erythematosus, psoriasis and lichen planus. TCs are known for both their antiproliferative effect, mediated by reduction of keratinocyte size and proliferation, and their vasoconstrictive effect on dermal capillaries. Vasoconstriction assays of TC are employed in predicting the clinical activity of these compounds,

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

* 1st Place, 29th Philippine Medical Association Original Paper Presentation, May 16, 2023

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providing a basis for tiered classification schemes according to potency. There are two most cited classification systems – the United States' classification system (Group I-VII) and France's classification systems (ultra high, high, moderate, and low potency TC), which were further condensed by the World Health Organization into a single system.^{1,2,3,4} (Table 1) Other factors that can affect the potency of TCs include drug-related factors such as concentration/potency, total amount, duration, vehicle, concomitant use of occlusive dressings and intrinsic characteristics of the agent may contribute to potency variation. Patient-related factors are particularly important, including age, surface area, location of body surface, presence or absence of inflammation, integrity of skin.^{1,2} Notably, skin thickness differs in various body surfaces, increasing in thickness as follows: mucous membrane, scrotum, eyelids, face, chest and back, upper arms and legs, lower arms and legs, dorsa of hands and feet, palmar and plantar skin, and nails.⁵ Guidelines for appropriate TC use include the following: 1) dosing should not exceed twice daily; 2) application is limited to 1-2 weeks after which steroid holiday or pulse therapy can be done; and 3) high potency TC should be used only for short term flare control and on thick skin such as the palms and soles, moderate potency TC are limited to the trunk and extremities and low potency TC are applied on the face, neck, axilla and intertriginous areas.⁶ Steroid holiday or pulse therapy serves to decrease the incidence of tachyphylaxis, where the skin develops tolerance to the vasoconstrictive action of TC. Vasoconstriction usually occurs after 4 days of therapy, mandating a discontinuance of the drug after 4-7 days before it is restarted.⁷ Despite being effective, TCs are known to have adverse effects ranging from cutaneous reactions such as telangiectasia, skin atrophy, impaired wound healing, hirsutism, hypopigmentation, rosacea/perioral dermatitis, tinea incognito, acne flares, photosensitivity, purpura and xerosis. In

Ethiopia, Bilal et al. (2018) reported that most common adverse effects are allergic reactions (23.4%).⁸

There are currently no studies documenting the inappropriate use of topical corticosteroids in the Philippines, as of the authors' knowledge. Factors related to TC abuse include medical practice wise (misdiagnosis, poor doctor-patient communication, improperly filled prescriptions), pharmaceutical practice-wise (source of prescription, easy accessibility), media-wise (internet and social media consults, advertisements), and patient/consumer-wise (poor patient-doctor communication, poor patient education, usage of TC, economics).⁹ Other studies have been done in tertiary hospitals and centers^{9,10,11}, community pharmacies and cosmetic shops¹². Data collection was from 3 to 5 months^{9,10,11,12}. In our local pharmacies, TCs are touted to be as prescription-only drugs.¹³ However, there are anecdotal experiences of consumers availing of these drugs without prescriptions. In several online stores, consumers can procure Elica (mometasone furoate 0.1%, a class II potency), Cosmetique (betamethasone + erythromycin and hydrocortisone + erythromycin, a combination of TC and antibiotic), and LS BL cream (clobetasol propionate 0.05% + ketoconazole), among others, without a prescription.^{14,15} This unrestricted access puts uninformed patients at risk of adverse events, such as that of a locally reported case in 2019 of staphylococcal scalded skin syndrome.¹⁶ The infection was reportedly associated with topical-steroid induced iatrogenic Cushing syndrome, where LS BL cream was applied 3 times a day for 10 weeks. The patient unfortunately expired, prompting the Food and Drug Administration (FDA) to release an advisory reminding the public that pharmacies are not allowed to dispense TCs without a prescription, that these drugs have multiple side effects especially those related to the development of Cushing syndrome, and that the

purchase of medications in non-FDA-approved online stores are not recommended.¹⁷ In a subsequent FDA Advisory No. 2019-143, the agency stated that "... betamethasone 17-valerate and clobetasol propionate are not allowed to be part of cosmetic products as these are classified as drug products in the Philippines..." further emphasizing that the prolonged use of TC may cause adverse effects.¹⁸

Additionally, this study hopes to identify the possible factors associated with inappropriate TC use. In India, a third world country like the Philippines¹⁹, the reasons for inappropriate TC use range from the problems in the health system such as unavailability of dermatologists in their area, inadequate execution of laws, to lack of education of not only patients but undergraduate medical students or general practitioners as well.²⁰ By identifying then addressing these factors, adverse effects of inappropriate TC use will be prevented, ineffective and costly treatment will be avoided, and delay in diagnosis due to masking of steroids will be prevented. Moreover, this study will also contribute in improving patient care and active merchant surveillance. In a prevalence study by Sinha et al. addressing inappropriate TC use, treatment was focused not only on cessation of usage but also on tapering of TCs with less potent steroids. Patients presenting with stinging, pruritus and photosensitivity were given emollients and sunscreens.²¹ With that, the objectives includes: (1) to determine the prevalence of inappropriate use of topical corticosteroids by patients in an Out Patient Department (OPD), Department of Dermatology, tertiary hospital in Metro Manila. (2) to determine the association of inappropriate use of topical corticosteroids by patients and the following factors: clinicoepidemiologic factors (age, location, sex, educational attainment, employment status, civil status, primary dermatosis), accessibility factors (source of information of the product, source of the product

procurement, source of instructions on application), awareness factors (FDA advisory on TC use, prolonged TC use, adverse effects due to TC use) (3) to identify the reasons patients inappropriately use topical corticosteroids (4) to determine the incidence of adverse effects among patients with appropriate and inappropriate use of topical corticosteroids (5) to determine the association of appropriate and inappropriate use of topical corticosteroids to adverse effects.

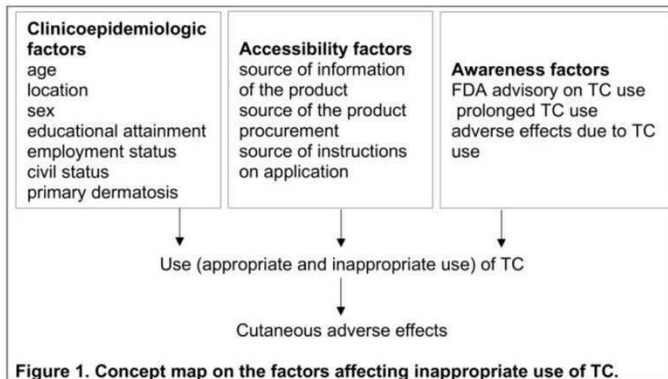
Materials and Methods

Study Design

This study is a prospective, cross-sectional observational study on the use of TCs of patients using an interview semi-structured questionnaire in the Dermatology OPD of a tertiary hospital in the Philippines for 5 months (September 2021-January 2022) utilizing both telemedicine and face-to-face (FTF) consults via convenience non-probability sampling.

The conceptual framework (*figure 1*) presented the clinicoepidemiological characteristics of those with inappropriate TC use was hypothesized to be in the age range of 19 to 29, single, females who were students who reached any college level or finished with a college degree.^{9,10,11,12} In terms of location, a higher occurrence of inappropriate use may be seen among those residing outside of Metro Manila possibly due to less strict regulations as compared to those from Metro Manila. In terms of accessibility factors, majority of inappropriate users may have sourced information from relatives and friends, while appropriate users are hypothesized to have received information from doctors. In terms of procurement, inappropriate users may have probably purchased the items from online stores, or received from relatives and friends. In terms of awareness factors, both user types may vary on awareness of corresponding FDA advisories on

TCs and the associated adverse effects.²² The incidence of adverse effects is expected to occur more with those who used TC inappropriately.



Operational Definition of Variables

I. Factors associated with TC use

a. Dependent Variable

- i. **TC use** pertains to the behavior of application of TC for the dermatoses for which the patient is currently seeking consult, (a) **Inappropriate use** – use of TC that is self-prescribed (regardless of duration of usage) OR prescribed by a doctor but used longer than prescribed or used for more than 2 weeks without follow-up consult (b) **Appropriate use** – use of TC which is use of TCs not falling under inappropriate use criteria.

b. Independent Variables

- i. **TCs** are topical forms of corticosteroids in pure or with combination will be classified based on TC, percentage and vehicle into the following: (1) ultrapotent (ie. clobetasol propionate, halobetasol propionate), (2) high (ie betamethasone propionate, mometasone furoate), (3) moderate (ie. triamcinolone acetonide) and (4) low potency (ie. hydrocortisone acetate, desonide), as well as brand. Drug factors such as frequency of application, longest continuous duration

of application, applied with occlusion and patient factors such as primary area (mucous membrane, scrotum, eyelids, face, chest or back, upper arms and legs, lower arms and legs, dorsa of hands and feet, palmar and plantar skin, nails and others) and surface area applied using palm method.

ii. Clinicoepidemiologic factors include (a)

- Age** – It will be categorized into the following: 0 to 9 years, 10 to 19 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, above 60 years. (b) **Sex**– It will be categorized into (1) male and (2) female. (c) **Location**– The primary address of the patient will be categorized into (1) within Metro Manila and (2) outside Metro Manila. (d) **Educational attainment** – it will be categorized into (1) no formal education or stopped at any grade school level, (2) stopped at any high school level (3) reached any college level or finished with a college degree. (e) **Employment status**– it will be categorized into (1) unemployed, (2) student, (3) employed. (f) **Civil status**– it will be categorized into (1) single/separated/widowed and (2) married/ live-in. (g) **Primary dermatosis**– it will be categorized into (1) infectious dermatoses (fungal, bacterial, viral, arthropod) (2) dermatitis (3) pigmentary dermatoses (4) acneiform and (5) others.

- iii. **Accessibility factors** include (a) **source of information of the TC**– these will be categorized into (1) advertisement (online, radio, TV, others) (2) relatives and friends, (3) prescribed by doctor (for current disease, for previous disease) (4) prescribed by dermatologist (for current

disease, for previous disease) (5) suggested by paramedical (nurse, pharmacist) (6) Others. (b) **Source of the TC procurement-** these will be categorized into (1) pharmacy (prescription-only, over-the-counter), (2) in stores, (3) online (4) relatives and friends (5) doctors (6) others. (c) **Source of instructions on application of TC-** these will be categorized into (1) label on box/container (2) relatives and friends (3) prescribed by non-dermatologist (4) prescribed by dermatologist (5) suggested by paramedical (nurse, pharmacist) (6) others.

iv. Awareness factors include (a) **FDA advisory on TC-** This pertains to the awareness of the patients on the existence of the FDA advisory on TC use (FDA Advisory 2019-388: Incorrect use of anti-fungal corticosteroid combination therapy). (b) **TC use should not be used for prolonged periods-** This pertains to the awareness of the TC cannot be used for prolonged periods. (c) **TC use can result into adverse effects-** This pertains to the awareness of the patients on the possibility of adverse effects with TC use. These will be categorized into yes or no.

II. Reason includes the reasons for TC use and the causes that led to TC use.

III. Adverse effects (AE) pertains to the unwanted or harmful reaction experienced following the administration of a drug or combination of the drug that manifests cutaneous noted to be present upon patient examination (hypopigmentation, striae, skin atrophy, allergic contact dermatitis, tinea incognito, acne flares, telangiectasia, xerosis, photosensitivity, purpura and others).

Patient Recruitment

Inclusion criteria of the study were patients who sought consult in the Dermatology OPD, while for patients who are incapacitated or those unable to give consent due to developmental, physical or mental inability to comprehend, the caregiver/legally authorized representative (LAR) may answer the survey. Minors may also give assent. Exclusion criteria included those who previously answered the survey but were unreachable by audio call for interview during the research period. Withdrawal criteria of the study included those who withdrew from the study and were unable to complete the interview.

Sample size computed was 255 and this was based on the following assumptions: prevalence of inappropriate use of TCs of 79%⁸, Z score of 1.96 and margin of error of 0.05. Assuming a 10% non-response rate, the total sample size was 286.

$$N = ((Z\alpha/2)^2)(P(1-P))/\epsilon^2;$$

where, n= the required sample size, P=the prevalence of inappropriate use of TCs, Z= Z score at 95% confidence interval=1.96, E = the margin of error=0.05

Materials and Procedures

After their dermatologic consultation, patient's consent to participate in the study was obtained via FTF or text message. They were then interviewed by the investigators using a pre-tested semi-structured questionnaire (Figure 2) to collect quantitative and qualitative data. De-identification was done. In place of patient's names, each patient was assigned a 4-digit ID number by the investigator. The investigator then confirmed TC use by either of the following: (1) name of the product, (2) prescription, (3) seeing the used product, or (4) photos or packets of community-available products (printed and online) (Figure 3).

For any adverse effects on the skin, the patient or caregiver/LAR was asked if there was presence of adverse effects and was shown photos of the different cutaneous adverse effects. If the patient presents with adverse effects located on the applied area, identification of the adverse effect and photo documentation of the affected body part was done with the consent/assent for the photograph. At the end of the interview, the patient was advised to discontinue or taper the use (if applicable) of the corresponding TC. Patient education was given regarding the development of possible adverse effects, the need to regularly seek consult for usage, the appropriate duration of use, and the need for follow-up with their dermatologist. If with adverse effects, they were also referred or treated accordingly. Permission to conduct this study was approved by the Research Ethical Board.

Demographic Characteristics (ID of patient)			
DC1. Gender	DC2. Age of the patient (years)	DC3. Date of Birth (mm-yy)	(ID/NAME/YY)
DC4. Address/Residence (Municipality/City)	DC5. Address/Residence (Province)	DC6. Employment Status	DC7. Civil Status (Married/single)
DC8. Education (M)	DC9. College/vocation	DC10. Unemployed	DC11. Single/Divorced/Widowed
DC12. Male (0-999)	DC13. High school	DC14. Student	DC15. Married/Divorced
DC16. Female (0-999)	DC17. Elementary/No formal education	DC18. Unemployed	
DC19. Diagnosis/Primary Dermatitis (Based from RANBHS Inhouse Chart, un-coded area)			
(5. Topical Corticosteroid use: ☐ Yes ☐ No (Only report if aware)			
Confirmation of consistency (5)			
DC20. Confirmation of topical corticosteroids and its combinations	DC21. Use of topical corticosteroids		
☐ Name of product	☐ Misuse		
☐ Prescription	☐ Not prescribed		
☐ Using the used product	☐ Prescribed but used longer than prescribed or chronic use (more than 2 weeks with no follow up)		
☐ Showing patches or patches of consistency	☐ Proper Use		
☐ Sending patches (printed and uncut)	☐ Photographed (ID number, TC99, in 003, TC13)		
History of Topical Corticosteroids (TC)			
TC1. Brand/Type of Topical Corticosteroids (TC)			
TC2. Topical corticosteroid used (with %)	TC3. Frequency of application (Day)		
TC4. Drug in Combination (if any, with %)	TC5. Longest continuous duration of application		
TC6. Vehicle	TC7. Applied with condition (identify how)		
☐ Ointment	☐ Topical		
☐ Cream	☐ Topical		
☐ Lotion	TC8. Areas applied		
☐ Others	☐ Mucous membrane		
TC9. Application of Topical Corticosteroid	☐ Scrotum		
☐ Ultra High potency topical corticosteroid	☐ Eyelids		
☐ High potency topical corticosteroid	☐ Face		
☐ Moderate potency topical corticosteroid	☐ Neck or back		
☐ Low potency topical corticosteroids	☐ Upper arms and legs		
	☐ Lower arms and legs		
	☐ Dorsal of hands and feet		
	☐ Palmar and plantar skin		
	☐ Nails		
	☐ Others		
Adverse Effect (AE)			
AE1. How did you learn of the type of corticosteroid?	AE2. Where indicated was the brand/type of the topical corticosteroid?	AE3. When did you suspect the topical corticosteroid?	
☐ Advertisement	☐ I believe I was informed	☐ Pharmacy	
☐ Doctor	☐ Healthcare workers	☐ Over-the-counter only	
☐ Radio	☐ Healthcare workers	☐ Over the counter	
☐ Television	☐ Prescribed by doctor	☐ Online (please indicate online store/websites)	
☐ Relatives and friends	☐ Non dermatologist		
☐ Prescribed by non dermatologist	☐ Dermatologist		
☐ Non dermatologist (for chronic skin disease)	☐ Reported by pharmaceutical	☐ Healthcare workers	
☐ Non dermatologist (for previous skin disease)	☐ Nurse	☐ Doctor	
☐ Prescribed by dermatologist	☐ Pharmacist	☐ I left over from previous prescription of _____	
☐ Dermatologist (for chronic skin disease)	☐ Jail doctor	☐ Others	
☐ Dermatologist (for previous skin disease)	☐ Others		
☐ Reported by pharmaceutical			
☐ Nurse			
☐ Pharmacist			
☐ Jail doctor			
☐ Others			
Reasons (AR)			
AR1. Did you know that the Food and Drug Administration has released an advisory (FDA-2011) on October 26, 2012 on to avoid using (anti-fungal) corticosteroid products without proper consultation from a dermatologist, to buy medicines in FDA licensed drug stores and avoid buying online?	☐ Yes (not) ☐ No (mind)		
AR2. Did you know that you cannot apply topical corticosteroids for prolonged periods?	☐ Yes (not) ☐ No (mind)		
AR3. Did you know it can result into side effects/long-term drug?	☐ Yes (not) ☐ No (mind)		
Rate of use (R)			
R1. Reason for use of Topical Corticosteroids and its combinations (DoNot Jang bold and write me! please)			
Adverse Effect (AE)			
AE1. Did you have any adverse effect? ☐ Yes ☐ No			
R1. If yes, what cutaneous adverse effect happened?			
☐ Itching/eczema			
☐ Skin atrophy			
☐ Melasma/pigmentation			
☐ Striae/micropits			
☐ Acne flares			
☐ Photosensitivity			
☐ Purpura			
☐ Dermos			
☐ Allergic contact dermatitis			
☐ Striae			
☐ Others			
☐ Photographic File name (ID number_ADR1_in_003_ADR1)			

Figure 2. Data collection form



Statistical Analysis

Data from FTF and telemedicine consults were collected. The data was inputted into the Microsoft Excel 2016 for storage. Missing data was excluded. The data was processed using SAS Enterprise Guide for descriptive and inferential statistics. Descriptive statistics was used to identify the prevalence of inappropriate use of TC, the frequency of the drug and patient factors, factors influencing behavior, and adverse effects. Moreover, the frequency of the product per brand and where it was procured was also obtained. Logistic regression was used to determine the factors (clinicoepidemiologic, access, awareness) that influence inappropriate TC use, and the association of inappropriate TC use to AEs. Statistical significance was set at <0.05 .

RESULTS

Eight hundred one patients were interviewed, 56.53% (147 out of 260 TC users) of whom inappropriately used TC (Figure 4). These patients used TCs once a day (n=74) to twice a day (n=65) for 1 day to 2 weeks (n=74) without occlusion (n=140). Among patients who inappropriately used TC, clobetasol propionate,

and ultra high potency TC in combination with ketoconazole (LS BL cream) were the most commonly used combination (Table 2), usually procured over-the-counter in pharmacies (Table 3). For patient factors, TCs were commonly applied on lower arms and legs, upper arms and legs and face, on around <1-1% body surface area for inappropriate use. (Table 2).

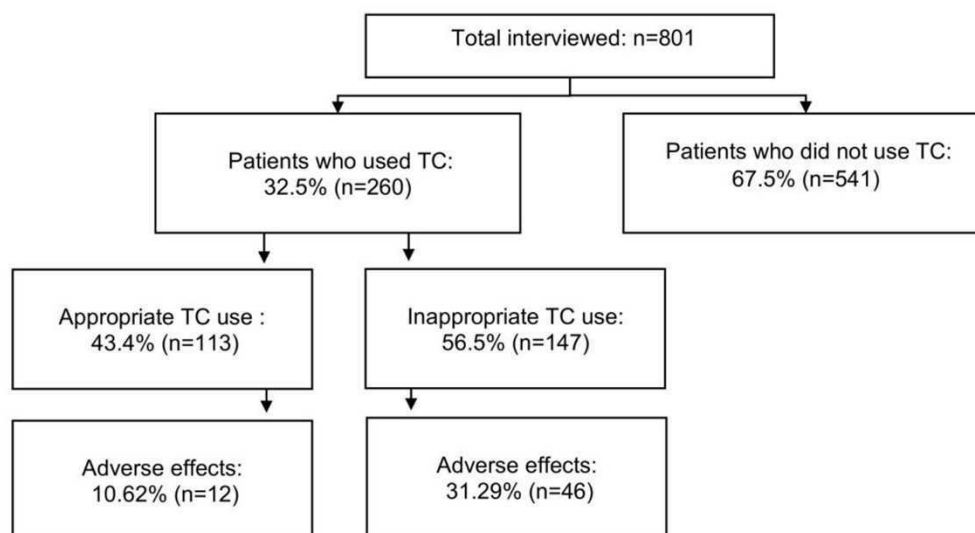


Figure 4. Prevalence of use of TC and Incidence of AE among patients who inappropriately use TC

Factors Associated with Inappropriate Topical Corticosteroid Use by Patients

Clinicoepidemiologic factors were not associated with inappropriate use of TC except for the primary dermatosis. Accessibility and awareness factors were associated with inappropriate TC use. The odds that a person experienced dermatitis inappropriately used TC was 2.82 (95% CI: 1.7, 4.7) times more likely than a person with other dermatoses. A person with acneiform dermatosis inappropriately used TC 82.6% (95% CI: .1, .4) less often than a person with other dermatosis (Table 4).

In terms of accessibility, as compared to a person whose source of information were dermatologists, the odds that a person whose source of information of the product were relatives and friends was 437 (95% CI: 25.9, >1000) times more likely to inappropriately use TC. While the odds that a person whose source of information was advertisement was 74 (95% CI: 3.9, >1000) times more likely and paramedical was 41 (95% CI: 1.9, 902.2) times more likely to inappropriately use TC as compared to a person whose source of information of the product were dermatologists. The source of information prescribed by doctors (dermatologist and non dermatologist) were not significantly associated with inappropriate use (Table 4).

For the source of product procurement, the odds that a person whose source of TC were relatives/friends inappropriately used TC was 60 (95% CI: 3.1, >1000) times more likely as compared to a person whose source of TC were doctors. Those who procured from the pharmacy (over the counter) were 24.6 (95% CI: 8.7, 69.8) times more likely to inappropriately use TC. Those who procured from stores were 10.6 (95% CI: 2.3, 49.6) times more likely and those who procured online were 9.8 (95% CI: 1.4, 70.7) times more likely to inappropriately use TC as compared to those whose source of TC were doctors (*Table 4*).

The odds that a person whose source of instructions on application of TC were from relatives/friends is 337 (95% CI: 19.8, >1000) times more likely to inappropriately use TC as compared to a person whose source of instructions on application of TC were dermatologists. The odds that a person whose source of instructions on application of TC was only from his knowledge (others) is 193 (95% CI: 11.1, >1000) times more likely to inappropriately use TC as compared to a person whose source of instructions on application of TC were dermatologists. The odds that a person whose source of instructions on application of TC were only on label on box/container is 43 (95% CI: 1.98, 945.9) times more likely to inappropriately use TC as compared to a person whose source of instructions on application of TC were dermatologists. The odds that a person whose source of instructions on application of TC were from paramedical suggestions is 37 (95% CI: 1.6, 858.5) times more likely to inappropriately use TC as compared to a person whose source of instructions on application of TC were dermatologists (*Table 4*).

In terms of awareness factors, the odds that a person who was not aware on FDA advisory on TC inappropriately used TC was 2.1 (95% CI: 1.2, 3.6) times more likely as compared to a person who

was aware on FDA advisory on TC. The odds that a person who was not aware that TC cannot be applied for prolonged periods inappropriately used TC was 5.5 (95% CI: 3.2, 9.3) times more likely as compared to a person who was aware that TC cannot be applied for prolonged periods. The odds that a person who was not aware that TC use can result to AE inappropriately used TC was 4.5 (95% CI: 2.6, 7.7) times more likely as compared to a person who was aware that TC use can result to AE (*Table 4*).

Reasons Patients Inappropriately Used Topical Corticosteroids

The reasons patients inappropriately used TC were the following: suggestion of family, friends, pharmacists and even celebrities (n=32) to use the medication since it has been effective in their experience and the treatment needed for their disease (n=28). Other reasons for TC use include effect of medication (n=20) on decreasing pruritus, erythema and improving hair growth, unable to consult (n=17), general sentiment of wanting to get better (n=16), effectiveness of medication (n=10) as it has previously treated disease, due to being advised by the doctors (n=7), financial constraints (n=7), worsening disease (n=7) where in there is recurrence or rebound effect after application and lastly, convenience (n=3). (*Table 5*)

Incidence of Adverse Effects Among those who Use Topical Corticosteroids

The incidence of AE among all patients who used TC is at 22.3% (n=58 out of 260) (*Figure 4*). Hypopigmentation (n=16), skin atrophy (n=8), striae (n=7) and allergic contact dermatitis (n=7) were the most common AE (*Figure 5*) among those who used TC (*Table 6*). Among those who inappropriately used TC, hypopigmentation was the most common adverse effect (*Table 6*).



Figure 5. Photos of cutaneous adverse reactions documented in the study

Association of Inappropriate Topical Corticosteroid Use with Incidence of Adverse Effects

The odds that a person inappropriately used TC had an AE was 3.8 (95% CI: 1.9, 7.7) times more likely as compared to a person who had appropriately used TC (Table 7). This was reflected in the incidence of AE that slightly higher among patients who inappropriately use TC at 31.29% (n=46 out of 147) (Figure 4) as compared to those who appropriately use TC at 10.62% (n=12 out of 113) (Figure 4).

DISCUSSION

For the first objective, the overall prevalence of inappropriate TC use in our study was as high as 18.35% (147 out of 801) while in other studies from India and Ethiopia had ranged from 3.76% to 11.77%^{10,20}. It can be considered that this is possibly an effect of the pandemic due to the limited access to FTF consults.

In a study by Lao et al (2018), 64% of patients practice self-medication with topical agents and the most common agents used were combinations of corticosteroids, antibiotics and antifungals at 31% and pure corticosteroids at 11%²³.

In our study, 51% applied pure corticosteroids while 39% were in combination with ketoconazole as the most commonly used combination for patients who have inappropriately used TC. Similarly, the most common inappropriately used TC included clobetasol propionate (50%)²⁰ which is an ultra-high potency applied once a day (52-67.8%)^{8,10,20,24} for 1 day to 2 weeks as compared to others studies for less than a month up to a year^{8,10,20,24}. The lower extremities was the most common site of application followed by the face covering <1-1% body surface area while other studies state the face^{8,20,24} as the most common location covering up to around 9% of the

body surface area.²¹ The combination of clobetasol and ketoconazole- LS BL Cream was the most common brand used by patients who inappropriately used TC. This was commonly procured over-the counter in pharmacies (n=41), stores (n=8) and relative and friends (n=6). The next brands were unrecalled (n=25) procured from the pharmacy (n=14) and doctors (n=22) then followed by Dermovate and Elica commonly procured over-the counter and prescription in pharmacies (n=10).

For the second objective, the clinicoepidemiologic characteristics in our study was similar to previous studies from India and Ethiopia. Of those who inappropriately used TC, majority belonged to 20 to 29 years old age group^{8,10,20,24} who were single^{8,10,20,24} female^{8,10,24} college graduates²⁰. Though in our study, those employed living in the metropolitan area were the majority who inappropriately used TC as compared to other literature presented that majority of the employment status were of students^{10,20,24}. The clinicoepidemiologic factors²² in our study were not significantly associated with inappropriate TC use. Notably, Bilal stated a significant association was established between over-the-counter use (inappropriate use) and educational attainment, with an increasing use among those of higher educational background⁸. This is probably due to the ability to purchase of the group in our study as they are employed with college graduates who are single who also gave the reason that they were unable to consult due to the pandemic and work. The only significantly associated clinicoepidemiologic factor is the type of dermatoses, specifically dermatitis type of diagnosis. This is possibly explained by TC as the treatment used for dermatitis cases such as seborrheic dermatitis, atopic dermatitis, hand dermatitis to name a few. In other studies, users consume these TCs predominantly for dermatophytosis treatment.^{10,20}

In the United Kingdom (UK), there are three main sources of drugs namely prescription-only medicines, over-the-counter drugs under the supervision of a pharmacist, and widely-available drugs in shops and hotels.²⁵ On the other hand In India, majority of inappropriate users were able to procure TCs through over-the-counter means, as well as from other family members or peers^{10,20,24}. Accessibility to the drug is a concern as the source of information, procurement and instruction consistently show relatives and friends as to have a significant association with inappropriate use of TC as compared to the source from doctors or dermatologists. The suggestion of family, friends, pharmacists and endorsers is also the most common reason for inappropriate TC use as the medication was effective in their experience. Thus, it is crucial to note that the family often functions as a body of self-perpetuated knowledge²⁶. This was consistent with other significant associations in the study including the pharmacy (over the counter) and paramedical (nurses and pharmacist) as a source of accessibility as compared to doctors or dermatologists. Another study also states that the major factor responsible for topical corticosteroid abuse in India is the fact that topical corticosteroids are available over-the-counter²⁰. The vital part of having over-the-counter is dependent on the pharmacist's knowledge of the indications and contraindications and ability to appropriately prescribe. If there is a lapse in the consumers and pharmacist knowledge, topical corticosteroids should be kept as a Prescription-only medication.

Other significantly associated accessibility factors to inappropriately use TC as compared to the source from doctors or dermatologists include advertisement as a source of information, stores and online as a source of procurement and their own knowledge and labels as the source of instruction. For advertisements, stores, online and to their own knowledge which were seen as a

source in health care information in the decision to self-medicate. Online stores are also associated with inappropriate TC use and this is driven by the reasons of convenience. As label on the box/container as a source of instruction is associated with inappropriate use, a way to address the knowledge of the consumers includes the example of the Swedish National Board of Health and Welfare on labelling instructions (including purpose of the drug, recommended dosage, frequency, period, and warnings).²⁶

The lack of awareness in regard to the FDA advisory is associated with inappropriate TC use. The FDA has made efforts through posting advisories such as the FDA advisory 2019-388 on the incorrect use of anti-fungal corticosteroid combination therapy¹⁷ which reflects that those who are not aware on FDA advisory inappropriately uses TC 2.1 times more likely as compared to a person who is aware on FDA advisory. This shows that the role of regulation may be vital to decreasing inappropriate use of TC. The FDA is able to do surveillance as they are able to release other advisories on other TC but release of these advisories may not be reaching some of the consumers as they are only online and tighter regulations may be needed. In terms of awareness on the use and adverse effects of TC, 73.5% who inappropriately applied TC were not aware that it should not be applied for prolonged periods but even more (76.19%) were not aware that TC use can result into adverse effects. Being unaware of this, patients were at a 4-5 fold risk of inappropriately using TC as compared to TC users who were aware. Similarly in India, Mahar noted that 96.8% of patients using TCs were unaware about the adverse effects, Awareness may be increased through agency advisories and established guidelines on judicious TC use and AEs that may result from inappropriate use. Awareness of consumers is critical in the addressing inappropriate TC use.

For the third objective, majority of the patient's reason for inappropriate use of TC was due to the suggestion of family, friends, pharmacists and even celebrities to use the medication since it has been effective in their experience consistent with the majority of the source of accessibility, followed by the treatment needed for their disease. An anecdote states that the use of clobetasol and ketoconazole for seborrheic dermatitis on the face has been used in their community as it has been effective. The effect of the medication such as decreasing pruritus, erythema and improving hair growth was also a reason for use of TC. Other reasons for TC use include general sentiment of wanting to get better, unable to consult due to the pandemic and work, effectiveness of medication as it has previously treated their disease. But at the same time, some experience worsening disease which prompted them to continue the use of TC wherein there could be recurrence or rebound effect after application. Financial constraints with the belief that the medication is the first aid since consulting would mean additional costs such as transportation and additional tests. This is where the benefit to making only topical hydrocortisone 1% an over-the-counter drug include consumers savings in time costs (travel, waiting, and consultation time) and consumer savings in money costs (travelling expenses and prescription charges)²⁵. Some considered convenience of using the medications especially those available online or in stores without having to consult. This was supported by the odds that a person whose source of TC were online would inappropriately used TC 9.8 times more likely as compared to a person whose source of TC were doctors. The reasons for other studies was different namely from the purpose of fair complexion, beautification purposes to dermatologists not being available which are not mentioned in our study.

For the last objectives, the incidence of AE among all patients who used TC is at 22.3% (n=58 out of 260) (Table 7). Hypopigmentation, striae and skin atrophy were the most common adverse effects since the primary type of dermatosis associated was dermatitis. While other literature cites Allergic reactions: (23.4%)⁸ and Tinea incognito: 171 (52.77%)²⁰ to be the most common side effects since the most common dermatosis seen were fungal infections. The inappropriate TC use should be prevented as there was a 3.8 times likelihood to develop adverse effects as compared to a person who has appropriately used TC. Similarly, Bilal et al. (2018) has established a three- to five-fold risk of AEs for those who sourced out information regarding TCs through peers⁸. Hence, the factors associated with inappropriate TC use should be addressed to decrease the likelihood of adverse effects from occurring.

In summary, 56.53% inappropriately used TC and this was associated with a diagnosis of dermatitis, lack of knowledge regarding its adverse effects especially after prolonged use, and self-medication upon recommendation of family and friends. Revealing that accessibility and awareness factors were both associated with behavior of use of TC. Hypopigmentation was the most common AE documented. There is 3.8 times likelihood for a person who has inappropriately used TC to have an AE as compared to a person who has appropriately used TC.

CONCLUSION

Based on our results on awareness, there may be lapse in the consumers and pharmacist knowledge on TC use. Hence it is advisable to document this and possibly keep topical corticosteroids as a prescription-only medication. As the most common type are the ultrapotent class of TC, FDA should find other avenues to disseminate information for consumers and have tighter regulations by continuously monitoring

online shops, stores and pharmacies. Advertisements/ labels should include proper information as it is a source of information that is associated with inappropriate TC use.

There is a need to create awareness and educate consumers on TC use. We can remind patients to inform their family and friends as it appears to be a major factor in the inappropriate use of TC. For all cases, especially dermatitis type of cases, as doctors we should ensure to explain the TC use. In conclusion, as a dermatologist, there is a need to educate the general public regarding proper TC use. Patient encounters at the clinic may be a good opportunity to reinforce guidelines on the use of TC.

LIMITATIONS AND RECOMMENDATIONS

It should be noted that the prevalence was based on patients at the out-patient dermatology clinic in a tertiary hospital. With that, it may or may not accurately reflect the community data especially for those who consult are those probably with adverse effects or with no resolution with the use of TCs. It may not get the prevalence of those who used TCs with resolution of cutaneous problems. This study limits the questionnaire to patients and will not include other contributing factors such as pharmacist, and doctors or medical student's knowledge of prescribing TC. Selection bias was dependent on the availability of the patient. To address this, the patients who were unavailable were contacted again during the data collection period. Information bias may be present because the informed consent/assent form contained the mention of TC and the questionnaire contained AE. To prevent this, the patients were initially asked if they applied any medication and if they could name the medication and reasons of use remained to be an open-ended question. Another recommendation would include documentation of systemic side effects such as cushingoid features (Hirsutism, Buffalo hump) and cataracts.

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Appendix

Table 1. World Health Organization (WHO) Classification of Topical Corticosteroids³ – classification of potency of topical corticosteroids

United Kingdom and France's Classification	United States' classification	
Ultra high potency TCs	Group I	- clobetasol propionate cream (0.05%) - diflorasone diacetate ointment (0.05%) - halobetasol propionate ointment (0.05%) ^a - halobetasol propionate cream (0.05%) ^{a,b} - halobetasol propionate lotion (0.05%) ^b
High potency TCs	Group II	- amcinonide ointment (0.1%) - betamethasone dipropionate ointment (0.05%) - desoximetasone (cream or ointment) (0.025%) - fluocinonide (cream, ointment, or gel) (0.05%) - halcinonide cream (0.1%)
	Group III	- netamethasone dipropionate cream (0.05%) - betamethasone valerate ointment (0.1%) - diflorasone diacetate cream (0.05%) - triamcinolone acetonide ointment (0.1%) - mometasone furoate ointment (0.1%) ^{a,b} - fluticasone propionate ointment (0.005%) ^a
Moderate potency TCs	Group IV	- desoximetasone cream (0.05%) - fluocinonide acetonide ointment (0.025%) - fluocinolone acetonide cream (0.02%) ^a - hydrocortisone valerate ointment (0.2%) - triamcinolone acetonide cream (0.1%) - betamethasone valerate foam (0.12%) ^a - clocortolone pivalate cream (0.1%) ^a - flurandrenolide ointment (0.05%) ^a
	Group V	- betamethasone dipropionate lotion (0.02%) - betamethasone valerate cream (0.1%) - fluocinonide acetonide cream (0.025%) - hydrocortisone butyrate cream (0.1%) - hydrocortisone valerate cream (0.2%) - triamcinolone acetonide lotion (0.1%) - triamcinolone acetonide cream (0.1%) - prednicarbate cream (0.1%) ^a
Low potency TCs	Group VI	- betamethasone valerate lotion (0.05%) - desonide cream (0.05%)

		• fluocinolone acetonide solution (0.01%) • alclometasone dipropionate ointment (0.05%) ^a • alclometasone dipropionate cream (0.05%) ^a
	Group VII	• dexamethasone sodium phosphate cream (0.1%) • hydrocortisone acetate cream (1%) • methylprednisolone acetate cream (0.25%) • topicals with flumethasone and prednisolone ^a

^a Del Rosso, J., & Friedlander, S. F. (2005). Corticosteroids: Options in the era of steroid-sparing therapy.²

^b Horn, E., Domm, S., Katz, H., Lebwohl, M., Mrowietz, U., & Kragballe, K. (2010). TCs in psoriasis: strategies for improving safety.⁴

Table 2. Frequency of drug and patient factors with its corresponding TC use.

Variable Category	Appropriate use of TC (%) n=113	Inappropriate use of TC (%) n=147
Drug factors		
TC		
clobetasol propionate 0.05%	47.79	61.22
mometasone furoate 0.1%	13.27	10.88
betamethasone dipropionate 0.05%	9.73	6.8
hydrocortisone 1%	7.08	6.12
betamethasone valerate 0.05%	7.08	4.08
Others	15.04	10.88
Combination		
None	89.38	51.02
Ketoconazole	0	39.46
Petroleum Jelly	1.77	2.04
Gentamycin	1.77	1.36
Calcipotriol	1.77	1.36
Isoconazole nitrate	1.77	1.36
others	3.54	3.4
Vehicle		
cream	45.13	64.63
ointment	43.36	32.65
lotion	10.62	2.04
solution	0.88	0
gel	0	0.68
Potency		
Ultra high potency topical corticosteroids	53.1	64.63
High potency topical corticosteroids	23.01	19.05
Moderate potency topical corticosteroids	12.39	8.84
Low potency topical corticosteroids	11.5	7.48
Brand		
Unrecalled	53.1	17.01
LS BL Cream (Shanghai Baolong Pharmaceutical)	0	39.46
Dermovate (GSK)	14.16	10.2
Elica (Bayer)	6.19	8.84
Frostlike (Tianjin Pacific pharmaceutical Ltd.)	1.77	4.76
Others	24.78	19.73
Frequency (per day)		
once a day	18.58	46.94
twice a day	75.22	44.22
more than twice a day	3.54	5.44
Duration		
1 day to 2 weeks	76.99	50.34
3 weeks to 1 month	13.27	15.65
6 weeks to 3 months	6.19	12.24
4 months to 6 months	0.88	5.44
7 months to 9 months	0	0.68
10 months to 1 year	0.88	7.48
More than 1 year	1.77	8.16
Occlusion		
NO	92.92	95.24
YES	7.08	4.76
Patient factors		
Area applied		
Lower arms and legs	22.12	21.77
Face	18.58	20.41
Upper arms and legs	15.04	21.09
Chest or back	22.12	14.29
Dorsa of hands and feet	7.96	9.52
Others	14.16	12.93
Surface area		
<1% to 1%	37.17	40.82
2% to 4.5%	23.89	23.13
5% to 9%	15.93	9.52
10% to 18%	4.42	8.16
19% to 36%	4.42	6.8
37% to 72%	9.73	4.08
73% to 95%	4.42	7.48

Table 3. Frequency of brands of TC and where it was procured

Brand (Company)	Source of product procurement (number)						
	Pharmacy (Prescription only)	Pharmacy (OTC)	Stores	Online	Relative and friend	Doctor	Others
Unrecalled	40	14	1	2	5	22	1
LS BL Cream (Shanghai Baolong Pharmaceutical)	1	41	8	2	6	0	0
Dermovate (GSK)	16	10	0	1	2	0	2
Elica (Bayer)	8	8	0	0	1	3	0
Frostlike (Tianjin Pacific pharmaceutical ltd.)	1	1	4	2	0	1	0
Betnovate (GSK)	4	2	0	0	0	1	0
Daivobet (Leo Pharmacy)	2	2	0	0	0	2	0
Glevate (Glenmark)	0	0	0	0	0	3	2
Halovate (Glenmark)	1	2	0	0	0	1	0
Travacort (Leo Pharmacy)	3	1	0	0	0	0	0
Others	15	6	2	1	1	6	0

Table 4. Logistic regression of factors vs appropriate and inappropriate TC use

Variable Category	Total (n)	No use of TC (frequency, % n=541)	Appropriate use of TC (frequency, % n=113)	Inappropriate use of TC (frequency, % n=147)	Odds Ratio* (CI)
Clinicoepidemiologic factors					
Age					
50 to 59 years	68	43 (7.95%)	10 (8.85%)	15 (10.20%)	1.296 (.5, 3.6)
above 60 years.	93	58 (10.72%)	15 (13.27%)	20 (13.61%)	1.281 (.5, 3.4)
10 to 19 years	91	59 (10.91%)	13 (11.50%)	19 (12.93%)	1.196 (4, 3.2)
40 to 49 years	91	58 (10.72%)	17 (15.04%)	16 (10.88%)	1.025 (.4, 2.8)
0 to 9 years	37	26 (4.81%)	4 (3.54%)	7 (4.76%)	1
30 to 39 years	137	91 (16.82%)	22 (19.47%)	24 (16.33%)	0.98 (.4, 2.5)
20 to 29 years	284	206 (38.08%)	32 (28.32%)	46 (31.29%)	0.829 (.3, 2.0)
Sex					
Female	491	330 (61%)	71 (62.83%)	90 (61.22%)	1.01 (.7, 1.5)
Male	310	211 (39%)	42 (37.17%)	57 (38.78%)	1
Location					
Outside Metro Manila	266	177 (32.72%)	38 (33.63%)	51 (34.69%)	1.093 (.7, 1.6)
Within Metro Manila	535	364 (67.28%)	75 (66.37%)	96 (65.31%)	1
Educational attainment					
High school level	176	113 (20.89%)	24 (21.24%)	39 (26.53%)	1.208 (.7, 2.2)
No formal education/ grade school	103	70 (12.94%)	13 (11.50%)	20 (13.61%)	1
College level	522	358 (66.17%)	76 (67.26%)	88 (59.86%)	0.86 (.5, 1.5)
Employment status					
Unemployed	255	161 (29.76%)	44 (38.94%)	50 (34.01%)	1
Student	198	137 (25.32%)	23 (20.35%)	38 (25.85%)	0.893 (.5, 1.4)
Employed	348	243 (44.92%)	46 (40.71%)	59 (40.14%)	0.782 (.5, 1.2)
Civil status					
Married/ live-in.	233	145 (26.8%)	43 (38.05%)	45 (30.61%)	1
Single/separated/widowed	568	396 (73.2%)	70 (61.95%)	102 (69.39%)	0.83 (.6, 1.2)
Primary Dermatitis					
Dermatitis	140	49 (9.06%)	47 (41.59%)	44 (29.93%)	2.82* (1.7, 4.7)
Others	285	179 (33.09%)	49 (43.36%)	57 (38.78%)	1
Infectious	184	142 (26.25%)	6 (5.31%)	36 (24.49%)	796 (.5, 1.3)
Pigmentary	38	27 (4.99%)	9 (7.96%)	2 (1.36%)	.233 (.1, 1.0)
Acneiform	154	144 (26.62%)	2 (1.77%)	8 (5.44%)	.174* (.1, .4)

Accessibility factors					
Source of information					
Relatives and friends	79	<Not Applicable>	0	79 (53.74%)	437.795* (25.9, >1000)
Advertisement	13		0	13 (8.84%)	74.342* (3.9, >1000)
Suggested by paramedical	7		0	7 (4.76%)	41.301* (1.9, 902.2)
Others	1		0	1 (0.68%)	8.27 (.1, 777.6)
Prescribed by non dermatologist	24		13 (11.5%)	11 (7.48%)	2.346 (.97, 5.7)
Prescribed by dermatologist	136		100 (88.5%)	36 (24.49%)	1
Source of the product procurement					
Relatives and friends	15	<Not Applicable>	0	15 (10.2%)	60.843* (3.1, >1000)
Pharmacy, over-the-counter	87		6 (5.31%)	81 (55.1)	24.613* (8.7, 69.8)
In stores	15		2 (1.77%)	13 (8.84%)	10.6* (2.3, 49.6)
Online	8		1 (0.88%)	7 (4.76%)	9.815* (1.4, 70.7)
Doctors	39		26 (23.01%)	13 (8.84%)	1
Others	5		4 (3.54%)	1 (0.68%)	0.654 (.1, 5.5)
Pharmacy, Prescription-only	91		74 (65.49%)	17 (11.56%)	0.461 (.2, 1.1)
Source of instructions on application of TC					
Relatives and friends	58	<Not Applicable>	0	58 (39.46%)	337.481* (19.8, >1000)
Others	33		0	33 (22.45%)	193.233* (11.1, >1000)
Label on box/container	7		0	7 (4.76%)	43.26* (1.98, 945.9)
Suggested by paramedical (nurse, pharmacist)	6		0	6 (4.08%)	37.492* (1.6, 858.5)
Prescribed by non-dermatologist	23		14 (12.39%)	9 (6.12%)	1.89 (.8, 4.7)
Prescribed by dermatologist	133		99 (87.61%)	34 (23.13%)	1
Awareness factors					
FDA advisory on TC					
No	178	<Not Applicable>	67 (59.29%)	111 (75.51%)	2.117* (1.2, 3.6)
Yes	82		46 (40.71%)	36 (24.49%)	1
Awareness that TC cannot be applied for prolonged periods					
No	146	<Not Applicable>	38 (33.63%)	108 (73.47%)	5.466* (3.2, 9.3)
Yes	114		75 (66.37%)	39 (26.53%)	1
TC use can result into adverse effects					
No	159	<Not Applicable>	47 (41.59%)	112 (76.19%)	4.494* (2.6, 7.7)
Yes	101		66 (58.41%)	35 (23.81%)	1

*significantly affects the behavior of inappropriate use of TC

Table 5. Purpose and reason for use of TC of appropriate and inappropriate use

Reason for use of TC	Appropriate use of TC (frequency)	Inappropriate use of TC (frequency)
Advised by others (non-doctors)	0	32
Treatment of disease	48	28
Effects of medication	11	20
Unable to consult	2	17
General sentiment of wanting to get better	7	16
Effectiveness of medication	0	10
Prescribed or advised by doctor	44	7
Financial constraints	0	7
Worsening disease	0	7
Convenience	1	3

Table 6. Frequency of Cutaneous Adverse Effects

Cutaneous Adverse effects	Use of TC	Appropriate use of TC	Inappropriate use of TC
Hypopigmentation	16	5	11
Skin atrophy	8	2	6
Striae	7	0	7
Allergic contact dermatitis	7	2	5
Tinea incognito	6	1	5
Acne flares	5	0	5
Others: worsening of infection	3	1	3
Telangiectasia	2	0	2
Xerosis	2	1	2

Table 7. Logistic regression of behavior of use of TC vs Presence of AE

Behavior of use of TC	With AE (frequency)	Without AE (frequency)	Odds Ratio*	Odds Ratio CI
Appropriate use	12	101	1	
Inappropriate use	46	101	3.833*	1.9, 7.7

*significant

Cost Effectiveness of Treatment for Moderate to Severe Psoriasis at the Rizal Medical Center*

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ABSTRACT

Background: Cost-effectiveness studies are important for chronic diseases such as psoriasis, which may cause significant financial burden and negatively affect the patient's quality of life.

Objectives: This study evaluated which among the treatment options, namely topicals + phototherapy (TP), topicals + systemic (TS), and topicals + biologics (TB), is the most cost-effective for the management of moderate to severe psoriasis at the Rizal Medical Center's Psoriasis Center.

Methods: A total of 65 moderate to severe psoriasis patients seen at the Rizal Medical Center's Psoriasis Center in 2021 were included in this retrospective cross-sectional study. Chart review was conducted to account all direct costs of treatment. The effectiveness in relation to the overall cost was assessed using the psoriasis area severity index (PASI) and the dermatological life quality index (DLQI).

Results: Our study showed that TS is the most cost-effective treatment for moderate to severe psoriasis with the lowest cost per PASI75 and DLQI<5 improvement valued at Php335.36, followed by TP valued at Php 762.87, and lastly by TB at Php 19,058.03. Despite TB incurring the highest cost, all patients in this treatment group showed the highest mean difference of PASI and DLQI.

Conclusions: Our findings suggest that topical with systemic medication is the most cost-effective treatment for moderate to severe psoriasis.

Keywords: psoriasis; psoriasis treatment; cost effectiveness

INTRODUCTION

In health care, treatment or therapy is cost-effective when the best result is achieved for a comparably reasonable price.¹ Understanding treatment efficacy in relation to cost may help both doctor and patient achieve maximum treatment results especially for long-term health conditions which may require treatment cycles. A chronic recurrent disease like psoriasis is a skin condition in which skin cells multiply up to ten times faster than usual. The scalp, elbows, knees, and lower back are the most common body areas for the pinkish to red plaques topped with white scales. It can be triggered by trauma, infection or stress.²

During the Psoriasis Day consortium in October 2020, the National Psoriasis Foundation USA revealed that 125 million individuals globally had psoriasis.³ In the Philippines, according to data obtained from Psoriasis Philippines, there are approximately 1 to 2 million Filipinos suffering in silence from psoriasis.⁴

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

*2nd Place, 29th Philippine Medical Association Original Research Presentation, May 16, 2023

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The Rizal Medical Center Department of Dermatology opened its Psoriasis Center on April 17, 2018, with the goal of providing patients with a broad range of diagnostic and treatment modalities.⁵ The center is constantly meeting the needs of patients, most of whom come from Metro Manila. Under the Psoriasis Philippines' Patient Rescue Program, the Rizal Med Psoriasis Center is a partner for patients from the southern and eastern parts of Luzon.⁶

Currently there is no absolute cure for psoriasis, and patients go through cycles of treatment as required, which might result in recurring costs. Topical, phototherapy, systemic, biologic and combination therapies are included in all established clinical practice guidelines for the condition. Last 2021, the center formulated its own clinical pathway to standardize the care for psoriasis patients based on the disease severity. Cost-effectiveness of treatment is of great importance given the financial impact of the disease to the health care institution and most especially to the patients.⁷

Significance of the Study

The data gathered in this study may be utilized for financial and program planning, and may have the potential in identifying areas for rational budget allocation. The findings of this study may also be used to identify areas for center development and hospital fund management toward increased patient access to treatments and, more importantly, the efficacy of treatment protocols. Additional guidance that could be derived from this study would be on how to maximize patient response to treatment with the reasonable cost to the hospital and the center.

Cost-effectiveness analysis of treatment is of growing importance in all health care systems. These types of studies that compared the different psoriasis treatment modalities were already done

in countries like Malaysia, Finland, and the US.^{9,10,11} However, there is no published data in the Philippines on the cost-effectiveness of treatment for psoriasis. At the Rizal Medical Center, the Psoriasis Center continually finds ways to provide effective and affordable care. It is of great value to the center and to the patients to know which among the treatments for psoriasis is the most cost effective.

Research Objectives

A. General Objectives

This study aimed to determine the most cost-effective treatment for moderate to severe psoriasis based on the clinical pathway at the Rizal Medical Center Psoriasis Center

B. Specific Objectives

1. Described the characteristics of the psoriasis patients with moderate to severe disease in terms of:
 - 1.1 age
 - 1.2 gender;
 - 1.3 disease duration;
 - 1.4 Psoriasis Area Severity Index (PASI) baseline score;
 - 1.5 Dermatology Life Quality Index (DLQI) baseline score; and
 - 1.6 Presence of Psoriatic Arthritis
2. Described the characteristics of moderate to severe psoriasis patients according to treatment modality:
 - 2.1 Phototherapy $\pm$ Topical medication
 - 2.2 Systemic $\pm$ Topical medication
 - 2.3 Biologics $\pm$ Topical medication
3. Determined the distribution of cost diagnostic and treatment modality per patient:

- 3.1 applicable diagnostic test (blood chemistry, imaging, urinalysis, gene expert, etc);
- 3.2 topical medications;
- 3.3 phototherapy cost;
- 3.4 systemic medications; and
- 3.5 biologics
4. Determined the proportion of patients who improved after 3 months of treatment per treatment modality
5. Evaluated and compared the three treatment modalities according to cost and effectiveness

METHODOLOGY

Study Design

A cross-sectional study was conducted at the Rizal Medical Center's Psoriasis Center involving patients with moderate to severe psoriasis given any of the 3 treatment options: topical + phototherapy (TP), topical + systemic (TS) and topical + biologics (TB) from January to December of the year 2021.

Study Population

This study involved individuals diagnosed with moderate to severe psoriasis with psoriasis activity severity index (PASI) of >10 and/or dermatology quality life index (DLQI) of >10 . Other inclusion criteria were as follows:

- age 19 years old and above
- seen during teledermatology or physical consult at the out-patient department
- managed with phototherapy, systemic or biologics
- diagnosed case of psoriasis with or without biopsy
- with or without comorbidities (Hypertension, Diabetes Mellitus, Malignancy, etc.)

The exclusion criteria were as follows:

- patients without recorded Psoriasis Area and Severity Index (PASI) or Dermatology Quality Life Index (DLQI) score
- patients who were managed with more than one type of treatment excluding topical medications
- mild psoriasis
- hospitalized patients
- patients lost to follow up for a minimum of 3 months

Sampling Design

Total enumerative sampling was utilized for this study to appropriately estimate the total cost incurred for each treatment modality in the given year. All charts of patients that were able to satisfy the selection criteria were included to better estimate the parameters involved in the study.

Data Collection

Clinical data of the eligible participants were obtained from the psoriasis census, teledermatology census, phototherapy outpatient department (OPD) charts, and electronic health records (EHR). Demographic profile as well as the PASI and DLQI were gathered from the EHR in categorizing the disease severity.

The total cost was computed based on the number of consults for 3 consecutive months. Direct cost of treatment which included diagnostics and phototherapy cost were acquired from the hospital's actual charges whereas cost of medications like topicals, systemics and biologics were based on the Drug Price Reference Index of the Department of Health (DOH) or, if not available, by the local pharmacy and manufacturer's suggested retail price (SRP) especially for biologics.

Statistical Analysis

The cost was computed at baseline and after 12 weeks. Descriptive statistics, frequency distribution, and percentages were used to summarize the demographic profile of the patients, as well as the disease severity of the respondents, treatment modality costs and efficacy. Effectiveness of treatment was measured by an improvement of 75% from baseline of PASI (PASI 75) or a change of DLQI to ≤ 5 after 3 months. The cost per treatment was estimated by itemizing the actual cost per consult or visit, which included diagnostic tests, phototherapy sessions, systemic and biologic medications.

Paired t-test was used to determine if there is a significant difference on the PASI and DLQI score before and after the treatment, per treatment modality. One-way ANOVA was used to determine if there was a significant difference of PASI and DLQI improvement among treatment modalities. Post-hoc analysis Turkey-Kramer Honest Significant Difference (HDS) test was then employed for test with $p < 0.05$. To evaluate data with an atypical distribution, Kruskal-Wallis and Dunn's test were used. To ascertain the degree of correlation between the three treatment options' costs and patient improvement levels, Pearson R correlation was used.

All valid data were included in the analysis. Null hypothesis was rejected at 0.05 α -level of significance. SPSS version 26 (IBM Corp, Armonk, NY) was used for the data analysis.

Results

A total of 581 psoriasis patients were seen at the study center in the year 2021. Screening for eligible participants was done, excluded from the study were 32 pediatric patients ages 18 years old and below, 330 patients who were lost to follow up for 3 months, and 154 patients who had mild disease and thus were managed only with topical medications. The remaining 65 patients were included in the study. (Figure 1)

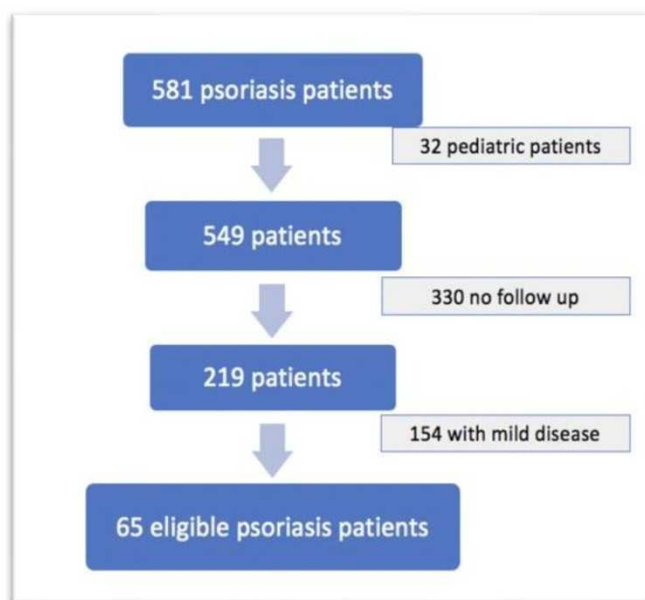


Figure 1. Eligible participants selection

The demographic characteristics for each type of treatment are shown in Table 1. There are three treatment groups for the patients: topical + phototherapy (TP), topical + systemic (TS), and topical + biologics (TB). The majority of the respondents were female (58.46%) between the ages 46–85 (53.85%), and had physical consults (56.92%). Among the participants, 33.85% had psoriatic arthritis. The mean PASI and DLQI were 17.02 (SD=6.52) and 15.71 (SD=5.96), respectively.

Table 1. Demographic Characteristics of the Respondents

Demographic Characteristics of the Respondents according to Treatment Modality (N = 65)				
Characteristics	Treatment Modality (N = 65)			Total (N= 65)
	Topical + Phototherapy (TP) (n=28)	Topical + Systemic (TS) (n=28)	Topical + Biologics (TB) (n=9)	
Age (Years; f, %)				
18 to 30 Years Old	11 (39.29%)	8 (28.57%)	1 (11.11%)	20 (30.77%)
31 to 45 Years Old	3 (10.71%)	3 (10.71%)	2 (22.22%)	8 (12.31%)
46 to 60 Years Old	13 (46.43%)	17 (60.71%)	5 (55.56%)	35 (53.85%)
More than 60 Years Old	1 (3.57%)	0 (0.00%)	1 (11.11%)	2 (3.08%)
Sex (f, %)				
Male	12 (42.86%)	10 (35.71%)	5 (55.56%)	27 (41.54%)
Female	16 (57.14%)	18 (64.29%)	4 (44.44%)	38 (58.46%)
Presence of Psoriatic Arthritis (f, %)	7 (25.00%)	12 (42.86%)	3 (33.33%)	22 (33.85%)
Type of Consultation (f, %)				
Physical Consultation	28 (100.00%)	1 (3.57%)	8 (88.89%)	37 (56.92%)
Teledermatology	0 (0.00%)	27 (96.43%)	1 (11.11%)	28 (43.08%)
Baseline Psoriasis Area Severity Index (PASI; $\bar{x}$, SD)	15.21 (4.81)	16.79 (5.76)	23.38 (9.63)	17.02 (6.52)
Baseline Dermatology Life Quality Index (DLQI; $\bar{x}$, SD)	16.61 (6.18)	14.25 (5.47)	17.44 (6.37)	15.71 (5.96)

The within-group and between-group comparisons of the PASI and DLQI according to treatment modality is presented in Table 2. It can be noted from the table that within-group comparisons indicated a significant decline in the mean PASI scores of the three treatment modalities from baseline to endline ($p < 0.05$). Between-group analyses of the mean PASI difference scores of the three treatment modalities indicated that at least one of the three treatment modalities had a significantly different mean score. Post-hoc analysis indicated that the mean PASI severity difference scores of TB group was significantly higher compared to both TP and TS. However, the post-hoc comparison of the mean PASI difference scores between the TP and the TS groups was not statistically different ($p > 0.05$). It is also interesting to note that among the different treatment modalities, 66.67% of the TB

group had improvement in PASI score of at least 75%, while 28.57% of the TP group and 17.86% of the TS had improvement in PASI scores of at least 75% from baseline to endline.

On the other hand, the mean DLQI scores of the three treatment modalities significantly decreased ($p < 0.05$) from baseline to endline. Between-group comparison indicates that there was a statistically significant difference in the mean DLQI difference scores between TS and TB, while DLQI score difference between TS and TP, and TB and TP were not statistically different. An improvement of 5 score units in DLQI was observed in 88.89% for the TB group, while it was 57.14% for the remaining two groups.

Table2. Comparisons of Psoriasis Area Severity and Dermatology Life Quality Indices

Between-Group and Within-Group Comparisons of the Psoriasis Area Severity Index and Dermatology Life Quality Index of the Respondents According to Treatment Modality (N = 65)

Variable and Treatment Modality	Within-Group Comparisons ^a				Between-Group Comparison ^a	
	Baseline Mean (SD)	Endline Mean (SD)	Frequency (%) with Improvement ^b	p-value (Two-Tailed)	Mean Difference (SD)	p-value (Two-Tailed)
Psoriasis Area Severity Index						
Topical + Phototherapy (TP)	15.21 (4.81)	8.01 (5.76)	8 (28.57%)	0.001†	7.20 (6.63) ^a	
Topical + Systemic (TS)	16.79 (5.76)	8.40 (5.47)	5 (17.86%)	0.001†	8.34 (6.52) ^a	0.010†
Topical + Biologics (TB)	23.38 (9.63)	6.21 (7.72)	6 (66.67%)	0.008†	15.59 (9.50) ^b	
Dermatology Life Quality Index						
Topical + Phototherapy (TP)	16.61 (6.18)	9.13 (7.45)	16 (57.14%)	0.001†	7.48 (7.56) ^{ab}	
Topical + Systemic (TS)	14.25 (5.47)	8.29 (5.97)	16 (57.14%)	0.001†	5.96 (6.43) ^a	0.044*
Topical + Biologics (TB)	17.44 (6.37)	4.56 (4.85)	8 (88.89%)	0.001†	12.89 (7.42) ^b	

^aBetween-group comparisons were conducted using One-Way Analysis of Variance (ANOVA) and post-hoc analyses were conducted using Turkey-Kramer Honest Significant Difference (HDS) test. Within-group comparisons were conducted using paired t-test.

^bSignificant improvement on PASI score is at ≥75% change in baseline PASI score; significant improvement on DLQI score ≤5 than baseline DLQI score.

*Significant at 0.05

†Significant at 0.01

The distribution of the different expenses of the participants according to treatment modality is illustrated in Table 3. For patients in the TP group, most did not have diagnostic tests. The most frequently performed test were the complete blood count and liver function tests (ALT and AST) for all treatment groups. In addition, more than two-thirds of the participants in the TB group had chest x-ray, while only 7.14% and 39.29% of those managed with TP and TS groups underwent the same diagnostic procedure, respectively. The mean expenditure of the TP, TS, and TB groups for the different diagnostic and laboratory tests were PHP 1,487.50 (SD=510.63), PHP 2,144.20 (SD=880.61), and PHP 4,104.38 (SD=3,394.40), respectively.

The most commonly prescribed topical medications in patients under the TP treatment

group were halobetasol cream (71.43%), clobetasol ointment (60.71%), and calcipotriol ointment (50.00%). On the other hand, the most commonly utilized topical medications in the TS group were clobetasol ointment (89.29%) and calcipotriol ointment (53.57%). And in the TB group, it was clobetasol ointment and halobetasol cream (66.67%). For topical medications, the mean expenditures were PHP 4,727.71 (SD=2,152.30) for TP, PHP 3,251.02 (SD=2,464.65) for TS, and PHP 2,348.32 (SD=2,039.84) for TB group. (Appendix II)

The mean expenditure of TP for the phototherapy sessions was PHP 8,028.57 (SD=3,672.41), while the TS group, who were all given methotrexate, had an average expenditure of PHP 200.26 (SD=54.37). In the TB group, two kinds of biologics were given, namely ixekizumab and

secukinumab, with a total mean expenditure of PHP 165,525.59 (SD=72,412.90).

In summary, the mean total expenditure of TP was PHP 13,016.99 (SD=3,989.37), TS was PHP 5,317.54 (SD=2,334.54), and TB group was

PHP 171,600.58 (SD=71,933.40). Comparative analyses indicated that the mean total expenditure of the three treatment modalities were significantly different ($p=0.001$). In particular, TB had the highest mean total expenditure, followed by TP, and the last being the TS.

Table3. Distribution of expenditure of respondents according to treatment modality

Medical Expenditures	Treatment Modality (N = 65)		
	Topical + Phototherapy (TP) (n=28)	Topical + Systemic (TS) (n=28)	Topical + Biologics (TB) (n=9)
Diagnostic Test/Laboratory fees*	[n=5] 1,487.50 (510.63)	[n=25] 2,144.20 (880.61)	[n=8] 4,104.38 (3,394.40)
Topical Medications (PHP; $\bar{x}$, SD)	4,727.71 (2,152.30)	3,251.02 (2,464.65)	2,348.32 (2,039.84)
Specific Modalities (PHP; $\bar{x}$, SD)			
Phototherapy	8,028.57 (3,672.41)	—	—
Systemic Medication (<i>methotrexate</i>)	—	200.26 (54.37)	—
Biologics	—	—	165,525.59 (72,412.90)
• Secukinumab (n=7)	—	—	135,090.61 (46,135.60)
• Ixekizumab (n=2)	—	—	272,048
Average Total Expenses (PHP; $\bar{x}$, SD)	13,016.99 (3,983.37)	5,317.75 (2,334.54)	171,600.58 (71,933.40)

*not all patients have undergone diagnostic tests

The association of the PASI and DLQI mean difference scores and the treatment costs according to treatment modality is illustrated in Table 4. The correlation of all PASI mean difference scores (from baseline to endline) with the treatment cost were very weak to weak and were not statistically significant ($p>0.05$), regardless of the treatment modality. Although the r -value for the correlation between PASI and TB treatment is -0.04, the p -value is more than 0.05, indicating that the association is not significant. Likewise, the association of the DLQI mean difference scores and treatment cost ranged from very weak to weak and were all not statistically significant

($p>0.05$) for all treatment modalities. Hence, the increase in total cost does not guarantee an increase in the PASI/DLQI score difference.

Table4. Association of Psoriasis Area Severity and Dermatology Life Quality Indices Scores and Treatment Cost according to Treatment Modality

Association of the Psoriasis Area Severity and Dermatology Life Quality Indices Mean Difference Scores and the Treatment Costs according to Treatment Modality (N = 65)

Treatment Modalities	PASI and Treatment Cost			DLQI and Treatment Cost		
	r-value	p-value (Two-Tailed)	Interpretation ^a	r-value	p-value (Two-Tailed)	Interpretation ^a
Topical + Phototherapy (TP)	0.36	0.060	Weak, Positive Not Significant	0.15	0.445	Very Weak, Positive Not Significant
Topical + Systemic (TS)	0.03	0.869	Very Weak, Positive Not Significant	0.35	0.072	Weak, Positive Not Significant
Topical + Biologics (TB)	-0.04	0.912	Very Weak, Negative Not Significant	0.23	0.550	Weak, Positive Not Significant

^aCorrelation Coefficient (r-value) Interpretation: 0.0 to 0.20 = Very Weak, 0.21 to 0.40 = Weak, 0.41 to 0.60 = Moderate, 0.61 to 0.80 = Strong, 0.81 to 1.00 = Very Strong

^bSignificant at 0.05

^cSignificant at 0.01

Table 5 shows the summary of base-case results of the cost- effectiveness analysis from the societal perspective over a 3-month period. TB modality has the highest percentage of patients in terms of overall effectiveness on both PASI and

DLQI. However, in terms of cos effectiveness, TS was shown to be the most cost-effective for having the lowest cost per PASI-75 and/ or DLQI ≤5, valued at 335.36 Php.

Table5. Base-Case Result of the Cost-Effectiveness

Treatment Modalities	Total Cost	Effectiveness (%) ^a	Cost-effectiveness ^b
Topical + Phototherapy (TP)	12,968.78	60.71 (17/28)	762.87
Topical + Systemic (TS)	5,365.75	57.14 (16/28)	335.36
Topical + Biologics (TB)	171,522.24	100.00 (9/9)	19,058.03

^aEffectiveness (%) = percentage of patients achieved PASI-75 and/or DLQI ≤5.

^bCost-effectiveness = total cost divides by the number of patients achieved PASI-75 and/or DLQI ≤5.

DISCUSSION

This study is the first in the Philippines that aims to estimate the cost of psoriasis treatments and determine which treatment option is the most cost effective. The three treatment options compared are based on the clinical pathway guideline currently followed in the study center. The results of this study indicate that TS is the most cost-effective, despite TB demonstrating the highest result in terms of effectiveness. This is

important because cost-effectiveness analysis determines the most cost-effective method by taking into consideration both cost and efficacy.

In this study, the significant decrease in PASI and DLQI scores compared to baseline showed that all treatment modalities are effective on psoriasis patients with moderate to severe disease. However, the baseline PASI and DLQI scores and the mean score differences of patients

treated with TB are significantly higher compared to TP and TS. The same is observed in a study by Mattei et al., where patients with moderate-to-severe plaque psoriasis receiving biological therapies have considerably high mean PASI and DLQI scores.¹² A higher baseline PASI and DLQI score for biologics treatment means that in this institution, biologics are chosen as treatment for severe psoriasis cases. A literature review by Ruiter et al. showed that in most cases, treatment with biologic is the option given to patients when conventional therapies such as TP and TS fail.¹³ It is also important to note that the effectiveness of treatment as shown by the improvement of PASI and DLQI from baseline for patients receiving TP and TS are comparably not significant from each other.

The same result was observed in a study in Malaysia by Azizam et al. involving 90 patients with moderate to severe psoriasis which showed that systemic treatment is the most cost-effective option among the three modalities.⁹ This finding is also supported by a meta-analysis study by Hankin, et al where the authors concluded that the most cost-effective treatment is methotrexate.¹¹ A study conducted in Germany also recommended methotrexate to be the first line treatment as it is the most cost-effective, followed by biologics.¹⁴ To the knowledge of the authors, there are no other published articles that contradict these findings.

These results build on existing evidence that systemic therapy is the most cost-effective among the treatment options for moderate to severe psoriasis. Although it improved PASI and DLQI scores by half as much as biologics, its price was just 3-4% of the total cost of TB and 40% of the cost of TP. The clinical pathway used at the Rizal Medical Center's Psoriasis Center (Annex I) suggested that for moderate to severe psoriasis,

the patients are advised first to add phototherapy as adjunct to topical medications. It is only in instances when phototherapy treatment is not available, contraindicated, failed or not preferred by the patient, then the next option will be systemic therapy followed lastly by biologics. Given the results of this study, this may help in improving the clinical pathway by determining the appropriate order of treatment options, keeping in mind that we aim for the best treatment outcome with the least possible cost for the patients.

It is important to note that although TB is the highest costing treatment, it has the highest improvement in terms of PASI and DLQI scores. The current challenge is to reduce the cost of biologics and increase the distribution of biologics to people affected with severe psoriasis. This information can clarify how effectively biologic treatments differ from phototherapy and oral systemic medications, to answer patients' concerns about the high expense of biologic therapy.

The reliability of this data is impacted by limitations such as the small sample size and short study period of 3 months. This holds true in evaluating further the relationship of PASI and DLQI to treatment cost particularly in the TB group where a bigger sample size and longer duration of data collection is preferred to generate more precise and more reliable estimates. The study also only determined the direct costs of psoriasis treatment and not included the indirect costs such as transportation cost, food allowance, absenteeism and loss of productivity which is substantial to determine the true cost of psoriasis treatment. Another limitation is the exclusion of the income class and lifestyle of subjects in this study as these also play an important role in optimizing the improvement. Also, there are subjects who might have done their diagnostic tests outside the study center, and therefore did not reflect the actual costs. Although the costs of the topical

medications are standardized according to the Drug Price Reference Index (DPRI) and the local pharmacy, the totaled quantity was based on the prescription given during tele dermatology and fingertip unit (FTU) in the physical charts which may only be an approximate of the actual consumption of the topical medication. The side effects of these treatments are another crucial factor to take into account, as well as the possible inconsistency of the PASI and BSA because of observer variability. Another limitation is patient's compliance to treatment at home especially those in the TS group since it is considerably important and essential and may have hampered in achieving PASI75. Lastly, this study covered only the year 2021, which is included in the COVID-19 pandemic years, when access to health care was greatly affected by various community quarantine implementations.

Further studies are needed to determine both direct and indirect costs to quantify the burden of treatment cost in the health care and societal perspective. A prospective study carried out over a longer period of time (6 months or more) will also provide a more accurate calculation of actual costs, especially for topical medications, and will predict the immediate and long-term consequences of therapy, taking into account not only the side effects but also the quality of life and disease activity.

CONCLUSION

Economic burden is high for psoriasis, it being a chronic disease, which also means dealing with lifelong care and treatment. This study showed that the combination of topical plus systemic treatment is the most cost-effective treatment for moderate to severe psoriasis. Although least cost-effective, biologics demonstrated the highest improvement in PASI and DLQI.

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Health-related Internet Usage in the Service Outpatient Department of De La Salle University Medical Center*

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ABSTRACT

Background: Health related internet usage is common among patients globally. The literature review showed no local study regarding health-related internet usage in the Philippines hence investigation of internet use for medical information in the outpatient department was done

Objective: To describe the health-related internet usage; its prevalence, reasons & experience on use, perceived effects and sources of medical information in the Outpatient Department of a tertiary Hospital.

Method: A single center, observational, cross-sectional study utilizing a modified 33-item self-administered questionnaire about Health-related Internet usage of patients consulting at the service outpatient department of De La Salle University Medical Center, Dasmariñas City, Cavite, Philippines from September-October 2020. 381 eligible participants were included in the study based on the computed sample size. The data were reported as frequencies and percentage distribution.

Results: Majority of the participants belongs to the 26-35 years old group (32.02%) and most were Females (69%). Most used the Internet in general (88%) and Health-related internet usage was high among these users (78.42%). Despite the high internet usage, majority stated that the primary source of medical information was Doctors (76.25%). Commercial websites such as (Google & Yahoo) were the most commonly used during health-related searches (40.49%) and most searches were

about their medical condition (36.22%). Most of the participants stated that sometimes they trust information from the internet (58.63%) and find it useful (68%). Forty five percent stated that medical information obtained from the internet were applied without consulting a doctor and subsequently, many does not disclose this information during medical consultation with a doctor (64%). Participants stated that their primary reason for Health-related internet use was personal knowledge about medical condition (57%). Also, most of the participants believed that Health-related searches do not have an effect on their medical condition (62%) and relationship with their doctor (61%).

Conclusion: The study clearly indicated that Health-related Internet Usage was a common practice in the outpatient department. Although, majority of the patients stated that their Doctors were the primary source of medical information, many individuals still do not divulge medical information obtained from the internet hence physicians should regularly inquire regarding health-related internet usage and educate regarding erroneous online medical information to correct misperception that may affect their health. Lastly, due to the overwhelming use of the internet among patients, health institutions and practitioners may develop mobile friendly applications to render sufficient medical service and provide holistic care to patients especially in this time of pandemic.

Keywords: Health related Internet Usage, Outpatient Department, Patients

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

* 3rd Place, 29th Philippine Medical Association Original Paper Presentation, May 16, 2023

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INTRODUCTION

Access to massive health-related information from online sources result to increase freedom of patient to conduct their own searches concerning their disease management and alternative treatments prior or after medical consultation with a physician (14). Almost 13 million health-related searches conducted daily worldwide in the recent years (2). Despite the seeming value of Internet as source of health information, it is also one of the rich cradles of potentially alarming information about health and illness, and most of which with uncertain validity and this leads to potential increase in doubt and fear about their disease, particularly among anxious patient about their health^[12].

Among the survey findings of social media dashboard "Hootsuite" on its January 2018 report entitled "Digital in 2018", there were almost 67 million internet users in the Philippines and majority is active on social media and there was noted 12% increase in the number of internet users from the previous year. This survey report may indicate a rich front for increased online health seeking behavior especially for patient who are anxious and curious about their condition and turn to online sources for medical information.

The internet is an abundant source of health information for patients attending the primary care^[1,4,6,11,13,15,19,21,22,24] and Emergency room setting^[3]. Most of these online health information seekers are patient who have chronic diseases looking for disease-specific information. ^[2,3,11,12]. However, not only patients for consultations utilize the internet for health information, it was also evident among medical practitioners and students particularly those in the younger age group ^[3,10,13,19,21]. Studies conducted on internet usage among patients usually develop or adopt self-reported survey questions to assess and determine how prevalent online seeking behavior

and the factors associated with its usage ^[2,10,14,15]. Despite the great value of the internet sources for medical information, physician remains the most trusted source of information for patients ^[3,6]. Moreover, several studies done abroad reported high prevalence of health information searches and associated

beneficial and harmful effects on the user^[1,3,11,19,24]. Lastly, there was high internet usage in the local setup, 7 out of 10 Filipinos have used the internet for different purpose according to the latest Health Survey in 2017^[17]. One local study done by Hechanova & Ortega (2014) has concluded that many Filipino had use the internet not for health-related reason but primarily for basic communication. The literature review failed to show evidence of local study regarding health-related internet usage among patient. Hence, exploration of outpatient online usage specifically for health information and adaptation of internet survey questions was done to describe the health-related internet use of patients consulting at the service outpatient of De La Salle University Medical Center, Dasmariñas City, Cavite, Philippines. The study serves as the baseline research on health related internet usage in the Philippines.

GENERAL OBJECTIVE

- To describe the health related internet use of patients consulting at the service outpatient department of De La Salle University Medical Center

SPECIFIC OBJECTIVES

- To determine the prevalence of health-related internet usage among patients consulting at the outpatient department of De La Salle University Medical Center
- To identify the main sources of medical information of patients consulting at the service outpatient of De La Salle University Medical Center

- To determine the reasons and experiences on Health related internet use of patients consulting at the service outpatient department of De La Salle University Medical Center
- To describe the perceived effects of health related internet use of patients consulting at the service outpatient of De La Salle University Medical Center

METHODOLOGY

STUDY DESIGN

A cross sectional study design using a modified self-administered 33-item survey questionnaire adapted from the study of AlGhamdi and Moussa (2012).

STUDY POPULATION

The study included adult patient aged 18-65 years old consulting at the Service Outpatient department of De La Salle University Medical Center (DLSUMC)

INCLUSION CRITERIA

1. Adult male or female patient aged 18-65 years old with acute or chronic disease
2. Patients consulting in the department of Family and Community Medicine, Obstetrics and Gynecology, Surgery, Internal Medicine, Orthopedics, Otorhinolaryngology Head and Neck Surgery and Ophthalmology.

EXCLUSION CRITERIA

1. Patients requiring emergency room management
2. Psychiatric patients
3. Post-stroke patients with inability to write without companion

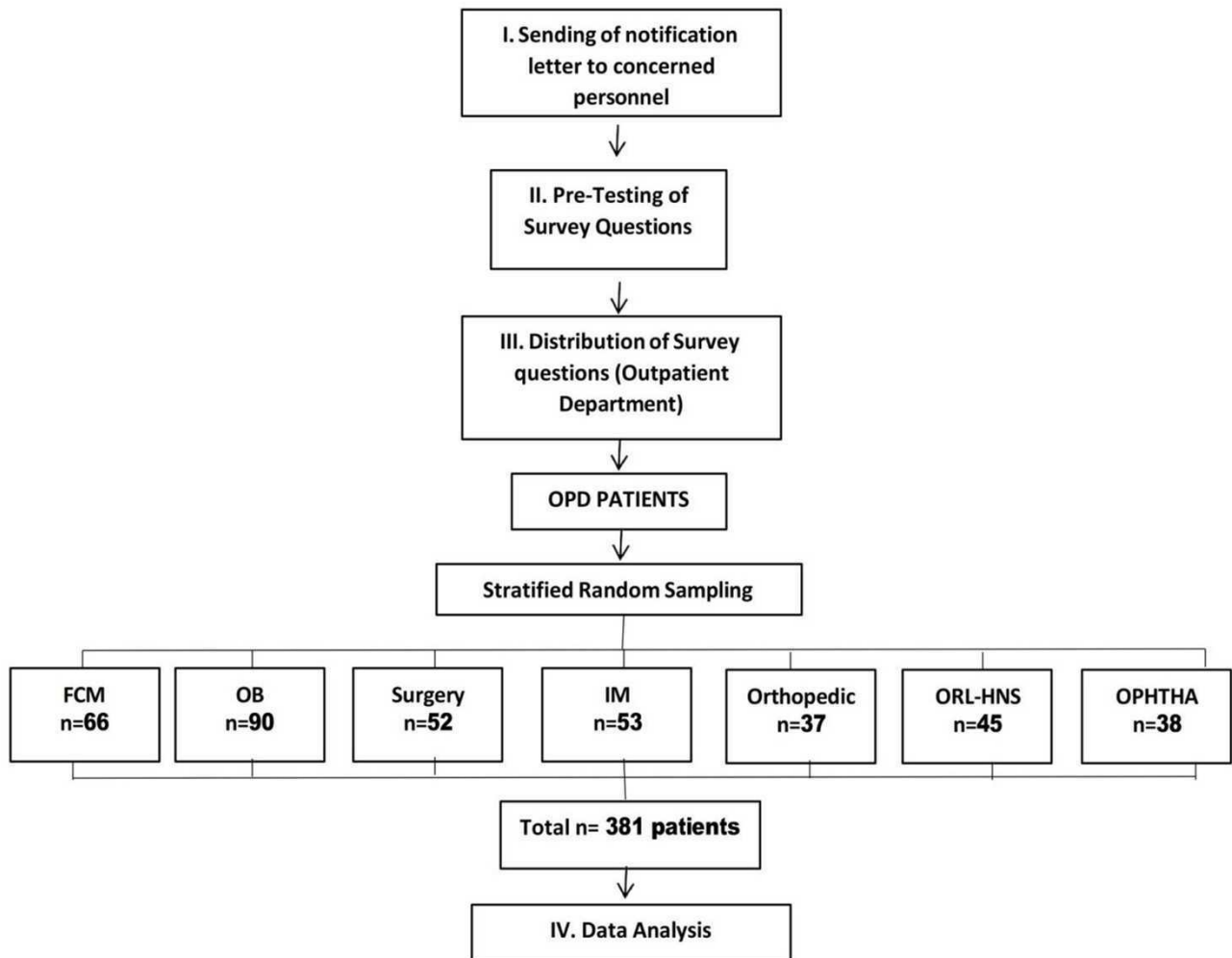
4. Post-operation patients with inability to write without companion
5. Stretcher-borne patients
6. Patients with blindness without companion
7. Pediatric patients

SAMPLE SIZE

The sample size was based on the service outpatient census of the year 2019. A total of 37,634 individual coming from the combined departmental census was used. Since there was no locally available frequency of Health-related internet usage, an estimated frequency of 50% was used at 95% confidence interval, resulting to 381 samples computed from Open Epi Online calculator.

SAMPLING METHOD

The service patient population included only the following departments: 1-Family and Community Medicine, 2-Obstetrics and Gynecology, 3-Surgery, 4-Internal Medicine, 5-Orthopedics, 6-Otorhinolaryngology Head and Neck Surgery, 7-Ophthalmology. Study participants from each department were selected via Stratified random sampling based on the highest monthly census from the previous year (October 2019). The computed samples per department were as follows: Family and Community Medicine=66, Obstetrics and Gynecology=90, Surgery=52, Internal Medicine=53, Orthopedics=37, Otorhinolaryngology Head and Neck Surgery=45, Ophthalmology=38.

DATA COLLECTION PROCESS DIAGRAM

PART I. Notification letters were furnished by the researcher and sent to the medical director and other concerned institutional officers informing them of the study information to be forwarded to the concerned department heads.

PART II. Pre-testing of the questionnaire was done at the service outpatient department of De La Salle University Medical Center. A total of 21 respondents were given the study questionnaire. The 21 respondents were equally distributed among the departments included in the study (3 patients for each department). Each participant was asked to sign an informed consent and given the

questionnaire with the printed instructions of the study. The participants were given 30 minutes to complete the questionnaire and were returned to the researcher or the research assistant. The result of the initial pre testing showed that participants had difficulty in following the instructions on skipping some survey questions (Question 9 and 18 of the survey questions) hence the instructions for skipping were marked and enlarged. Furthermore, the researcher or research assistant reminded the instructions to the participants on the actual data collection.

PART III. The study was conducted at the service outpatient department of De La Salle University Medical Center for 1 month and had been approved by the institutional technical and ethics review board. During the triaging of the patient, each patient was numbered accordingly per department. Participants received a brown envelope labeled with a unique ID number assigned by the researcher per patient containing the questionnaire, informed consent, and printed instructions of the study. Each patient was asked to sign an informed consent prior to inclusion to the study. For patients with writing disability, the companion or caregiver answered in behalf but the researcher and assistant made sure that the answer still came from the patient. The researcher and assistant dispersed the questionnaires among the consenting subjects: Each participant was allowed to answer the questionnaire for 30 minutes and the completed survey questions were collected immediately by the researcher or research assistant. All questionnaires were collected and checked for completeness by the research assistant or researcher. Answered questionnaires were placed in the same envelope and collected upon completion.

DATA COLLECTION TOOL

The survey questions were based on the 41-item internet questionnaire by Alghamdi and Moussa (Appendix H). The said questionnaire was validated in Saudi Arabia and was pilot tested prior to administration to study participants. However, the result of the pilot testing was not provided by the authors.

The research article and internet questionnaire were acquired through the library services of the Romeo P. Ariniego MD library clinical key subscriptions upon the request of the researcher. The said questionnaire was utilized in the outpatient department of a hospital in Saudi Arabia hence some items were not applicable in

the local setting. The researcher modified the questions accordingly: survey items and questions in the said questionnaire were re-arranged and some survey questions were added, altered or deleted based on the suggestions of consultant in the Department of Family and Community Medicine of De La Salle Health Medical and Health Sciences Institute, resulting to a 33-item survey questions. The modified questionnaire (English Version) was then submitted for translation to Tagalog version to the College of Liberal Arts and Communication of De La Salle University-Dasmariñas thru Ms. May L. Mojica, a Filipino academician who had Master of Arts in Filipino and Doctorate degree of Philosophy in Philippine Studies-Language, Culture and Media. The completed Tagalog version (**See Appendix A**) of the modified questionnaire was utilized on the target population at the outpatient department.

The 33-item translated survey questions were subdivided into 6 parts:

1. Demographic Profile
2. Extent of internet Usage
3. Sources of Medical Information
4. Health-related Internet use Experience
5. Reasons for health-related Internet Use
6. Effects of Health-related Internet use

The first part was about the demographic profile or personal information of the respondent such as (1) age, (2) sex, (3) marital status, (4) highest educational level, (5) household average monthly income, (6) occupation, (7) residence, and (8) frequency of visit to the doctor.

The second part was about the respondent's extent of internet use (Questions number 9-16). Included information are the following: (9) usage of the internet (10) usage of email, (11) language/s used during 8 searches, (12) type of internet connection, (13) devices used during internet use,

(14) location of internet use, (15) number of monthly medical websites visited, and lastly (16) frequency of internet use for medical information per month.

The third part (Questions 17-21), included the (17) main sources of medical information, (18) health-related internet usage by the respondent, (19) medical websites used for searches, (20) types of information being search in the internet and (21) criteria for choosing the website or medical information for health-related Internet usage.

The fourth part of the questionnaire was about the internet experience (Questions number 22-25). Included questions were on (22) reliability of online medical information, (23) application of online medical information without consulting a doctor, (24) online purchase of medicines and lastly, (25) procurement of online herbal treatments. Likert scale (Always, Often, Sometimes, Rarely or Never) was utilized to measure each question.

The fifth part (Question 26) asked on what are the reasons for health-related internet use like wanting to learn more about the condition, not getting enough information from the doctor, not convinced by the information given by doctor and lastly other reasons for health-related internet use. At the end of the section (Question 27-33), respondents were asked if internet use to obtain medical information were useful, harmful or neither harmful nor useful (27). Succeeding questions included (28) adequacy of medical information from the internet, internet search before coming to the clinic (29), discussion of information gathered from internet to the doctor (30), effect of discussion of information with doctor on medical condition (31) and relationship with doctor (32). The last question for effect, asked if after consultation, respondent would still search from the internet for medical information (33).

DATA ANALYSIS

All data collected from the questionnaires were encoded using Microsoft Excel. The data collected were reported as frequencies and percentage distribution; nominal data were arranged from the highest to lowest frequency.

BIOETHICAL CONSIDERATION

The research protocol was evaluated by the Institutional and Ethics review board and Data Privacy Office of the De La Salle Medical and Health Science Institute. The study was approved for implementation on September 23, 2020 with Independent Ethics Committee Protocol Tracking No. 2020-070-A. Prior to the implementation of the questionnaire, informed consent (**See Appendix B**) was elicited from all the respondents and confidentiality of test results were protected and preserved in accordance with the Data Privacy Act of 2012.

RESULTS

The study included 381 participants. The sample size was computed based on the Service Outpatient Departmental Census of 2019. Response rate was 100% and all questionnaires distributed were returned.

A. Demographic Profile

Most of the respondents belong to the 26-35 age group (32%), were females (69%), married (49%), high school graduates (32.02%), unemployed (43.31%), no income (58 %), living in urban places (56.69%) and only had visited a doctor once (58.01 %). (**See Table 1.0**)

B. Extent of Internet Use

Majority of the participants used the internet (88.98%). Of the internet users, most have emails (72.30%); utilized English as their main language when browsing (63.44%). Mobile data and mobile phone were the primary form

of internet connection & device used (59.71%, 78.06% respectively) and most used the internet at home (56.83%). Most individual utilized less than 5 websites every month for internet searches (59.71%) and most health-related searches were 1-5 times per month (57.19%). (See Table 2.0)

C. Sources of Medical Information

The primary source of medical information was from Doctors (76.25%) and followed by internet sources (20.31%). Other respondents also mentioned other Medias such as radio and TV programs as source of their medical information (3.44%). (See Figure 1.0)

D. Health-related Internet Usage

Among the internet users, health-related internet use was prevalent (78.42% 266/339). Most of the medical information seekers utilized commercial websites such as Google and Yahoo during their online searches (See Figure 2). Most of the health-related searches focused on respondent's medical condition (36.22%), followed by searching about the medical condition of a family member (35.20%) and lastly on general medical information (28.57%). The criteria used by respondents to evaluate the quality of information from the internet includes: Design of the websites (22.86%), belonging to a medical institution (26.49%), majority (29.61%) stated that they do not trust information unless it comes from a doctor and some considered the internet as a reliable source of medical information (21.03%). (See Table 3.0)

E. Experience on Health-related Internet Use

Most of the participants stated they sometimes trust information from the internet (58.63%) followed by those who always trust the internet for medical information (25.90%).

Many stated they sometimes applied the medical information obtained from the internet without consulting a doctor fewer than those who never applied the information (45.32% vs 34.17%). Lastly, online buying of medications and herbal treatments were not prevalent among the group (0.72%, 1.44% respectively). (See Table 4.0)

F. Motives for Health-related Internet Use

Participants stated that their primary reason for health-related internet use was personal learning about medical condition (57%) followed by lack of information from doctor (26%) and lastly, lack of confidence from doctor's information (15% 40/266). Other reasons (2%) were: "some doctors from public hospitals do not provide adequate answers to queries", "searching for first aid to simple illnesses", "easy access to internet sources", "convenience" and "additional knowledge on a particular disease". (See Figure 3.0)

G. Effect of Health-related Internet Use

Respondents stated that medical information coming from the internet was useful to them (68%) followed by those who think it is neither useful nor harmful (29%). And few seem to think medical information obtained from internet sources were harmful (3%). Regarding the adequacy of Medical information from the internet, many find it partially enough (44%) compared to those otherwise find it is very deficient (38%), and very few find it enough (11%). Before consultation with a doctor, majority did not do health-related searches compared to those who did (52% vs 48%). Ask regarding if they did share the information with the doctor, most responded that they did not disclose it to the health practitioner (64%). Most of the participants also believed that Health-related searches do not have effect on their medical condition (62%) and their

relationship with their doctor (61%). Lastly, asked if after doctor consultation, many participants stated that they would not do Health-related internet searches compared to those who will search for additional medical information (54% vs 46%). (See Table 5.0)

DISCUSSIONS

The study described the health-related internet use of patients in a subset of population attending a private institution particularly patients consulting at the service outpatient department of De La Salle University Medical Center, Cavite, Philippines. The prevalence of Health-related internet usage was high at (78.42%) along with those who have Internet access (88%). The number of Internet users in the outpatient department was higher than the Philippines' Internet Penetration rate (67%) shown by the Digital2020 report done by Simon Kemp but comparable with the Internet usage report shown on the Philippines National Demographic and Health Survey 2017 and by the study of Cooley showing 89% had internet access and searches for health information online. Another comparable study was by Schwartz (2006) reported that majority of their respondents (74%) who had internet access and had used the internet to find health information for themselves or in behalf of a family member focusing on disease-specific information. However, several studies also showed a lower internet usage among patients (1,15,19). The high usage of the internet for health information in the local setting poses a risk for possible proliferation of incorrect medical information by unvalidated online sources.

The high internet usage in study may be attributed to the current pandemic in which many people were advised to stay at home due to lockdown protocols and quarantine measures. This is supported by the study result showing that Internet usage was highest at Home (56.83%). Another reason is that most individual included in

the study belongs to the younger age group of 18-25 & 26-35 years old (23% & 32%), several studies showed that younger age group was associated with higher Health-related searches (1,10,16,17). Among the internet users, Mobile phone and data were also the most commonly used device/mode during online searches (78%). This is lower than the observed mobile internet user's prevalence (97%) in the Digital 2020 report on the Philippines but both significantly showed the importance of this device in accessing the internet for online inquiries in the local setting.

Despite the high internet usage, majority of participants (76%) identified that Doctors were their primary source of medical information as also seen in the other studies on health-related Internet usage (1,3,6,8). Although, the primary reason for health-related search was personal learning about their medical condition (57%). Some identified lack of information and unreliability of information from doctors as their motive for health related internet search (26%, 15% respectively). This may be attributed to limited real-time consultation and increased telemedicine consultation in which there is limited interaction between the patient and physician.

Another finding of the study is that commercial websites with search engines such as Yahoo, Google were the most used during health-related searches. This is similar with the Digital 2020 report on the Philippines which showed that Google.com & Yahoo.com were included among the TOP 5 mostly used website with the highest monthly traffic (Rank 1 for Google and Rank 5 for yahoo). Search engines were also the predominantly used websites during health-related searches in different studies (8,15,19). The study also showed that most of the participants searched about their medical condition (36.22%) followed by searching about the medical condition of a family member (35.20%) and lastly on general

medical information (28.57%). Most of them based their choice of website on whether the information was from a medical institution more than the design of the website. Also most subjects expressed that they do not trust information unless it comes from a doctor and but respondents still trust the internet as source of medical information. Regarding Internet experience, the study showed that half of the respondents sometimes trust (58.63%) and applied the information gathered from online sources without consulting a doctor (45.32%). Online purchases of medications or herbal products were uncommon in the study group. Many study participants viewed that information gathered from the internet regarding health useful (68%) but stated that it's only partially sufficient (44%). Few studies showed the same result, in which participants believed the usefulness of online information^(1,19). And half did not seek Health- related information from the internet prior to their doctor visit (52%). Ask regarding if information obtained was shared to Doctor during consultation, most signified that they do not disclose it to their physician (64%). Hence the belief of the majority of respondents that Health-related searches did not have an effect on their medical condition (62%) or their relationship with their physician (61%). The non-disclosure of medical information coming from the internet to Physician was also fairly common among patients^(4,19). Lastly, regarding Health-related Internet usage, most won't do online searches for medical information after consultation (54%).

LIMITATIONS

Many studies had been done abroad regarding how patients utilized the Internet for medical information or Health-related Internet Usage but this study served as the pioneer study in the Philippines concerning this widely used and growing health seeking behavior among patients. Despite a small sample size compared to other similar studies on health-related internet usage;

this study selected the study participants via stratified sampling method increasing it reliability and representation of the sample population. Although done in a pandemic setting, the researcher was able to complete the distribution of the questionnaire in the outpatient department with strict observance of health protocols.

CONCLUSIONS

The study clearly showed that Health-related Internet Usage was predominantly done in the outpatient department prior to medical consultation. A majority of individual had searched the Internet for medical information citing several reasons which may affect their medical condition and their relationship with their physician. Although, majority of the patients stated that their Doctors were the primary source of medical information. Most of the patients still trust the information coming from Internet sources and find it useful. Moreover, many do not disclose it to their physician. It is recommended that as primary care physician, inquiry regarding the health related internet usage be done on every patient since medical information obtained from the internet can be erroneous which may affect the medical condition of the individual. Also during inquiry, physician can correct misperception and relieve anxiety from online medical information thus strengthening the doctor- patient relationship.

The majority use commercial websites with search engines for obtaining medical information followed by webpages of doctors, medical associations and hospital, and few utilized social networking sites for medical information. And the most common mode of access is via mobile phone using mobile data and usually done at home. Sadly, majority of those doing Health-related searches on the internet, believe that it does not affect their medical condition and their relationship with their doctor. Hence, Health practitioners and institutions can utilize these

websites or design mobile applications to further enhance their medical services through providing easy access to adequate and correct online medical information to patients.

ACKNOWLEDGEMENTS: I thank Dr. Celso Pagatpatan for the support in making this research possible

CONFLICT OF INTERESTS: No relevant disclosures

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Table 1.0 Demographic Profiles of Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=381.

Variables	Frequency	Percentage
1. Age group (in years)		
18-25	89	23.36
26-35	122	32.02
36-45	45	11.81
46-55	80	20.99
56-65	45	11.81
2. Sex		
Male	117	30.71
Female	264	69.29
3. Marital Status		
Married	188	49.35
Single	142	37.27
Divorced	21	5.51
Widowed	15	3.94
Separated	15	3.94
4. Highest Educational Attainment		
Elementary undergraduate	3	0.79
Elementary graduate	13	3.41
High School undergraduate	16	4.19
High School graduate	122	32.02
College undergraduate	89	23.4
College graduate	110	28.87
Vocational Course Graduate	28	7.32
5. Household Average Monthly Income		
No income	219	57.48
Less than 5,000 Pesos	43	11.29
Between 5,000 and 10,000 Pesos	74	19.42
Between 10,000 and 15,000 Pesos	26	6.82
Between 15,000 and 20,000 Pesos	7	1.84
More than 20,000 Pesos	12	3.15
6. Occupation		
Unemployed	165	43.31
Employed	130	34.12
Student	54	14.17
Self-employed	32	8.40
7. Residence		
Urban	216	56.69
Rural	165	43.31
8. Number of Doctor visit		
Once	221	58.01
Two to five times	126	33.07
More than 5 times	34	8.92

Table 2.0 Frequency and Percentage Distribution of the Internet Users, Email Users, Language, Type of Internet Connection, Device, Location, Number of Monthly Website and Number of Monthly Health-related searches among Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=339

Variables	Frequency	Percentage
1. Internet Users	339/381*	88.98
2. Email Users	245	72.30
3. Language Used		
English	215	63.44
Filipino	124	36.56
4. Type of Internet Connection		
Mobile Data	202	59.71
Wireless (Wi-Fi)	96	28.42
DSL	40	11.87
5. Device used during searches		
Mobile Phone	265	78.06
Computer (Laptops/Desktops)	62	18.35
IpAD/Tablets	12	3.60
6. Location of Internet Use		
Home	193	56.83
Mobile phone	93	27.70
Work	49	14.39
Internet café	4	1.08
7. Number of Monthly Websites usage		
None	132	38.85
Less than 5 websites	202	59.71
Five or more websites	5	1.44
8. Number of Monthly Health-related internet searches		
None	116	34.17
Less than 5 times	194	57.19
Between 5 and 20 times	24	7.19
More than 20 times	5	1.45

NOTE: * This is the total participants included in the study, of which 339 were the internet users in the group. Non-internet users were told to skip questions on items 2-8

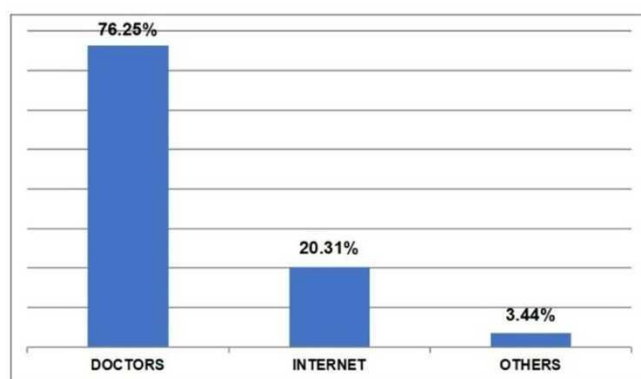
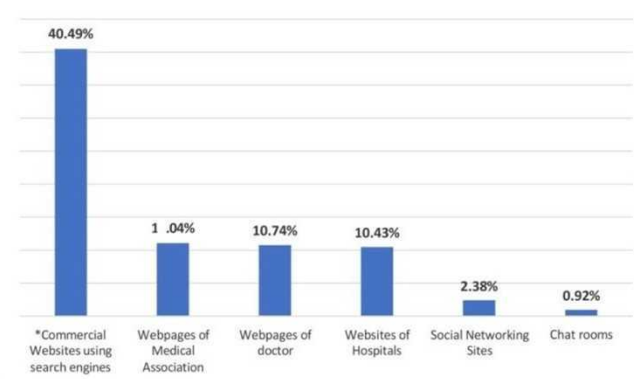


Figure 1.0 Sources of Medical Information among Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=381



* Commercial websites are defined as websites using search engines like Google and Yahoo

Figure 2.0. Type of Websites Used by Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=339

Table 3.0 Frequency and Percentage distribution of the Type & Criteria of Medical Information obtained from the Internet, used by Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=266*

Variables	Frequency	Percentage
1. Type of Information being search		
Medical Condition	96	36.22
Medical Condition of other member of the family	93	35.02
General Medical Information	77	28.76
2. Criteria/Evaluation of Information from the Internet		
Design of website		
I do not trust information unless it was from a doctor	79	29.61
Belonging to a medical Institution	70	26.49
Design of website	61	22.86
I trust any information obtained from the Internet	56	21.03

NOTE: * This is the number of individuals who do Health-related Internet usage among the internet users

Table 4.0 Frequency and Percentage Distribution of Reliability of Medical Information, Application of Medical Information, Online purchase of Medicines & Herbal Treatments by Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=266*

Variables	Frequency N=266	Percentage
1. Trust in the information from the Internet		
Always	69	25.90
Often	13	5.00
Sometimes	156	58.63
Rarely	13	5.00
Never	15	5.47
2. Application of Internet Information without consulting a doctor		
Always	7	2.51
Often	24	9.00
Sometimes	120	45.32
Rarely	24	9.00
Never	91	34.17
3. Buying Medicines online		
Always	2	0.72
Often	2	0.72
Sometimes	7	2.75
Rarely	6	2.25
Never	249	93.56
6. Buying Medicinal Herbal treatments online		
Always	4	1.44
Often	3	1.00
Sometimes	19	7.25
Rarely	2	0.82
Never	238	89.49

NOTE: * This is the number of individuals who do Health-related Internet usage among the internet users

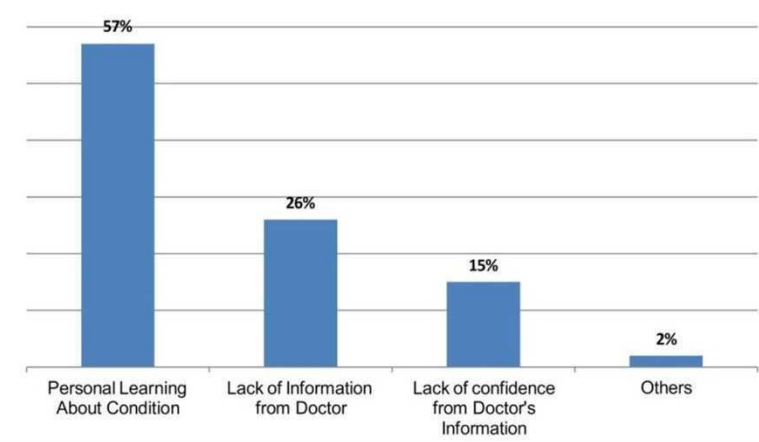


Figure 3.0 Reasons for Health-related Internet Usage of Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=266

Table 5.0 Frequency and Percentage distribution on the Effect of Health-related Internet usage, Adequacy of Medical Information from the internet, Health-related Internet usage before and after Clinic Visit, Sharing of Medical Information to doctor, and effect of Health-related use on Medical Condition and Doctor-Patient relationship among Patients ≥ 18 years old in the Service Outpatient Department of De La Salle University Medical Center, October 2020, n=266*

Variables	Frequency	Percentage
1. Effect of Internet Use on Medical Condition		
Useful	181	68
Harmful	8	3
Neither	77	29
2. Adequacy of Medical information from the internet		
Enough	29	11
Partially Enough	117	44
Deficient	19	7
Very Deficient	101	38
3. Health-related Internet Usage before clinic visit		
No	138	52
Yes	128	48
4. Sharing Medical Information obtained from the internet to Doctor		
No	170	64
Yes	96	36
5. Effect of Health-related internet usage to condition		
No effect	165	62
Positive effect	90	34
Negative effect	11	4
6. Effect of Health-related internet usage to doctor-patient relationship		
No effect	162	61
Positive effect	93	35
Negative effect	11	4
7. Health-related Internet usage after clinic visit		
No	144	54
Yes	122	46

NOTE: * This is the number of individuals who do Health-related Internet usage among the internet users

Effectiveness of Ultraviolet C-Light in Eliminating Microbial Pathogens from Stethoscope used in the Neonatal Intensive Care Unit of East Avenue Medical Center*

Glendie Patricia Bakilan-Gallardo, MD¹; Ma. Theresa Policarpio, MD¹

ABSTRACT

Background: Instruments used to examine infected patients may be contaminated by disease-causing microorganisms during contact. If these instruments are not sterilized properly prior to being used on other patients, pathogen transfer may occur via this route. Stethoscopes are the most commonly used equipment by healthcare providers. Microbes and viruses may be transmitted from one patient to another and from healthcare worker to patient via stethoscope membranes.

Objective: To determine the effectiveness of ultraviolet c-light in eliminating microbial pathogens from stethoscopes used in the Neonatal Intensive Care Unit of East Avenue Medical Center.

Methodology: This is a two-arm, double blind, randomized controlled trial. The minimum sample size computed for this study was 26 stethoscopes. Thirteen (13) stethoscopes each were randomly allocated to Ultraviolet C (Group A) and standard of care (Group B) groups.

Data Analysis: Summary statistics were reported in tables as means, standard deviations, percentages and frequencies min-max for quantitative discrete outcome measures or percentages for qualitative measures.

Results: The predominant microbial pathogens colonized in the stethoscopes were different species of Coagulase Negative Staphylococcus (CoNS) namely: *Staphylococcus Heamolyticus* (34.62%), *Staphylococcus Epidermidis* (26.92%) and *Staphylococcus Hominis* (19.23%). Both UVC light and standard of care were equally effective in decreasing the CFUs on the stethoscopes. There was no significant difference in the post-test colony-forming units (CFUs) between the two groups ($t = -.594, p > .05$).

Conclusion: UVC light sterilization is comparative to the standard of care in eliminating microbial pathogens. It works faster and is more reliable, durable and cost-effective. It is recommended as an alternative method for decontaminating stethoscopes used at the EAMC-NICU due to its numerous advantages.

Keywords: *ultraviolet c light, neonatal intensive care unit, stethoscope*

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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INTRODUCTION

Background of the Study

Special care should be exercised when handling newborn skin since it is the main port of entry for infections. Hand washing is the best way to prevent microbial pathogens from spreading. However, this may not be enough to eradicate microbes that may be spread via medical equipment or devices commonly used by physicians and other healthcare providers.

Instruments used to examine infected patients may be contaminated by disease-causing microorganisms during contact. If these instruments are not meticulously cleaned and sterilized prior to being used on other patients, these pathogens may be transmitted from one patient to another.

Stethoscopes are the most commonly used equipment by healthcare providers. Microbes and viruses may be transmitted from one patient to another and from healthcare worker to patient via stethoscope membranes.¹

Gastmeier et al in 2003 reported that strains of *Klebsiella pneumoniae* were found on the stethoscopes of incubators at a neonatal intensive care unit in Germany. Clinical isolates of this bacteria were found in the blood of two patients.²

Cleaning, disinfection and sterilization are essential in preventing the spread of infections.³ According to Gurevich et al, sterilization is defined as destruction of all microorganisms, endospores and viruses.⁴

Rutala et al concluded that ethanol and isopropyl alcohol, commonly used as disinfectants, are only effective for eradicating vegetative bacteria and viruses but not spores.⁵

Nosocomial infections often result from inadequate or superficial management of cleaning, disinfection and sterilization.⁶ Cross-infections are transmitted from one patient to another through contaminated equipment, instruments and materials and are major causes of nosocomial diseases. Healthcare-associated infections have a huge impact on the patient's condition including prolonged hospital stay, more nursing care and rehabilitation and increased health complications that may ultimately result in death.

Ultraviolet (UV) C light has already been used for stimulation of vitamin D production, for psoriasis treatment and for air, water and environmental sanitation purposes. At its typical wavelength of 200-280 nm, UVC radiation induces pyrimidine dimers in thymine and cytosine, breaking DNA molecules, inactivating germs and preventing growth and reproduction.⁷

The nursing bottle sterilizer has been reported to sterilize and eliminate 99.9% of bacteria on surfaces using UV-C light. The sterilizer measures 325mm x 340mm x 403mm and weighs 5kgs. It has a power consumption of 80W, a voltage of AC 220V/60Hz and UV lamp of 4W. Aside from its UV Sterilizing properties, it also has heater a fan which dries the items inside the portable device. It can sterilize, dry, and store items such as baby bottles, bottle nipples, pacifiers, breast pump parts, utensils, plates and teething toys. It can also sterilize mobile phones, remote controls, stuffed toys and accessories. This device is relatively safe since it is enclosed by a tinted glass and vessel, preventing the UVC light from penetrating the eyes. KCL Korea Conformity Laboratories has validated the sterilizer's ability to eliminate harmful bacteria including *Escherichia Coli*, *Staphylococcus Aureus*, *Salmonella Typhimurium* and *Pseudomonas Aeruginosa*.

In this study, the device will be used as an alternative to sterilize stethoscopes used at the Neonatal Intensive Care Unit of the East Avenue Medical Center.

Significance of the Study

Elimination of microbial pathogen spread in Neonatal Intensive Care Units is crucial in the successful management of newborns. Hence, additional means to prevent infection should be investigated.

The UVC light sterilizer may be a user-friendly and cost-effective way of disinfection that can help in preventing nosocomial infections which lead to longer hospital stays and cause greater economic burden to the patients' families.

The data gathered from this study may help supplement current literature on the use of UVC light sterilizers to eliminate pathogens on stethoscopes and other medical equipment or devices. Based on the results of the study, recommendations on the use of this sterilizer in the EAMC-NICU may also be made.

Review of Related Literature

The negative impact of nosocomial infections including damage to patient health, clinical complications, mortality and prolonged hospital stay leading to extended care and increased costs has been widely documented in literature.⁸

Health care-associated infections (HAI) are a significant public health problem worldwide,^{9,10} with significant negative consequences, including impairment of patient's health, mortality and longer hospitalization, with the need for longer treatment and the associated higher costs.^{11,12} The main vehicle for microbe transmission are the hands of health care professionals,^{11,13} but contaminated medical devices such as stethoscopes, otoscopes and thermometers may also transmit microorganisms to patients.^{9,10,14} In

particular, stethoscopes, probably the most widely used medical device, may cause cross-contamination if not disinfected properly.^{15,16}

All objects that come into contact with and are shared between personnel and patients are possible carriers of microorganisms. Lee et al in 2012 reported that the hands of health care personnel are the main vehicles of transmission of microbes and viruses.¹⁴

In addition, although the importance of careful disinfection of these tools has been repeatedly suggested,^{11,15,17,18} their disinfection is not yet common practice. The US Centres for Disease Control and Prevention (CDC) published medical equipment disinfection guidelines to minimize the risk of cross-infections. These guidelines follow the Spaulding classification, categorizing medical devices for the type of contact for which are used (critical, semi-critical, non-critical items). Stethoscopes belong to the non-critical contact category and it is recommended that these be disinfected for "each patient or once daily or once weekly".⁵

The role of the stethoscope in spreading bacteria cannot be overemphasized. Hence, cleaning of stethoscopes between patients is recommended to avoid increasing contamination.²⁰

Longtin Y et al in 2014 documented that the substantial bacterial contamination level on stethoscopes is similar to that on physicians' hands, which are a major source of nosocomial infections.²¹

Following contact with infected skin, pathogens can attach and grow on the diaphragms of stethoscopes. Without proper disinfection, these pathogens may be transmitted to other patients.²² The diaphragm and bell of stethoscopes are colonized with micro-organisms around 87.3% of the time. It has been reported that

14% of stethoscopes carry MRSA while 16.5% carry gram-negative species.²³

The World Health Organization (WHO) has defined Health-Care Associated Infections (HCAIs) as infections that patients acquire while receiving treatment for medical or surgical conditions and are the most frequent adverse events during care delivery.²⁴ Despite the difficulty in establishing a direct association between stethoscope contamination and HCAIs, microbial contamination of stethoscopes has been demonstrated and this may contribute to the spread of pathogens involved in HCAIs.²⁵

The results of the study of Parmaretal in 2004 showed that 66% ethyl alcohol was an effective disinfectant for each of the 100 stethoscopes used in their study. Four samples were taken: One before cleaning (Group A), one immediately after cleaning (Group B), one after five days without cleaning (Group C), and one five days after cleaning once a day (Group D). Ninety percent (90%) of the stethoscopes in Group A were contaminated. A significant reduction in the contamination rate of stethoscopes was noted in Group B (28%) and in Group D (25%). In Group C, the rate of contamination was 95%. No statistically significant differences were found between Groups A and C.²⁶

Datta et al in 2018 documented that Isopropyl Alcohol (IPA) was significantly effective as a disinfectant. A total of 100 stethoscope diaphragms were analyzed before and after cleaning with IPA. Fifty-six membranes were noted to be colonized before disinfection. After disinfection, there were only five colonized membranes ($p < 0.001$).²⁷

In addition, Raghubanshi et al in 2017 reported that both 90% ethanol and IPA are equally effective in decontaminating diaphragm of the stethoscopes.¹⁸

In another study by Gurevich et al in 1996, it was documented that wiping the head of a stethoscope with a 70% alcohol pledget or wiping it with the antiseptic used for hand hygiene or a hospital surface disinfectant greatly reduced disease and usually eliminated the bioburden of aerobic bacterial contamination. However, not all microbial pathogens are removed by this method. Alcohol-based hand rubs that have been used for hygienic hand disinfection in hospitals are not enough to kill microbial DNA especially microbes which are resistant to the bactericidal effect of the alcohol.²⁸

The use of an Ethanol-Based Hand Sanitizer (EBHS) (gel or foam) was also reported to be effective for disinfection.²⁹⁻³¹

In a study conducted by Grandiere-Perez et al in 2015 it was noted that prior to disinfection, 38 out of 40 stethoscopes examined were culture positive with a mean of 29.9 CFU per culture plate. After disinfection, the mean was 1.1 CFU $p < 0.001$.²⁹

Similarly, Schroeder et al in 2009 found a mean of 28.4 CFU (95% CI, 20.2–36.6), in the pre-wash sample, and a mean of 3.2 (95% CI, 1.8–4.6; $p < 0.001$) in the post-wash sample.³¹

The use of disinfectant wipes is a practical and fast method for disinfecting stethoscopes and other authors have also evaluated the effectiveness of this method.^{30,32,33}

Leprat et al in 1998 demonstrated the effectiveness of wipes with benzalkonium against *coagulase-negative staphylococci* (CNS), CNS resistant to methicillin (MR-CNS) and *methicillin-susceptible Staphylococcus aureus* (MSSA). After cleaning, all contaminated stethoscopes showed no bacterial growth. However, in developing countries, they are not easily available because of their cost.³³

Ultraviolet (UV) C radiation denatures the DNA of microorganisms which have a high absorbance of the UV spectrum at 254 nm via formation of pyrimidine dimers. The bacteria are inactivated through DNA replication blockage.³⁴

Several previous studies have demonstrated that the use of UVC on a wheeled device to disinfect hospital rooms and environments is plausible, fast, and practicable. Nerandzic et al in 2012 tested portable units emitting UVC for disinfection of the environment.³⁵

The results of the study of Leontsini et al in 2012 showed the contamination of the stethoscopes with different species of *coagulase negative Staphylococcus* (CoNS) with high antibiotic resistance and possess the potential risk of causing hospital infections.³⁶

Earpieces of stethoscopes are also frequently colonized with microorganisms either by the hands of the users or by the users' ear canals.³⁷ The use of Ultraviolet C light (UVC) emitted by Light Emitting Diodes (LEDs) has been proposed and investigated as a method for disinfecting the stethoscope membrane.³⁸

In a 2015 study by Messina et al, a prototype UVC light was configured as a simple circular cover for application to stethoscope head. The size of the cover was obtained by analyzing the classical dimensions of stethoscope membranes and the design was created using Sketchup 3D modeling software and a 3D printer. A significant reduction in CFU counts after Ultraviolet C-light treatment ($P < .01$) was found for all bacteria: *E. faecalis* (85.5%), *S. aureus* (87.5%), *E. coli* (94.3%) and *P. aeruginosa* (74.9%). The results showed that the treatment technique was effective and efficient in disinfecting the membranes.³⁸

In another study in 2016, Messina et al conducted a pre- and post-intervention study to verify the effectiveness and reliability of UVC LEDs in stethoscope membrane disinfection after prolonged use. UVC LEDs demonstrated the capacity to maintain high levels of disinfection after more than 240 hours of use and they were effective against common microorganisms that are causative agents of HCAs including *S. aureus* and *E. coli*. Statistically significant differences ($p < 0.001$) were also found relating to the reduction of specific bacteria (no CFUs observed for *S. aureus* and *E. coli*). The authors concluded that after prolonged use of the UVC light, it was still effective in reducing microbial contamination.³⁹

Several things need to be considered when comparing disinfection of stethoscopes using alcohol versus UVC light. The UVC sterilizer, though obviously more expensive, is durable and more cost effective since there is no need for other materials such as alcohol and cotton balls.

OBJECTIVES of the STUDY

General Objective

To determine the effectiveness of ultraviolet c-light in eliminating microbial pathogens from stethoscopes used in the Neonatal Intensive Care Unit of East Avenue Medical Center

Specific Objectives

1. To determine the prevalence of identified microbial pathogens colonizing the stethoscopes before exposure to UVC light and standard of care
2. To determine the quantity of growth (in Colony Forming Units/CFUs) present in the stethoscopes used at NICU-EAMC before exposure to UVC light and standard of care
3. To determine the effect of UV-C light and standard of care in reducing isolated pathogens in stethoscopes used at NICU-EAMC

4. To compare the effectiveness of UVC light and the standard of care in eliminating microbial pathogens from stethoscopes used in the NICU-EAMC

OPERATIONAL DEFINITION OF TERMS AND VARIABLES

Stethoscope– medical device that is used in the NICU section for auscultation of admitted patients

Colony-forming unit (CFU)–used to estimate the number of bacterial growth in the study

Pre-test – before exposure to the different interventions

Post-test – after exposure to the different interventions

UVC light (ECOMOM) – A UV lamp (253.7nm) incorporated in the nursing bottle sterilizer portable machine that is operated by touch icon in the operating panel. It is operated by tapping the icon in the operation panel. It features a touch type button, which is simple and convenient to use. It also releases anion which is excellent for removing contaminated substances, dirt and odors to every corner inside the stored item which is not sterilized by UV. Moreover; it has a PTC fan drying method heater that efficiently dries the remaining humidity and moisture in the item thereby combating the reproducing power of virus in humid condition. The device has a surface of high-class stainless steel inner reflection plate that can refract UV rays to reach all corners, which increases sterilization efficiency.

Propan-2-ol, Propan-1-ol, MectroniumEthylsulfate (STERILIUM) – A classic alcohol-based hand disinfection which is used in the NICU Section as standard of care for disinfecting functional stethoscopes

METHODOLOGY

Research Design

This is a two-arm, double blind, randomized controlled trial.

Sample Size Computation

The minimum sample size computed for this study is 26 stethoscopes with culture growth based on a 95% of detecting at 1% level of significance, a decrease in the average number of colony forming units from 35 in the control group to 2 in the experimental group according to the study of Mesina et al in 2015. Thirteen (13) stethoscopes each were randomly allocated to Ultraviolet C (Group A) and standard of care (Group B) groups.

The sample size was determined based on the average of the total number of functional stethoscopes for the past two years (2020 – 2021) with $n = 52$, 95% confidence interval and 90% response rate distribution among the participants in either Group A or B.

Statistical Analysis

Valid data from evaluable subjects were included in the analysis. Missing values were accounted for during the statistical analysis of outcome variables. Summary statistics were reported in tables as means, standard deviations, percentages, and frequencies min-max for quantitative discrete outcome measures (e.g. number of colony forming units) or % for qualitative measures (e.g. reduction in CFU count). Dependent and independent sample t-tests were used to compare CFU counts before and after the intervention to determine significant differences in CFU count reduction across the two intervention groups and to compare the reduction in CFU count between each active intervention group and control group. Statistical significance was based on a $p\text{-value} \leq 0.05$. Data processing and statistical

analyses were performed using the Statistical Package for Social Sciences (SPSS) version 28.

Description of the Study Procedure

Specific Methods and Techniques

Functional stethoscopes dedicated to patients at the NICU were numbered and collected individually with the use of sterile gloves to avoid contamination by the assistant investigator and were transferred to the isolated research study site. The assistant investigator then collected samples from the diaphragm of the stethoscopes in a circular motion, centrifugally, for about 10-15 minutes, using a sterile cotton tip swab. Each swab was placed inside a tube with brain heart infusion broth as culture media. The dates and times of specimen collection were recorded during the swabbing phase.

The samples were transported to the Microbiology section of the EAMC Laboratory in not more than 30 minutes after swabbing. Collected samples were incubated at 37 degrees Celsius for 24 hours after which the culture reading was done by a medical technologist who determined the presence of bacterial growth in the sample. Two samples with no growth were excluded from the study. Twenty six (26) sample cultures were positive for bacterial growth and were randomly grouped by the assistant investigator to Group A (UVC) and Group B (standard care with Propan-2-ol, Propan-1-ol, MecetroniumEthylsulfate) through drawing of lots.

GROUP A: Exposed to UVC light for 15 minutes (as per manufacturer's recommendation)

- a. The 15-minute sterilization process began with the activation of the sterilization button.
- b. The built-in timer displayed the remaining time for the sterilization process.

- c. An alarm sounded to signal the end of the sterilization process after which the device automatically turned off.

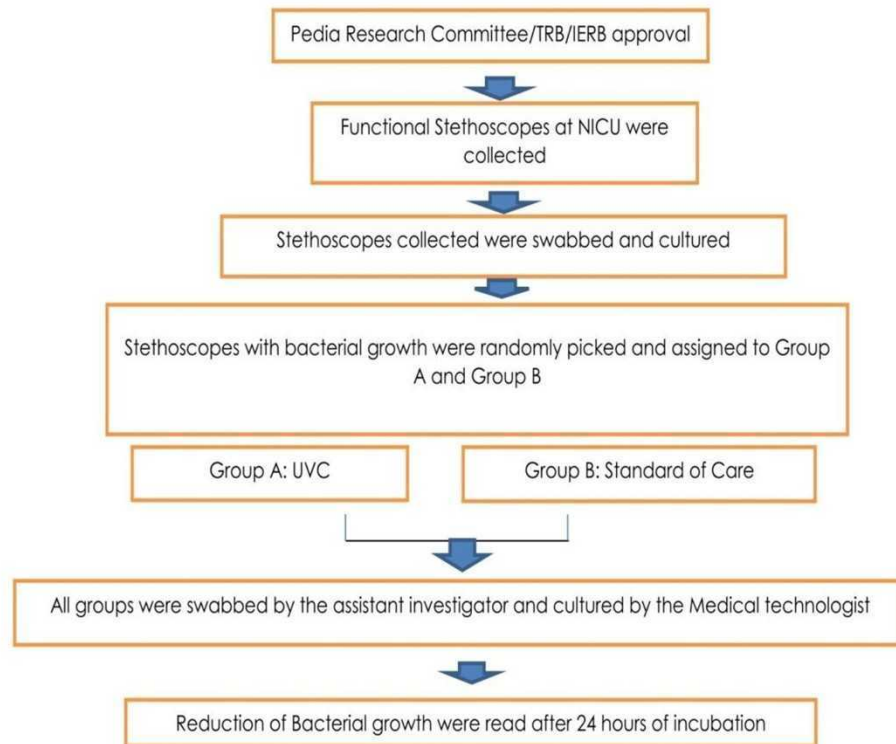
GROUP B: Disinfection with Propan-2-ol, Propan-1-ol, MecetroniumEthylsulfate

The assistant investigator disinfected each stethoscope belonging to this group for about 45 to 60 seconds using the standard of care used by the NICU staff.

After each disinfection, all stethoscopes from Group A and B were cultured by the same medical technologist in a manner similar to the process previously mentioned. The Medical Technologist was blinded with regard to the particular disinfection process used. The samples were all incubated at 37 °C and read after 24 hours. It was concluded that the specific intervention was not effective for those samples noted to have bacterial growth after the incubation period.

In order to prevent contamination of the samples, an isolated area in the NICU served as the location for sampling collection. All samples were kept at the EAMC-Laboratory Department following standard protocols.

Study Algorithm



Inclusion Criteria

Only functional stethoscopes with culture growth were included in the study.

Exclusion Criteria

Stethoscopes with no documented growth in the first culture were excluded from the study.

RESULTS

The frequency percentages of microbial pathogens were examined before exposure to UVC (Group 1) and the standard of care (Group 2).

Table 1 shows the frequency count of microbial pathogens presented in the study before exposure to the different interventions.

Table 1. Frequency Percentages of Microbial Pathogens

Microbial Pathogen	Group 1	%	Group 2	%	Total	%
<i>Pseudomonas aeruginosa</i>	0	0.00	1	7.69	1	3.85%
<i>Escherichia coli</i>	1	7.69	0	0.00	1	3.85%
<i>Klebsiella pneumoniae</i>	2	15.38	0	0.00	2	7.69%
<i>Staphylococcus epidermidis</i>	3	23.08	4	30.77	7	26.92%
<i>Staphylococcus haemolyticus</i>	5	38.46	4	30.77	9	34.62%
<i>Staphylococcus hominis</i>	2	15.38	3	23.08	5	19.23%
<i>Staphylococcus lentus</i>	0	0.00	1	7.69	1	3.85%
N	13	100.00	13	100.00	26	100.00%

In Group 1, the most frequent pathogens colonized were *Staphylococcus haemolyticus* (38.46%), *Staphylococcus epidermidis* (23.08%), *Staphylococcus hominis* and *Klebsiella Pneumoniae* (15.38%). In Group 2, the prevalent pathogens were *Staphylococcus haemolyticus* and *Staphylococcus Epidermidis* (30.77%) and

Staphylococcus hominis (23.08%). The microbial pathogens predominantly found on the stethoscopes included in the study were *Staphylococcus haemolyticus* (34.62%), *Staphyloccocus epidermidis* (26.92%) and *Staphylococcus hominis* (19.23%).

Table 2. Colony-forming Units before and after the different interventions
(Group 1: UVC exposed; Group 2: Standard of care)

Groups		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Steth Pre Group 1	89230.77	13	7595.54	2106.625
	Steth Post Group 1	5384.62	13	19414.50	5384.615
Pair 2	Steth Pre Group 2	76538.46	13	21926.45	6081.303
	Steth Post Group 2	10769.23	13	26287.36	7290.804

Table 2 shows the colony-forming units before and after the interventions. For Group 1 (UVC exposed), the CFU mean scale score was 89,230.77 (SD= 7,595.54) before the exposure to UVC light. After exposure to UVC light, CFU mean scale score of Group 1 decreased from 89230.77 to 5384.62. However, the CFU mean scale score of the group after exposure to UV light intervention became heterogeneous. This means that the intervention varied greatly within the group and the decrease in CFU was arbitrary.

Meanwhile, Group 2 (standard of care) had a CFU mean scale score of 76,538.46 (SD= 21,926.45) before the intervention. After exposure to the standard of care, the CFU mean scale score decreased to 10,769.23 (SD= 26,287.36). The CFU mean scale score of the group after their exposure to the standard of care became heterogeneous. This means that the intervention varied greatly within the group and the decrease in CFU was also arbitrary. Arbitrary means that interventions rely heavily on the type of microbial pathogens and/or CFU level of the stethoscopes before intervention.

Table 3. Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	StethPreGroup 1 - StethPostGroup 1	83846.154	20631.069	5722.029	71378.923	96313.384	14.653	12	.000
Pair 2	StethPreGroup 2 - StethPostGroup 2	65769.231	33030.677	9161.062	45808.992	85729.469	7.179	12	.000

Aside from observing the decrease in CFU mean scale scores to determine the effectiveness of UVC light and standard of care interventions in decreasing the CFUs of microbial pathogens of selected stethoscopes under investigation, the CFUs of groups 1 and 2 before and after intervention were analyzed.

The results of the paired sample t-tests of groups 1 and 2 before and after the intervention are presented in **Table 3**.

Pre-test and Post-test Comparison of Group 1. Using the dependent sample t-test, the pre-test and post-test CFUs of Group 1 were compared. There was a significant difference between the pre-test and post-test CFUs of Group 1 stethoscopes ($t = 14.653$ $p < .05$). This means that UVC light was effective in decreasing the CFUs of

microbial pathogens present in the stethoscopes under investigation.

Pre-test and Post-test Comparison of Group 2. Using the dependent sample t-test, the pre- and post-test CFUs of the samples in Group 2 were compared. There was a significant difference between the pre- and post-test CFUs of Group 2 stethoscopes ($t = 7.179$, $p < .05$). This means that standard of care was effective in decreasing CFUs of microbial pathogens present in the stethoscopes under investigation.

Both the UVC light and standard care interventions were proven to be effective in addressing the microbial pathogens of stethoscopes used in the study regardless of the CFU percentages or levels.

Table 4. Group Statistics

	Exposure	N	Mean	Std. Deviation	Std. Error Mean
Steth Pretest	1.00	13	89230.77	7595.545	2106.625
	2.00	13	76538.46	21926.450	6081.303
Steth Posttest	1.00	13	5384.62	19414.507	5384.615
	2.00	13	10769.23	26287.367	7290.804

To evaluate whether UVC light and/or standard of care of intervention was more effective in decreasing the CFUs of microbial pathogens among the stethoscopes under investigation, an independent sample t-test was performed.

Table 4 shows the summary of the group statistics of the pre- and post-test results of both the UVC light and standard of care groups. Number 1 represents the UVC light exposed group while number 2 represents the standard of care group. The pre-test CFU mean scale score of the UVC light group (mean = 89,230.77, standard deviation = 7,595.54) was much higher than the standard care group (mean = 76,538.46, SD = 21,926.45). On the

other hand, the post-test of the UVC light group was much lower (mean = 5,384, SD = 19,414.50) than the standard of care group (mean = 10,769.23, SD = 26,287.36). Based on the mean CFU mean scale score alone, the UVC light was more effective in decreasing the microbial pathogens among the selected stethoscopes under investigation compared to the standard of care intervention.

Table 5. Independent Samples

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	T	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
StethPretest	Equal variances assumed	.990	.330	1.972	24	.060	12692.308	6435.846	-590.626	25975.242
	Equal variances not assumed			1.972	14.839	.068	12692.308	6435.846	-1038.339	26422.954
StethPosttest	Equal variances assumed	1.484	.235	-.594	24	.558	-5384.615	9063.658	-24091.087	13321.856
	Equal variances not assumed			-.594	22.089	.558	-5384.615	9063.658	-24177.094	13407.863

To validate the statistical differences between the pre- and post-test CFUs of the two groups, an independent sample t-test was performed.

Table 5 shows the summary of the results of the independent sample t-tests. The equal variances assumed were used to determine the significant differences since the Levene's test for equality of variances showed no significant differences between the pre- and post-test CFUs of both the UV light ($F = .990, p > .05$) and standard of care ($F = .235, p > .05$) groups.

Before Intervention (Groups 1 and 2) There was no significant difference in the pre-test CFUs of both Group 1 and Group 2 stethoscopes ($t = 1.972, p > .05$). This means that the pre-test CFU scores of both groups were comparable before their respective interventions.

After Intervention (Groups 1 and 2) There was no significant difference in the post-test CFUs of Group 1 and Group 2 stethoscopes ($t = -.594, p > .05$). This means that the changes in the post-test CFU scores and/or microbial pathogens of the stethoscopes under investigation among the two groups were comparable.

Both the UVC light and standard of care interventions were effective in preventing the proliferation of microbial pathogens present on the stethoscopes as evidenced by the decreasing the CFUs on the stethoscopes. There was no significant difference in the post-test CFUs of the stethoscopes in the UVC light or standard of care groups.

DISCUSSION

In the present study, it was shown that there was no significant difference in the pre-test CFUs of both the UVC and standard of care groups ($t = 1.972, p > .05$). For that reason, the baseline CFUs of both groups were statistically equivalent or comparable to each other before exposure to UVC light or standard of care. Specifically in both groups, the predominant microbial pathogens colonized in the stethoscopes at NICU-EAMC were

different species of Coagulase Negative Staphylococcus (CoNS) namely: *Staphylococcus Hemolyticus* (34.62%), *Staphylococcus Epidermidis* (26.92%) and *Staphylococcus Hominis* (19.23%). As documented by previous studies, stethoscopes are a major source of nosocomial infections in the NICU.²² The diaphragm and bell of stethoscopes are colonized by microorganisms 87.3% of the time, 16.5% of which are gram-negative species.²⁴

Leontsini et al reported in 2012 that the contamination of the stethoscopes with different species of *Coagulase Negative Staphylococcus* (CoNS) had high antibiotic resistance and had the potential risk of causing hospital infections.³⁷

Stethoscopes have been recognized as important modes of bacterial transmission among patients. Strategies for the sterilization of stethoscopes such as the CDC recommendation of disinfection for each patient, once daily or once weekly should be employed in order to prevent hospital infections.^{20,21}

The present study demonstrated that there was a significant difference between the pre- and post-test CFUs of the Standard of Care stethoscope group ($t = 7.179$, $p < .05$). There was also a significant difference between the pre- and post-test CFUs of the UVC stethoscope group ($t = 14.653$, $p < .05$). Thus, UV light and standard of care were shown to be both effective in decreasing the CFUs of the stethoscopes. Furthermore, a comparison of the post-test CFUs in the UVC and standard of care stethoscope groups showed that there was no significant difference ($t = -.594$, $p > .05$). Based on the results of the study, it can be concluded that UVC light is as effective as the standard of care in decreasing CFUs of stethoscopes. Hence, UVC light may be an alternative method for decontaminating stethoscopes especially since 70% alcohol or

alcohol-based products are not enough to eliminate all microbial pathogens.

Various studies have supported the fact that the UVC technique is an effective and efficient way of disinfecting stethoscope membranes via DNA denaturation of the microorganisms.³⁵

Similarly, Messina et al also reported a significant reduction in CFU counts for all bacteria (85.5% *E. faecalis*, 87.5% *S. aureus*, 94.3% *E. coli*, and 74.9% for *P.aeruginosa* after UVC light treatment ($P < .01$). The treatment technique was effective in disinfecting the membranes of stethoscopes.⁴⁰

There are several advantages of UVC over alcohol-based disinfection. UVC is plausible, fast and practicable. Nerandzic et al in their 2012 study reported that portable units could emit UVC for disinfection of the entire environment.³⁶ Likewise, Messina et al documented that UVC LED eliminated *S. aureus* and *E. coli* growths on stethoscopes and could maintain high levels of disinfection after more than 240 hours of use. UVC light was found to be effective in reducing microbial contamination even after prolonged use.⁴⁰

UVC light sterilizer may seem to be a more expensive tool compared to isopropyl alcohol disinfection. However, it may actually be more cost-effective in the long run. UVC has longer durability and requires less consumables (e.g. alcohol and cotton balls). Moreover, UVC is effective against common microorganisms that are causative agents of HCAs. Hence, UVC light is an effective and reliable method for disinfecting stethoscope membranes.

CONCLUSION

Proper disinfection of stethoscopes after each use may help in reducing cross-contamination and subsequently, decrease the likelihood of healthcare associated infections.

UVC light sterilization is comparative to the standard of care in eliminating microbial pathogens. It works faster and is more reliable, durable and cost-effective. It is recommended as an alternative method for decontaminating stethoscopes used at the EAMC-NICU due to its numerous advantages.

LIMITATIONS OF THE STUDY

The study involved only a small sample size of stethoscopes used at the Neonatal Intensive Care Unit and did not include other areas in the hospital. In addition, the culture method used was limited to bacterial pathogens. Hence, the effectiveness of UVC light against viral or fungal pathogens was not evaluated. Lastly, the microbial pathogens present in each stethoscope was heterogenous, indicating that the intervention varied greatly within each group.

RECOMMENDATIONS

A larger sample size and inclusion of stethoscopes used in other areas of the hospital as well as other medical equipment utilized are recommended in order to more accurately establish the effectiveness of UVC light in a tertiary government hospital setting and to improve infection control measures.

The use of homologous pathogens and various culture media to include detection of viral and fungal pathogens is also recommended.

A follow-up study that would compare the three methods (UVC light alone, UVC light plus standard of care and standard of care alone) may also help in guiding health care professionals in choosing the most effective method of sterilization.

Strict adherence to existing standard disinfection protocols is vital to decrease the spread of nosocomial infections. Routine surveillance, frequent supervision and regular

training of personnel with regard to infection control measures should be implemented to ensure the sterility of equipment used in the NICU.

ETHICAL CONSIDERATIONS

Approval from the EAMC-IERB was sought prior to the conduct of the study. The research was done according to the principles of good clinical practice.

The data gathered may be presented in local and international conferences and the manuscript may be submitted for future publication.

The authors declare no conflicts of interest.

No funding was received for this study. The principal investigator shouldered all study-related expenses. However, the EAMC-Laboratory, through the PETRO office granted a 50% discount on the price of the cultures requested. In addition, the UVC sterilizer was donated by the company (Ecomom) to the Department of Pediatrics during the time of the pandemic when this study was conducted. No other support was received from the donors of the UVC sterilizer.

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The Prevalence of Toddlers at Risk for Developmental Delay during the Covid-19 Pandemic in the National Capital Region, Philippines: A Single Tertiary Hospital Study

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ABSTRACT

Background. With the COVID-19 lockdown restrictions, toddlers had significantly reduced environmental stimulus, leading to missed opportunities for learning and play, evidenced by declining developmental assessment scores.

Objectives. This was the first study in the Philippines to describe the prevalence of toddlers at risk for developmental delay during the COVID-19 pandemic. Using the Early Childhood Care and Development (ECCD) Checklist, factors correlated with increased risk of developmental delay were identified.

Methods. A descriptive cross sectional study was done among toddlers aged 12 to 36 months. The ECCD Checklist was administered to determine the children's risk of developmental delay. Chi-square and Multiple Logistic Regression were used to identify factors correlated with risk of developmental delay.

Results. 145 toddlers ($\mu=25.28\pm7.078$ months) were included in the study, and among which, 25.5% ($n=145$) were noted to be at risk for delays in one or more developmental domains, with prevalence

odds increased by two-fold among those with daily screen time of an hour or longer ($p=0.033$, $OR=3.055$). It was also found that 73.1% ($n=145$) of toddlers had daily screen time of an hour or longer, contrary to AAP recommendations.

Conclusion. During the COVID-19 pandemic, more toddlers were found to be at risk for developmental delay, with prevalence odds increased with longer screen time. Findings may guide educational sectors in formulating interventions to prevent developmental delays as the country moves through the new normal.

Keywords: *development, school, Filipino, toddlers, COVID-19 pandemic*

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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INTRODUCTION

Development during the first three years of life is crucial as synapses are formed at a faster rate during these years, allowing the brain to be especially responsive to external input. This provides for a more efficient way for the child to achieve optimal development cognitively, physically and socially.¹ Also, development during early childhood has been established to be predictive of further development of more complex skills later in childhood.²

With the start of the COVID-19 pandemic, lockdowns and quarantine restrictions were put in place, limiting the available stimulus that would have ideally helped better facilitate cognitive, social and motor development during the toddler years. In line with this, studies found that cognitive assessment scores measured during the pandemic among children below five years of age were significantly lower, which in these studies suggest correlation with less face to face interactions and more time on social media as a consequence being in lockdown.^{3,4} There were also studies noting lower scores in gross and fine motor skills among children with more screen time.⁵ In addition, other studies also described the negative impact of COVID-19 restrictions on social and emotional well-being, with children unable to experience social interaction with same-age peers, resulting to increased anxiety, clinginess, tantrums, and under-stimulation.⁶

In contrast, there were studies with contradicting findings which identified screen time to be positively correlated with better receptive as well as expressive language skills among toddlers.^{7,5}

Rationale of the study

All these studies highlighted the situation of early childhood development in countries worldwide during the COVID-19 Pandemic. None of it investigated the status of development among

toddlers in the Philippines, where one of the longest COVID-19 lockdowns in the world was in put in place. With this, our study aimed to describe the prevalence of the risk for developmental delay among toddlers aged 12 to 36 months during the COVID-19 pandemic, using the Early Childhood Care and Development (ECCD) Checklist. This thus provided a baseline data for early childhood development in the Philippines during the pandemic while also identifying factors correlated with increased risk for developmental delay.

The findings of the study was intended to serve as a guide for educational institutions as they formulate interventions that would help prevent developmental delays given the new setup adopted in lieu of the pandemic (i.e., online classes, hybrid school setup). All this to help children adapt better as the country moves through the new normal.

OPERATIONAL DEFINITIONS

Toddlers: Children aged 12 months and 0 days to 36 months and 365 days.

Participants: The child being evaluated for his or her cognitive, motor and social development during the COVID-19 Pandemic.

Respondents: Parents/ caregivers of the child being evaluated. He or she accomplished the ECCE Checklist, basing his or her answers on whether the participant is able to perform the items in the survey questionnaire.

Risk for developmental delay: A child who acquired a Scaled score of ≤ 6 on the Early Childhood Care and Development Checklist was considered at risk for developmental delays, and was advised to re-test after 3 to 6 months or seek consultation with a Developmental Pediatrician for further evaluation.

Average development: A child who acquired a Scaled score of ≥ 7 on the Early Childhood Care and Development Checklist was considered to average and advanced child development. In particular, a Scaled score of 7 to 13 was

considered to have average development, while a Scaled score between 14 to 19 was considered to have advanced development.

Cognitive development: Development of a child's ability to think, reason, use language, communicate, solve problems, and learn. This was measured using the items on Receptive Language, Expressive Language and Cognitive Development in the ECCD Checklist.

Motor development: Includes both gross motor development, including skills requiring coordination of large muscle groups; as well as fine motor development, including skills requiring coordination of smaller muscles of the body, such as the hands and face. This was measured using the items on Gross Motor and Fine Motor Development in the ECCD Checklist.

Social development: Development of children's relation to their social world and their ability to differentiate and express emotions and perceive emotional states of other individuals. This was measured using the items on Social Development in the ECCD Checklist.

Early Childhood Care and Development (ECCD) Checklist: A testing tool used to assess if a child is developing at par with age, or is at risk for developmental delays. It was designed by the National Nutrition Council of the Philippines to be administered in the community by teachers, child development workers, day care workers, parents and caregivers.

Duration of daily screen time: The amount of time the child spent watching any kind of video on the television or on other gadgets. Sample contents include, but are not limited to, the following: Educational materials that teach about letters, doodling, object identification, shapes, colors; and sing-along music videos. For the purposes of this study, this was divided into: <1 hour; ≥1 hour.

Duration of daily physical activities: The amount of time the child spent on activities that require movement of the extremities and facilitate energy expenditure. Sample activities include, but are not

limited to, the following: Walking, running, climb stairs, climbing. For the purposes of this study, this was divided into: <1 hour; ≥1 hour.

Duration of daily informal study: The amount of time the child spent on informal study activities without gadget use.

Sample activities include, but are not limited to, the following: Being read to, doodling. For the purposes of this study, this was divided into: <1 hour; ≥1 hour.

METHODS

Type of Study, Time Period and Target Population

This research utilized a cross sectional study design to describe the prevalence of toddlers at risk for developmental delay, among Social Service and private patients of pediatric consultants from a Tertiary Hospital in Quezon City, during the period of March 2020 to March 2022 (within the timeframe of the COVID-19 pandemic). This study also determined the factors associated with the risk for developmental delay among this population. Children born preterm, and those diagnosed with congenital anomalies, syndromes and disorders affecting cognitive, motor and social development were excluded from the study.

Description of Study Procedure

The study utilized convenience sampling, with data conveniently collected from the available pool of respondents. The limitation of this, however, is that it is difficult to generalize the results of the study to the population as a whole because of the possibility of under- or over-representation of a certain group. As in this study for example, more private patients were able to answer the online questionnaire, as compared to the social service patients, since the private patients had more access to the internet. With this, the study might generate biased results which could have been addressed if the respondents were recruited using random sampling.

The respondents were gathered from the pool of Social Service patients, and from the private patients of pediatric consultants of a Tertiary Hospital in Quezon City. The social service patients were recruited in the form of a text blast sent by doctors assigned at the OPD. The message, which included a brief description of the purpose of the study, was sent to potential respondents (the primary caregivers of the study participants). Respondents who agreed to be part of the study were given a Google Form link to the Informed Consent Form and the Survey Questionnaire. On the other hand, the private patients were recruited through their respective attending pediatricians. A formal letter was sent to the attending pediatricians to request for their permissions to have their patients participate in the study. The letter included a description of the study, along with a request to send a text or email blast to their private patients to participate in the study. Respondents who agreed to be part of the study, were instructed to message the Study Doctor who then sent the Google Form link to the Informed Consent Form and thereafter, the Survey Form.

Informed consent was obtained from the respondents prior to inclusion in the research. An online copy of the Informed Consent Form was emailed to the respondents, which was then sent back to the Study Team with their signatures affixed prior to answering the survey questionnaire.

Caregivers of the participants were asked to complete the survey questionnaire via Google Form which included items that identified demographic data, followed by the Early Childhood Care and Development (ECCD) Checklist for children aged 12 to 36 months.

The Philippine (ECCD) Checklist is a testing tool designed to be administered by service providers (teachers, rural health midwives, child development and day care workers), and parents

or caregivers, with the goal of determining whether a child is developing at par with age, or is at risk for developmental delays. This tool was not made with the intent to diagnose developmental delays and conditions, measure a child's intelligence quotient (IQ), nor gauge his academic achievement. It was designed to assess risks for developmental delays so that early interventions may be facilitated.¹⁰ The items in the ECCD checklist are divided into seven groups based on the following domains: 1) gross motor, 2) fine motor, 3) self-help, 4) receptive language, 5) expressive language, 6) cognitive, and 7) social-emotional. These items were statistically validated among a sample size of 10,915 Filipino children from the NCR, and from Regions III, VI, VII, VIII and XII.¹⁰

The ECCD was available in both English and Filipino versions created and validated by the National Nutrition Council. The respondents took around 30 minutes to 1 hour to answer the whole questionnaire, and they were encouraged to contact the Study Doctor when they wished to clarify about the items in the questionnaire.

Prior to giving the respondent a copy of the tool through the questionnaire in the Google Form, it was stated in the instructions that there are no right or wrong answers, nor good or bad scores. It was also detailed that the tool will determine the risk for developmental delays but will not diagnose the participant of any developmental condition without consultation with a Developmental Pediatrician. This was stated to address possible Social Desirability Bias or bias noted when respondents give answers that are socially acceptable; and in a way, ensure more accurate responses from the respondents. To administer the questionnaire and note the responses in the Google Form, the respondent either: 1) Observed the participant; or 2) Directly elicited the behavior or response from the participant (some items directly states what the child needs to perform while others

have an accompanying instruction on how the item can be elicited from the child).¹⁰

Those with incomplete data were excluded from the study. Results from the ECCD were then tallied on Microsoft Excel for Mac version 16.61.1 (2019), and the respondents' raw scores were translated into scaled scores included in the ECCD Checklist which helped to compare the scores even though the children had differing ages (thus, differing anticipated milestones per age) during the time of testing.¹⁰

Description of Outcome Measures

The outcome was the presence of risk for developmental delays, which was measured using the ECCD Checklist. The study determined the correlation of this with the following variables: 1) Number of hours of daily physical activity; 2) Number of hours of daily screen time; and 3) Number of hours of daily informal study sessions. These independent variables were noted to be associated with increased risk of developmental delay in previous studies.

Sample Size Estimation

Sample size was calculated based on the test of hypothesis for the difference in the proportion of language developmental delay among children with less than 2 hours of screen time versus those with 2 hours and over.⁵ Assuming that proportion of developmental delay among children with less than 2 hours of screen time is 45.7% and 22.6% among those with 2 hours or more with an error of 5%, power of 80%, and a one-tailed alternative hypothesis, initial sample size calculated is 51 per group or a total of 102 for 2 groups. Controlling for 4 more variables in the analysis with an additional 10% for each control variable, final sample size required is 143.

This sample size was deemed achievable given that the monthly deliveries in the Tertiary

Hospital involved in the study has been consistent at 100 deliveries per month (including both private and social service deliveries) even during the start pandemic.

Data Analysis

Descriptive statistics was used to study the demographics of the data collected. Determination of factors associated with developmental delay was analyzed using Univariate and Multivariate statistics. Chi-square test and Logistic Regression were used in the Univariate Analysis. Multiple Logistic Regression was utilized in the Multivariate Analysis, and the Prevalence Odds Ratios with a 95% confidence interval were also calculated. Level of significance was set at $\alpha = 0.05$. Data was analyzed using SPSS.

Ethical Considerations

The study abided by the Principles of the Declaration of Helsinki (2013) and was conducted along the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). The Clinical Protocol and all relevant documents were reviewed and approved by the Institutional Ethics Review Committee. The data was gathered from the medical records and only the investigator was allowed to view the patient's files. Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document was CODED and did not contain any identifying information in order to ensure confidentiality.

All study data were recorded and investigators were responsible for the integrity of the data i.e., accuracy, completeness, legibility, originality, timeliness and consistency. The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data. An Informed Consent was obtained prior to inclusion of the participant in the study.¹¹

By participating in the study, benefits included screening of the participants' risk for developmental delays, whether it be in the cognitive, motor or social domain. In such cases that a risk for delay was identified, the Study Doctor informs the respondent regarding the participant's results so as to facilitate follow up consultation with a Developmental Pediatrician. Possible inconveniences of participating in the study included the lengthiness of the questionnaire.

The principal investigator was the main person responsible for storage of data. All study-related documents such as all versions of the protocol, ethical clearance, data collection forms, and hard copies of source documents, signed informed consent forms shall be kept and stored by the Principal Investigator in strict confidentiality for at least 5 years after which they will be shredded. Data in electronic form will be stored in the project leader's personal laptop, which is password protected and will only be accessible to members of the study team. Hard copies of all documents will be stored in a cabinet with lock and key, in a secure room, accessible only to members of the research team.

RESULTS

The study included 145 participants aged 12 to 36 months who are either part of the Social Service Program or are private patients of pediatric consultants from a Tertiary Hospital in Quezon City, during the period of March 2020 to March 2022 (within the timeframe of the COVID-19 pandemic). Eligible participants were classified as either 1) At risk for developmental delay; or 2) With average development, based on their scaled scores in the ECCD Checklist individually accomplished by their caregivers. Baseline demographic characteristics of the study participants were tallied and are presented in Tables 1-3.

Majority of the study participants were males (77, 51.7%), with a mean age of 25.28 months. In terms of their physical activities during the period of March 2020 to March 2022, most of the participants had ≥ 1 hour of daily physical activity at 93.1% (135, n=145) despite lockdown restrictions. However, in terms of screen time, most of the participants at 73.1% (106, n=145) had ≥ 1 hour of screen time daily, which entails watching any kind of video on the television or on other gadgets; and in terms of informal study sessions, most of the participants at 61.4% (89, n=145) had < 1 hour of informal study sessions daily which entails spending time on informal study activities without gadget use (Table 1).

Table 1. Demographic Data of the Sample

Age (mo) Mean 25.28, Range 12-36	
Profile, n=145	n (%)
Sex	
Male	75 (51.7)
Female	70 (48.3)
No. of Hrs of Daily Physical Activity	
< 1 hour	10 (6.9)
≥ 1 hour	135 (93.1)
No. of Hrs of Daily Screen Time	
< 1 hour	39 (26.9)
≥ 1 hour	106 (73.1)
No. of Hrs of Daily Informal Study Sessions	
< 1 hour	56 (38.6)
≥ 1 hour	89 (61.4)

Tally of participants identified to be at risk for developmental delay in one or more domains is presented in Table 2. A total of 37 out of 145 participants or 25.5% were identified to be at risk for delays in one or more domains of development (either motor, cognitive, social or a combination).

6.9% or 10 of the 145 participants were identified to be at risk for Social Developmental Delay alone. Participants identified to be at risk for either Gross Motor Developmental Delay (16, 11%), Fine Motor Developmental Delay (5, 3.4%) or both, based on their scaled scores in the ECCD Checklist, were included in the tally of those at risk for Motor

Developmental Delay. With this, 12.4% or 18 of the 145 participants were identified to be at risk for Motor Developmental Delay alone. Participants identified to be at risk for either Receptive Language Developmental Delay (9, 6.2%), Expressive Language Developmental Delay (22, 15.2%), Cognitive Developmental Delay (7, 4.8%) or a combination, based on their scaled scores in the ECCD Checklist, were included in the tally of those at risk for 7 Cognitive Developmental Delay. With this, 16.6% or 24 of the 145 participants were identified to be at risk for Cognitive Developmental Delay alone (Table 2).

Table 2. Demographic Data of the Sample in Terms of Risk of Developmental Delay

	n (%)
Risk for Motor Developmental Delay	18 (12.4)
Gross Motor Developmental Delay	16 (11)
Fine Motor Developmental Delay	5 (3.4)
Risk for Cognitive Developmental Delay	24 (16.6)
Receptive Language Developmental Delay	9 (6.2)
Expressive Language Developmental Delay	22 (15.2)
Cognitive Developmental Delay	7 (4.8)
Risk for Social Developmental Delay	10 (6.9)
Risk for Developmental Delay in One or More Domains	37 (25.5)

Univariate and Multivariate analysis were both applied to determine whether there is an association between the risk of developmental delay in each domain (motor, cognitive, social, or the presence of any or all) and the 1) Composition of the household; 2) Hours spent daily for physical activity; 3) Daily screen time; and 4) Hours spent daily for informal study sessions. Chi-square test and Logistic Regression were used in the Univariate Analysis. Multiple Logistic Regression was utilized in the Multivariate Analysis, and the Prevalence Odds Ratios with a 95% confidence interval were also calculated. Level of significance was set at $\alpha = 0.05$.

Presented in Table 3.1 is the Univariate analyses for Risk of Developmental Delay. Participants who were identified to be at risk for developmental delays in one or more of the domains were included in the analysis of this section.

Risk for Developmental Delay was found to be highest among those with more than or equal to 1 hour of daily physical activity (35, 94.6%, $p=0.678$) and more than or equal to 1 hour of daily screen time (32, 86.5%, $p=0.033$). But in terms of hours of informal study sessions, developmental delay was highest in those with less than 1 hour of informal study sessions daily (165, 43.2%, $p=0.503$).

We also note that there is a significant difference between the risk of developmental delay in participants whose daily screen time is more than or equal to 1 hour compared to those with daily screen time of less than an hour ($p=0.033$). This congruent with the findings in the Multivariate analysis (Table 3.2), where a significant difference was also noted in the risk of developmental delay among those who had daily screen time of more than or equal to 1 hour ($p=0.034$) compared to

those who had screen time of less than 1 hour. These results suggest that odds that participants who had daily screen time of more than or equal to 1 hour have developmental delay are two times more likely compared to those who had screen time of less than 1 hour (OR=3.055, 95% CI=1.088 to 8.580).

In the Multivariate Analysis (Table 3.2), there were no associations found between risk of developmental delay, and hours of daily physical activity ($p=0.433$), and hours of daily informal study sessions ($p=0.327$).

Table 3.1. Univariate Analysis of Risk of Developmental Delay

Developmental delay, n=37	
n (%)	
No of Hrs of Daily Physical Activity	
<1 hour	2 (5.4)
≥1 hour	35 (94.6)
Pearson Chi-Square, $p=0.678$	
No of Hrs of Daily Screen Time	
<1 hour	5 (13.5)
≥1 hour	32 (86.5)
Pearson Chi-Square, $p=0.033$	
No of Hrs of Daily Informal Study Sessions	
<1 hour	165 (43.2)
≥1 hour	21 (56.8)
Pearson Chi-Square, $p=0.503$	

Table 3.2. Multivariate Analysis of Risk of Developmental Delay

	Sig.	OR	95% C.I. for OR	
			Lower	Upper
No of Hrs of Daily Physical Activity				
≥1 hour	0.433	1.968	0.362	10.716
No of Hrs of Daily Screen Time				
≥1 hour	0.034	3.055	1.088	8.580
No of Hrs of Daily Informal Study Sessions				
≥1 hour	0.327	0.666	0.295	1.502

Cognitive Developmental Delay

Risk for Cognitive Developmental Delay was found to be highest among those with more than or equal to 1 hour of daily physical activity (22, 91.7%, $p=0.761$), more than or equal to 1 hour of daily

screen time (21, 87.5%, $p=0.082$), and more than or equal to 1 hour of daily informal study sessions (13, 54.2%, $p=0.427$). There were no associations in the Multivariate analysis for Risk of Cognitive Developmental Delay (Table 4.2).

Table 4.1. Univariate Analysis of Risk of Cognitive Developmental Delay

Cognitive developmental delay, n=24	
n (%)	
Profile, n=145	
No of Hrs of Daily Physical Activity	
<1 hour	2 (8.3)
≥1 hour	22 (91.7)
Pearson Chi-Square, $p=0.761$	
No of Hrs of Daily Screen Time	
<1 hour	3 (12.5)
≥1 hour	21 (87.5)
Pearson Chi-Square, $p=0.082$	
No of Hrs of Daily Informal Study Sessions	
<1 hour	11 (45.8)
≥1 hour	13 (54.2)
Pearson Chi-Square, $p=0.427$	

Table 4.2. Multivariate Analysis of Risk of Cognitive Developmental Delay

	Sig.	OR	95% C.I. for OR	
			Lower	Upper
No of Hrs of Daily Physical Activity				
≥1 hour	0.939	1.070	0.189	6.051
No of Hrs of Daily Screen Time				
≥1 hour	0.89	3.025	0.845	10.834
No of Hrs of Daily Informal Study Sessions				
≥1 hour	0.406	0.669	0.259	1.728

Motor Developmental Delay

Risk for Motor Developmental Delay was found to be highest among those with more than or equal to 1 hour of daily physical activity (17, 94.5%, $p=0.810$), more than or equal to 1 hour of

daily screen time (16, 88.9%, $p=0.107$), and more than or equal to 1 hour of daily informal study sessions (12, 66.7%, $p=0.623$). There were no associations in the Multivariate analysis for Risk of Motor Developmental Delay (Table 5.2).

Table 5.1 Univariate Analysis of Risk of Motor Developmental Delay

Motor developmental delay, n=18	
	n (%)
No. of Hrs of Daily Physical Activity	
<1 hour	1 (5.5)
≥1 hour - <2 hours	17 (94.5)
Pearson Chi-Square, $p=0.810$	
No. of Hrs of Daily Screen Time	
<1 hour	2 (11.11)
≥1 hour	16 (88.9)
Pearson Chi-Square, $p=0.107$	
No. of Hrs of Daily Informal Study Sessions	
<1 hour	6 (33.3)
≥1 hour	12 (66.7)
Pearson Chi-Square, $p=0.623$	

Table 5.2. Multivariate Analysis of Risk of Motor Developmental Delay

	Sig.	OR	95% C.I. for OR	
			Lower	Upper
No of Hrs of Daily Physical Activity				
≥1 hour	0.871	1.208	0.124	11.814
No of Hrs of Daily Screen Time				
≥1 hour	0.125	3.284	0.718	15.029
No of Hrs of Daily Informal Study Sessions				
≥1 hour	0.718	1.230	0.401	3.771

Risk for Social Developmental Delay was found to be highest among those with more than or equal to 1 hour of daily physical activity (2, 20%, $p=0.090$) and more than or equal to 1 hour of daily screen time (1, 10%, $p=0.212$). But in terms of hours of

informal study sessions, social developmental delay was highest in those with less than 1 hour of informal study sessions daily (6, 60%, $p=0.150$). There were no associations in the Multivariate analysis for Risk of Social Developmental Delay (Table 6.2).

Table 6.1. Univariate Analysis of Risk of Social Developmental Delay

Social developmental delay, n=10	
	n (%)
No of Hrs of Daily Physical Activity	
<1 hour	2 (20)
≥1 hour	8 (80)
Pearson Chi-Square, $p=0.090$	
No of Hrs of Daily Screen Time	
<1 hour	1 (10)
≥1 hour	9 (90)
Pearson Chi-Square, $p=0.212$	
No of Hrs of Daily Informal Study Sessions	
<1 hour	6 (60)
≥1 hour	4 (40)
Pearson Chi-Square, $p=0.150$	

Table 6.2. Multivariate Analysis of Risk of Social Developmental Delay

	Sig.	OR	95% C.I. for OR	
			Lower	Upper
No of Hrs of Daily Physical Activity				
≥1 hour	0.357	0.414	0.063	2.708
No of Hrs of Daily Screen Time				
≥1 hour	0.241	3.545	0.428	29.359
No of Hrs of Daily Informal Study Sessions				
≥1 hour	0.305	0.470	0.111	1.990

DISCUSSION

Results of the study showed that 25.5% or 34 out of the 145 participants were identified to be at risk for developmental delays in one or more domains of development evaluated in the study (either motor, cognitive, social or a combination). In a pre-pandemic study done among Filipino children using the Griffiths Mental Development Scales (GMDS), it was revealed that risk for developmental delay is 5.4% at 6 months old, 19.1% at 12 months old and 11.0% at 24 months old.¹² With this, we identify an increase in the percentage of children at risk for developmental delays during the pandemic. But we take this comparison with a grain of salt since the scales used in this study and in the previous study were different.

Individually, 16.6% were noted to be at risk for Cognitive developmental delay, 12.4% for Motor developmental delay, and 6.9% for Social developmental delay,⁸ in line with other studies which identify increased risk for delay in language (cognitive), and fine motor (motor) skills among toddlers during the pandemic.^{12,13,14,15} With the pandemic, work-from-home setups were abound, decreasing parent-child interaction despite being together in one household during the lockdown. This could have potentially affected children's language development negatively as in our study.¹⁵

Risk of Developmental Delay and Daily Screen Time

In terms of screen time, more than half of the participants at 73.1% (106, n=145) had more than one hour of screen time daily, in line with international studies,^{5,16,17} which noted a daily screen time of more than one to two hours. This contradicts the AAP's guidelines which discourages screen time, except for video-chatting, in younger than 24 months; and which limits daily media exposure to 1 hour or less in older than 24 months.¹⁸ One possible reason for increased screen time during the pandemic could be related to the duration of

lockdown in the country, such that children from countries with longer lockdowns had increased screen time.¹⁹ In the same study, the longer the caregivers stayed at home to care for the children while also working from home, the more screen time the children had since they had limited access to other offline activities. This is consistent with our Philippine setting. With this, it must be emphasized to parents and caregivers that, since brain development is at its peak during early childhood, toddlers need more hands-on, unstructured, and social play, as opposed to passive learning from media, to enhance cognition and social skills.¹⁹

Our study also suggested that toddlers with daily screen time of an hour or more were more likely to have increased risk of developmental delay in one or more developmental domains. Several studies have noted this correlation, explaining that this might be due to lost opportunities to hone skills crucial to development.^{19,20,21,22,23}

While on screens, without physical interaction, children are more sedentary hence gross motor skills are not honed. Being on screens also disrupts social interactions thus cognition (expressive and receptive language skills), as well social skills, including nonverbal exchanges), are not honed.²⁰ Increased screen time, particularly during the lockdown, decreased time on other enriching activities, with children spending less time reading or being read to.^{19,21,22,23}

Risk of Developmental Delay and Daily Physical Activity

No significant correlation was found between the hours of daily physical activity and the risk of delay but more than half of the participants had more than an hour of daily physical activity at 93.1% despite lockdown restrictions. This is contrasting pre-pandemic data,²⁰ which identified that among children's different occupations or the "everyday activities that bring meaning and

purpose to life,”²¹ the time allotted for play is among the lowest. This may be explained by caregivers encouraging more physical activity during the lockdown to compensate for the lack of outdoor exposure.

Risk of Developmental Delay and Daily Informal Study Time

No significant correlation was found between the hours of daily informal study sessions and the risk of delay, but 61.4% of the participants spent more than an hour of informal study sessions without gadget use. This is consistent with pre-pandemic data, which notes that educational activities ranked second in activities children spend most of their time on.²⁴

CONCLUSION

Our study revealed that 25.5% of toddlers were identified to be at risk for developmental delays in motor, cognitive, and/or social development during the COVID-19 pandemic. In particular, toddlers are at an increased risk for cognitive and motor delay, which is consistent with international data. Furthermore, it was identified that the hours of daily screen time may be a factor correlated with risk for developmental delay.

Our study also found that more than half of toddlers had more than an hour of daily screen time, contrary to AAP recommendations. In relation to this, it was found that children with daily screen time of an hour or longer were more likely to have increased risk of delay in one or more developmental domains at 86.5%.

Our findings emphasize the need for educational interventions that would support those falling behind developmentally. This may also serve as a wakeup call to parents and child healthcare practitioners to reevaluate educational practices and lifestyles adopted during the pandemic. Child- and family-oriented institutions should develop programs that would assist caregivers in providing

an environment that is open to opportunities for play and learning in the “new normal”. The use of technology in education will surely prevail given the convenience it brought to our lives; but noting its pitfalls, we must work around it to help prevent the succeeding generations from falling into the same developmental setbacks. With growth at an overdrive during this period, we can still definitely influence the course of these toddlers’ development and create better opportunities for their future.

LIMITATION AND RECOMMENDATIONS

The following are the limitations of the study. First would be the small sample size and the exclusivity of the sampled population, with the authors recommending including a larger population spanning citywide and regional initiatives. Second, while caregivers may be the best informants of toddlers, single informant measurement may introduce memory and social desirability bias. Future studies could use of other objective measures of developmental outcomes. Finally, our cross-sectional findings cannot assume directional associations. The strength of the statistical design could be improved by ensuring a more homogenous population, though this does not account for confounding variables (i.e., parenting, attachment style).

ACKNOWLEDGEMENTS

We would like to acknowledge the following organizations for allowing us to present and share the knowledge across borders: St. Luke’s Medical Center Quezon City – Institute of Pediatrics and Child in Quezon City, Philippines; Quezon City Medical Society in Quezon City, Philippines; Philippine Society of Developmental and Behavioral in Manila, Philippines; International Play Association (IPA) in Glasgow, Scotland; and the European Pediatric Neurology Society (EPNS) in Prague, Czech Republic. Our heartfelt gratitude to everyone who helped accomplish this feat including my

batchmates, family, friends and mentors. To all children who lived through the COVID-19 pandemic and are now thriving through the “new normal,” may you grow into the amazing individuals you’re destined to be. We hope that through this, we would be able to help make the world beyond the pandemic a happier and healthier place to live in.

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Psoriasis Vulgaris with Pemphigus Foliaceus Treated with Methotrexate: A Case Report*

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ABSTRACT

Psoriasis is a systematic immune-mediated inflammatory disease where there is an increased cell turnover of the skin leading to scaling, drying, and erythema. The occurrence of pemphigus foliaceus, an autoimmune blistering disease (AIBD) characterized by flaccid bullae and erosions, is rare when concomitantly present with psoriasis. Treatment options for these diseases may overlap. We report a case of a 44-year-old female who presented with both psoriasis and pemphigus foliaceus successfully treated with methotrexate.

Introduction

Challenges in treatment can be encountered when two diseases co-exist. Chronic diseases like psoriasis and pemphigus would require long term cycles of treatment. Taking into consideration the effectiveness, safety and cost to the patient is paramount in achieving disease control and patient compliance. This report recognizes the challenges met in the course of treatment of this case diagnosed with both psoriasis and pemphigus.

Keywords: Psoriasis vulgaris; Pemphigus foliaceus; methotrexate; case report

CASE REPORT

A 44-year-old Filipino woman, who works as a teller with no known comorbidities was seen at the out-patient dermatology clinic with painful and occasionally pruritic erythematous scaly plaques and erosions on the body with no other systemic symptoms. Lesions started 5 months prior as few vesicles on the abdomen spreading to the back, face, and extremities (Figure 1). She was seen by general practitioner who managed her initially as a case of impetigo with oral and topical antibiotics. There was no relief from the initial prescription. A 4mm-skin punch biopsy was done on second opinion consult with a dermatologist which showed changes consistent with psoriasis. She was started on halobetasol cream and oral doxycycline but more lesions appeared with multiple flaccid blisters over the legs.

She was then given prednisone 40mg tablet once daily with tapering over an 8 day period. Still no relief prompting consult at our institution. On her first visit, she presented with eroded vesicles in a seborrheic distribution and the initial impression at this time was Pemphigus foliaceus. To confirm the diagnosis, skin punch biopsies were done. The first specimen was taken from an erythematous plaque on the back (Figure 5) and showed psoriasiform dermatitis suggestive of psoriasis (Figure 6). The second site was on a

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

* 1st Place, 29th Philippine Medical Association Case Report Presentation, May 16, 2023

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solitary vesicle on the outer right arm (Figure 7) which showed a subcorneal pustular dermatitis with spongiosis suggestive of a blistering disease (Figure 8). Direct Immunofluorescence of a perilesional area on the buttocks showed intercellular deposition of IgG and C3 (Figure 9) and ELISA showed anti-desmoglein 1 levels of >200 RU/ml (normal value: <20 RU/ml), consistent with pemphigus foliaceus. The final diagnoses based on histopathology for our patient is psoriasis with concomitant pemphigus foliaceus.

She was started on prednisone 50mg/tablet once daily, dapsone 50mg/tablet daily for 2 weeks, and mometasone furoate 0.1% lotion applied twice a day on affected areas. However, she reported an increase in erythema, weeping, and crusting (Figure 2). Upon evaluation, the increase in lesions was more attributable to dapsone with prednisone, leading to discontinuation of dapsone and tapering of prednisone by 5mg every 2-3 week. Methotrexate was then initiated at 10mg with folic acid rescue the next day.

The patient dramatically improved by week 2 of methotrexate with gradual hyperpigmentation of old lesions (Figure 3). For the next 3 months, methotrexate was maintained at 10mg weekly with continual tapering of prednisone. No new lesions were observed (Figure 4) and the patient reported no side effects during the treatment period. Regular follow up was done thru telemedicine with monthly monitoring of laboratory parameters.

DISCUSSION

Pemphigus foliaceus is a chronic autoimmune blistering disease characterized by crusted and eroded scaly plaques in a seborrheic distribution. It is caused by IgG antibodies attacking desmoglein-1 in the stratum corneum which is responsible for cell to cell adhesions.¹ Cases of bullous disease with psoriasis, although

rare, have been reported. Studies show that pemphigus increases the likelihood of having co-existent diseases like Sjögren syndrome, systemic lupus erythematosus, alopecia areata, with psoriasis being the most common concomitant disease.² In a case series with 145 patients diagnosed with psoriasis, pemphigus foliaceus was observed in 2.8% of the cases.³ There is no explanation for these associations as yet.

Many theories have been postulated to explain the co-existence of psoriasis and pemphigus. Inflammation in psoriatic lesions may upregulate antigens that may attack keratinocytes leading to acantholysis that present clinically as blisters. Another possible explanation is the epitope spreading phenomenon where a secondary autoimmune humoral response may occur due to the exposure of previously hidden antigen protein components during the primary inflammatory process of psoriasis. Another theory is the alteration of T-cell regulation in psoriasis with increased production of autoantibody. Plasminogen activity in pemphigus results in acantholysis and elevated levels of plasminogen activators are also present in psoriatic lesions, serving as another possible link.⁴ However, literature shows that the mean duration of AIBD preceded by psoriasis is 10 years while psoriasis occurring after the diagnosis of an AIBD is 4 years.³ In this case, it is unclear whether psoriasis or pemphigus foliaceus developed simultaneously given that the patient initially exhibited vesicles, or is one occurred before the other.

Systemic corticosteroid therapy is the first line treatment for pemphigus but not for psoriasis. Steroid sparing immunosuppressive agents like rituximab, azathioprine, mycophenolate mofetil, or mycophenolic acid may also be given as adjunct treatment. Dapsone up to 1.5mg/kg/day may be given for pemphigus foliaceus.^{5,8} However, this patient did not appear to respond well to the combination of prednisone and dapsone.

Dapsone Syndrome was considered which is characterized as an exfoliative dermatitis with systemic symptoms like fever, lymphadenopathy, and hepatotoxicity which has been reported with chronic use of the drug in cases like leprosy but the patient did not present with any systemic symptoms.^{6,7} Psoriasis flare-ups due to oral systemic steroids is also a possible reason for the worsening of lesions, however, it would typically present with pustular Von Zombusch type lesions usually with high doses or upon withdrawal of the drug.⁹

Methotrexate, which has anti-inflammatory and antiproliferative properties is a treatment option in both diseases. This was started along with prednisone at 1 mg/kg/day.^{8,10} In 2 weeks, the patient responded well with Pemphigus Disease Area Index (PDAI) activity of 4 (from 58 previously) and a Psoriasis Area and Severity Index (PASI) score of 10.4 to 4.8 in a span of 11 days. Methotrexate is the first line systemic non-biologic therapy for psoriasis and a third line therapy for pemphigus.^{5,8} Its safety and efficacy for psoriasis and pemphigus have been established in previous studies and is currently part of the treatment guidelines for both.^{8,11,12}

CONCLUSION

Epidemiologic evidence suggests that patients with psoriasis are significantly more likely to have co-existent psoriasis. Causal relationship is still not established but is shown to be attributed to the immunologic response of the body to both diseases.^{3,4}

Methotrexate can be safely given to this patient in targeting both psoriasis and pemphigus foliaceus. This patient's case demonstrated that the treatment combination of methotrexate and prednisone with topical steroids was well tolerated with no side effects and complete clearance of skin lesions was achieved after 4 months of treatment.

Figure 1



Figure 2



Figure 3

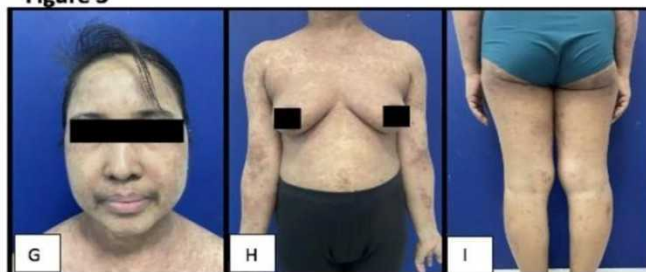


Figure 4

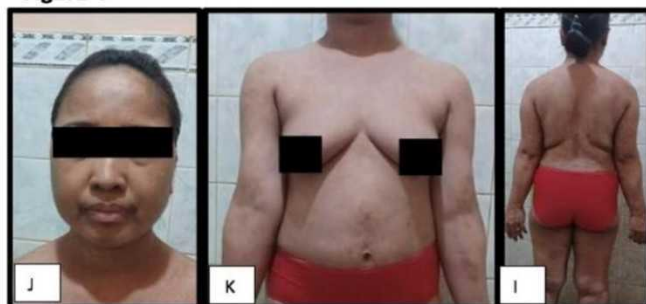
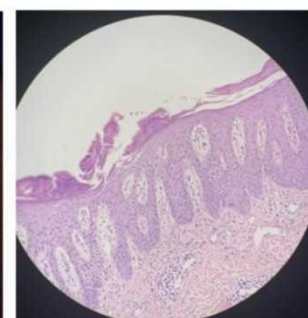


Figure 5



Figure 6



Psoriasiform hyperplasia, neutrophils in the stratum corneum, hypergranulosis, spongiosis, thinning of the papillary plate, dilated blood vessels and moderately dense superficial perivascular infiltrates of neutrophils and lymphocytes

Figure 7

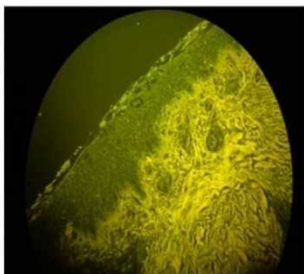


Figure 8

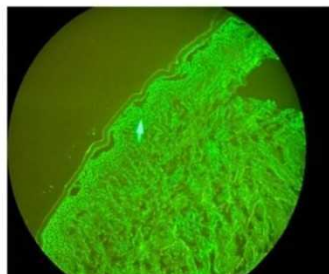


Subcorneal split, acantholysis, extravasated erythrocytes, spongiosis, lymphocytic and neutrophilic exocytosis

Figure 9



(+) Intercellular for IgG, Grade 2



(+) Intercellular for C3, Grade 3

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A Case of Constitutional Mismatch Repair Deficiency (CMMRD)*

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ABSTRACT

Constitutional mismatch repair deficiency (CMMRD) is a hereditary predisposition of malignancy evident in childhood leukemias, lymphomas, and malignant tumors of the brain, GI tract. It is a very rare condition that affects 1 per 1 million patients. Patients with CMMRD syndrome may also manifest with Neurofibromatosis Type 1 (NF1) phenotypic features, and benign masses, particularly in the gastrointestinal tract. This is a case of a 12-year old male who presented with phenotypic features of NF1, developed Acute Lymphoblastic Leukemia at 7 years old and went into remission. He subsequently developed synchronous Glioblastoma and Poorly differentiated Adenocarcinoma of the rectum. This report aims to raise awareness regarding the possibility of a CMMRD syndrome in pediatric patients who present with phenotypic features of NF1, and in those patients who present with two or more malignancies in their lifetime.

Keywords: *Constitutional mismatch repair deficiency (CMMRD), Glioblastoma Multiforme, Acute lymphoblastic leukemia, metachronous cancers, synchronous cancers*

INTRODUCTION

Constitutional Mismatch Repair Deficiency (CMMRD), also known as Biallelic Mismatch Repair deficiency (BMMRD) is a rare and aggressive autosomal recessive disorder linked with the predisposition of a child to develop synchronous or metachronous malignancies such as childhood leukemias, lymphomas, and malignant tumors. Aside from malignancies and hereditary involvement, patients with CMMRD also manifest with phenotypic features suggestive of neurofibromatosis type 1 (NF1)^[1]. CMMRD is a hereditary predisposition of malignancy which manifest from infancy up to young adulthood, with an incidence of one per 1 million patients worldwide. In CMMRD, mismatch repair genes such as mutS homolog 2 (MSH2), mutL homolog 1 (MLH1), mutS homolog 6 (MSH6), and post-meiotic segregation increased 2 (PMS2) are mutated. These mismatch repair genes are responsible for genetic stability and for repair of errors during DNA replication. Most patients diagnosed with CMMRD have mutations in PMS2 or MSH6 genes, and these mutations can lead to more malignancies. However, due to lack of specific clinical features of CMMRD, it causes delay in diagnosis, and worse, may not be diagnosed at all^{[1][2][3]}.

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

*2nd Place, 29th Philippine Medical Association Case Report Presentation, May 16, 2023

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CASE REPORT

This is the case of a 12-year-old male with phenotypic features of NF1 (multiple café au lait macules on the face, trunk, arms, legs and buttocks; axillary freckling; 1.5 x 1.5 cm firm non-tender, non-movable mass on the left antecubital fossa), who was diagnosed with Acute Lymphoblastic Leukemia, B-Cell Average Risk in December 2017. He initially presented with pallor, fever, and joint pains. He was treated with COG AALL0232 protocol until February 2021, with exit BMA done in March 2021 which showed a marrow in remission. Additional skin lesions include several hypopigmented spots on his face, trunk, arms, and legs.

There is a history of consanguinity: the Father's grandfather and the Mother's great-aunt were first degree cousins. Family medical history revealed colorectal cancer (grandfather), and Neurofibromatosis 1 (aunt who is 2nd/3rd degree cousin of both his parents).

In March 2022, he presented with headache and vomiting, with no neurologic deficits. Cranial MRI with IV contrast revealed mildly lobulated, intra-axial lesion measuring 30.3 x 25.2 x 25.0mm (AP x T x CC) along the cortical-subcortical region of the left frontal lobe at the level of corona radiata. He underwent craniotomy and gross total excision of tumor. Intraoperative findings revealed a 2x3cm mass at left frontal lobe with invasion of surrounding brain parenchyma. Histopathological examination revealed High Grade Round Cell Malignancy. Immunohistochemistry were negative for TDT, CD3, and CD79a, but positive for GFAP, and IDH1 which support the diagnosis of Glioblastoma. Further testing for CMMRD on the brain tumor was done which revealed: P53 mutant pattern (IHC), ATRX lost (IHC), MSH2 and MSH6: retained; PMS2 lost in tumor cells and normal cells (CMMRD pattern), MLH1 lost in most cells, PDL1 negative, CD8 32/mm2 plus perivascular lymphocytes. Impression:

Glioblastoma, IDH-wildtype. Genotype is still pending. The patient underwent radiotherapy with 54 Gy in 33 fractions, with concurrent chemotherapy with CCNU. During RT, he presented with headache, a repeat MRI done in June 2022 revealed that the previously described heterogeneously enhancing, mildly lobulated, intra-axial lesion in the left frontal lobe at the level of corona radiata was no longer visualized. But an ill to fairly defined avidly enhancing region is seen around the excision site in the left frontal lobe, with the presence of extensive vasogenic edema. This was read as possible post-RT changes vs tumor recurrence, and imaging after 3 months was suggested.

He was supposed to undergo 6 more cycles of maintenance chemotherapy with CCNU every 42 days. A repeat cranial MRI with IV contrast done post RT revealed slight increase in the size of the previously described avidly enhancing region around the excision site in the left frontal lobe, now measuring approximately 38.75 x 35.39 x 30.23 mm, with the internal component of exhibiting heterogeneity compared with the prior study. There is also progression of vasogenic edema with associated effacement of the adjacent sulci as well as interval increase in the degree of compression of the left lateral ventricle and rightward shifting of the midline structures now measuring about 10.31 mm (previously 8.30 mm).

1 week prior to his first maintenance chemotherapy, he presented with painless, hematochezia not associated with fever, abdominal pain, diarrhea, or constipation. He underwent esophagogastroduodenoscopy (EGD) and colonoscopy with biopsy. EGD findings were unremarkable, however colonoscopy findings revealed colonic polyp, sigmoid colon, 0-IIa, JNET type 2A, and rectal new growth, probably malignant. CEA was elevated with a value of 8.47 ng/mL. Histopathologic findings then revealed

poorly differentiated adenocarcinoma of the rectum. Abdominal MRI and PET-CT scan revealed a 3.2 x 1.8 x 3.6 cm hypermetabolic heterogeneously enhancing soft tissue mass in the right side of the rectum, with at least 6 Hypermetabolic subcentimeter to marginal sized interiliac and mesorectal lymph nodes, more on the right, likely representing metastases. The PET-CT also revealed the presence of a 3.6 x 4 cm heterogeneously enhancing mass in the left frontal lobe with surrounding edema, which has decreased FDG uptake, corresponding to glioblastoma recurrence.

As of writing, present working impression is: Constitutional Mismatch Repair Deficiency Syndrome: Poorly Differentiated Adenocarcinoma, rectum stage III; Glioblastoma, IHC-wildtype, S/P craniotomy and excision (March 2022), S/P concurrent chemotherapy-radiotherapy (August 2022) with tumor recurrence; ALL, B-cell, average risk S/P chemotherapy (Feb 2021) in remission. Because of the simultaneous occurrence of 2 primaries, plan is to give Immunotherapy with Pembrolizumab at 2 mg/kg every 21 days.

DISCUSSION

Here is a patient with phenotypic features of NF1, hypopigmented spots on the skin, with a history of consanguinity, who was diagnosed with acute lymphoblastic leukemia at the age of 7 years old, then developed synchronous Glioblastoma and Poorly differentiated adenocarcinoma of the rectum at 12 years old.

Development of second primary neoplasms is often multifactorial. Main risk factors include genetic and/or host predisposition in developing multiple malignancies^[4]. Involvement of different malignancies in childhood may be attributed to a genetic defect called Constitutional mismatch repair deficiency, which is a rare autosomal recessive disease. It is a hereditary cancer

predisposition in infancy or young adulthood caused by mutations in DNA mismatch repair (MMR) genes. MMR genes are responsible for eliminating mismatch of base to base deletions and insertions resulting from errors of DNA polymerase during DNA synthesis. These genes are specifically mutS homolog 2 (MSH2), mutL homolog 1 (MLH1), mutS homolog 6 (MSH6), and post-meiotic segregation increased 2 (PMS2); they are responsible for stabilization of genomes for error correction and apoptosis when damage to DNA ensue. Heterozygous (monoallelic) mutations in MMR genes affecting functionality of MMR may cause Lynch Syndrome (LS), formerly known as hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Identification of germline mutations in at least one of the repair genes is necessary for the definition of LS. On the other hand, CMMRD is brought on by Constitutional germline mutations in the LS-causing MMR genes^{[1][5]}. The hallmark of CMMRD is an early onset of cancer, with a median age of 7^[3].

Children with malignancies linked to CMMRD may not have a family history of Lynch-associated cancers but should nonetheless be tested for MMR gene abnormalities. The index case of CMMRD frequently lacks family history of cancers that would raise suspicion of the syndrome. Delays in diagnosis of CMMRD may be attributed to its complex nature, to be specific the lack of clear disease-specific clinical features covering the full spectrum of tumors associated with CMMRD, as well as diagnostic difficulties^{[1][5]}.

Data from the International Replication Repair Deficiency (IRRD) Consortium showed 193 tumors in 110 patients diagnosed with CMMRD. Brain tumors (High grade gliomas, medulloblastomas and CNS embryonal tumors) constitute 44%, GI cancers (most common of which are the colorectal carcinomas) constitute 27%, and

hematologic malignancies (most commonly Non-Hodgkin lymphomas, but also leukemias) constitute 19% of the tumors detected. Other malignancies include sarcomas, skin cancer, breast cancer, Wilm's and other kidney cancers, bladder cancers, retinoblastoma, neuroblastoma, ovarian, endometrial, and prostate cancers.^[6] Up to 25% of patients present with synchronous (diagnosed at the same time, or within 6 months of each other^[7]) malignancies.^[8]

Due to lack of clear disease-specific clinical features of CMMRD, the European consortium created criteria called "Care for CMMRD (C4CMMRD)" which is a scoring system that has high sensitivity for CMMRD and can help for further genetic testing and counseling. Table 1 shows the C4CMMRD scoring system, and a score of 3 points and higher is highly suggestive of CMMRD^{[1][3]} Patients have this score should undergo further testing for CMMRD.

Indications for CMMRD-Testing	More than 3 points
Malignancies or pre-malignancies: one is mandatory. If more than one is present add points	
LS carcinoma at age less than 25 years	3 points
Multiple bowel adenomas at age less than 25 years and absence of APC/MUTYH or a single grade dysplastic adenoma (also at age less than 25 years).	3 points
WHO grade III or IV glioma at age less than 25 years	2 points
NHL of T-cell lineage or sPNET at age less than 18 years	2 points
Any malignancy in a patient under 18 years	1 point
Additional features: if more than one of the following are present add points	
Clinical NFI diagnosis or more than 2 hyper/hypo-skin pigmentations (greater than 1 cm)	2 points
Diagnosis of LS in a 1st and/or 2nd degree relative	2 points
LS carcinoma, high grade glioma, sPNET, or NHL	1 point
Sibling with a childhood cancer	1 point
Multiple pilomatricomas present	2 points
One pilomatricoma present	1 point
Agenesis of the corpus callosum or non-therapy induced cavernoma	1 point
Consanguineous parents	1 point
Deficiency/reduced levels of IgG2/4 and or IgA	1 point

Table 1. Diagnostic scoring criteria for CMMRD from the European consortium

"Care for CMMRD"

Our patient has fulfilled several criteria including the following: 1) LS carcinoma at age less than 25 years (3 points); 2) presence of WHO Grade IV Glioma at age less than 25 years old (2 points); 3) malignancy (having acute lymphoblastic leukemia) under 18 years of age (1 point); 4) clinical NFI diagnosis of more than 2 hyperpigmented skin lesions (2 points); and 5) consanguineous parents

(1 point), all corresponding to 9 points, which is highly suggestive of CMMRD.

Microsatellite instability (MSI) and immunohistochemistry (IHC) analysis, followed by mutation analysis, are typically used to confirm the diagnosis. IHC is a helpful technique used in patients with CMMRD associated neoplasms

including brain tumors and directs subsequent mutation analysis in the four MMR-genes. The patient underwent IHC analysis, which revealed loss of MLH1 and PMS2, hence strongly supporting our diagnosis. Patients with CMMRD with mutations in PMS2, as well as MSH6 are at risk of developing more than one malignancy^[3]. In the case of our patient, he had acute lymphoblastic leukemia now in remission, high grade glioma, and rectaladenocarcinoma. MSI analysis follows current protocols used for LS-screening, but this analysis may be unreliable in CMMRD related brain tumors^{[2][9]}.

The International Replication Repair Deficiency (IRRD) Consortium published the CMMRD Diagnostic Criteria (Table 2). Our patient has hallmark CMMRD cancer on diagnosis, 1 positive ancillary test (MMR immunohistochemistry), and family history of consanguinity, with pending genotyping. At the moment, the patient is considered to have a Likely Diagnosis. Patients with Definite and Likely Diagnosis of CMMRD should undergo CMMRD surveillance as per published guidelines.^[10]

CRITERION		GERMLINE RESULT <i>PMS2, MSH6, MSH2, MLH1</i>	POSITIVE ANCILLARY TESTING	CLINICAL PHENOTYPE
Definitive Diagnosis (Strong Evidence of CMMRD)	1	Biallelic pathogenic variants (P/P), confirmed in trans	Not required unless unaffected >25 yrs, then one required	Not required if under age 25 (if no malignancy over age 25, ancillary testing required)
	2	Biallelic P/LP or LP/LP variants, confirmed in trans	One required unless unaffected by hallmark cancer, then 2 required	Hallmark CMMRD cancer diagnosis > or C4CMMRD criteria of 3 points (then 2 ancillary tests required)
	3	Heterozygous P or LP variant (+/- VUS or likely benign variants)	One required	Hallmark CMMRD cancer diagnosis
	4	No P or LP MMR variants (including VUS/VUS) or No testing available (i.e. deceased proband)	Two required	Hallmark CMMRD cancer diagnosis
Likely Diagnosis (Moderate evidence of CMMRD)	5	Biallelic P/LP or 5 LP/LP variants confirmed in trans	Not required	C4CMMRD criteria of 3 points
	6	Heterozygous P or LP variant or no testing available (i.e. deceased proband)	Two required	a. C4CMMRD criteria of 3 points b. Individual < age 18 with NF1 features (i.e. no malignancy or polyposis history polyposis history) c. Malignancy under age 30

Table 2. CMMRD Diagnostic Criteria, from International Replication Repair

Deficiency (IRRD) Consortium

Patients diagnosed with CMMRD have a median survival of 30 months from the time the primary tumor is diagnosed^[1]. However, surveillance seems to have an impact on survival as shown in the IRRD consortium data where patients who were undergoing full surveillance had

significantly better 4-year OS rates of 79% compared to those who underwent partial surveillance 55% survival, and no surveillance (15%) They also reported the high likelihood of transformation of low to high grade cancers among these patients.^[6]

Surveillance of CMMRD must be done from the time of diagnosis. The latest published guidelines include: Brain MRI at diagnosis and every 6 months for brain tumors; Whole body MRI to start at 6 years and once a year for all tumors; CBC to start at 1 year old and every 6 months for leukemias; Abdominal ultrasound to start at 1 year old and every 6 months for lymphomas; Upper GI endoscopy, Visual Capsule Endoscopy and Ileocolonoscopy to start at 4-6 years at least once a year but increases once polyps are found; and GYN exam, transV ultrasound to start at 20 years old and once yearly after that to look for GYN malignancies. It was noted that malignancies that were detected asymptotically had better survival rates than those that were detected symptomatically.^[10]

Aside from testing the affected child, the parents should also get genetic counseling that explains the clinical repercussions of a likely heterozygous mutation in both parents as well as the potential 25% probability of recurrence. Once a mutation has been discovered, predictive testing should be made available to all family members in accordance with the established interdisciplinary counseling guidelines. Determining recommendations for surveillance of affected patients is difficult due to the vast range of malignancies in CMMRD patients. The likelihood of finding related cancers, such as colon cancer or brain tumors, at an operable stage may be increased by early detection of CMMRD and subsequent cancer screening at regular intervals^[2]. In our case, patient's siblings who also has CALM, is advised to have a skin biopsy for IHC and genetic testing.

The ideal course of treatment for patients with CMMRD is not currently known. Several papers emphasize that special consideration should be given to the high risk of a second malignancy, the potential for greater cytotoxicity and decreased

efficacy of chemotherapeutic drugs due to constitutionally deficient mutation repair^[2]. Several commonly used chemotherapeutic drugs need a functioning MMR system to cause tumor destruction. MMR-deficient cells typically exhibit chemotherapy resistance with mercaptopurine and temozolomide, which are frequently used to treat glioma and hematological malignancies, respectively. MMR resistance is shown by temozolomide, the medication of choice for glioblastomas multiforme, a highly aggressive CMMRD-brain tumor. Since temozolomide is known to promote the accumulation of somatic mutations in patients, increasing the risk of subsequent tumors, its usage is now avoided in GBM associated with CMMRD. However, effective chemotherapeutic therapy for CMMRD cancer are still scarce, and novel effective medicines are urgently needed. No clear lack of efficacy of other therapeutic agents, such as alkylating agents, has been found.

There has now been a development of immunotherapies termed checkpoint inhibitors which counteract the actions of proteins that hamper the immune response to cancer. PD-L1 serves as a binding site for PD1 and is over expressed in several malignancies. When PD1 binds to PD-L1 inside the tumor, PD1 signaling is activated, which inhibits T cell activation and enables the tumor to resist immunological attack. Enhancing the anti-cancer T cell response and fostering anti-tumor activity can be achieved by inhibiting the interaction of PD1 and PD-L1. In CMMRD cancers, inhibiting PD-1 results in a significant clinical response, and CMMRD tumors respond to PD-1 blockers better than MMR-competent tumors. Children with CMMRD and recurrent GBM who were treated with PD1-blockers demonstrate tumor reduction in MRI scans, indicating a satisfactory therapeutic response. Immune-based therapies have been found to be efficacious in CMMRD related tumors, hence may prolong survival^{[1][10]}.

CONCLUSION

Because of its rarity and complexity, Constitutional Mismatch Repair Syndrome is often unrecognized and under diagnosed. Because these cases are rare and few have been reported, encountering a patient with this disease may pose diagnostic and therapeutic dilemmas. A high index of suspicion is needed for clinicians to be able to recognize this disease. We therefore encourage physicians who encounter pediatric patients with phenotypic features of NF1 to be more vigilant in obtaining detailed family histories of cancer or consanguinity, because early detection of the disease leads to surveillance, which can significantly alter the patient's survival.

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Subcorneal Pustular Dermatitis Type of IgA Pemphigus in a 35-Year-Old Female: A Case Report

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ABSTRACT

Introduction: IgA pemphigus is a rare, distinct variant of Pemphigus characterized by vesiculopustular eruptions mediated by IgA autoantibodies targeting keratinocyte cell surface antigens, desmogleins 1-3 and sometimes desmogleins 1 and 3. Its classical features have been described in literature but atypical cases have also been documented. This report presents such case posing a diagnostic dilemma.

Case Report: A 35-year-old female presented with a 16-year history of intermittent eruptions of multiple hyperpigmented, annular and circinate, desquamating plaques and coalescing flaccid pustules on erythematous bases on the scalp, neck, trunk, and extremities. Histopathologic examination revealed subcorneal pustular dermatitis, and direct immunofluorescence was positive for granular intercellular IgG and IgA deposits in the epidermis. Antinuclear antibody test was negative and C3 level was normal. Antibody tests against desmogleins 1 and 3 were both negative. Topical potent corticosteroid therapy resulted in complete resolution of all lesions in three weeks.

Conclusion: Diagnostic dilemmas arise when laboratory results do not correlate with clinical findings. Findings of IgA autoantibodies in patients

with pemphigus-like skin eruptions led to the diagnosis of subcorneal pustular dermatitis type of IgA pemphigus. Dapsone is the treatment of choice although topical potent corticosteroid alone may provide complete remission in some cases, avoiding the potential adverse effects of systemic therapy.

Keywords: IgA pemphigus, subcorneal pustular dermatitis, autoimmune blistering disease

Commercial funding: N/A

Conflict of interest: N/A

INTRODUCTION

IgA pemphigus is a rare, distinct variant of pemphigus with only approximately 70 cases reported until 2010.¹ It is characterized by vesiculopustular eruptions with subcorneal or intraepidermal blisters containing abundant neutrophils and evidence of IgA antibodies against keratinocyte cell surfaces. There are two types: subcorneal pustular dermatitis type and intraepidermal neutrophilic IgA dermatitis type. Clinically, it is impossible to distinguish between the two, and both histopathologic and immunofluorescence tests are necessary to ascertain the diagnosis.^{2,3}

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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The primary lesions of this disease are flaccid pustules on erythematous bases that easily rupture forming annular or circinate patterns. Frequently affected are the intertriginous areas but lesions may be generalized involving the scalp, trunk, and extremities.^{4,5} The consistent feature, however, is the absence of mucosal involvement which helps differentiate it from other blistering diseases.⁶ Histologic examination shows nonspecific subcorneal or intraepidermal pustules containing abundant neutrophils which may be found in a number of other conditions such as Sneddon-Wilkinson disease, pemphigus foliaceus, pustular psoriasis, acute generalized exanthematous pustulosis, and bullous impetigo.⁷ The diagnosis of IgA pemphigus is confirmed by performing direct immunofluorescence (DIF) test which demonstrates positive intercellular IgA deposition over the upper or whole epidermis, instead of intercellular IgG pattern seen in classic pemphigus.⁶

These classical features of IgA pemphigus are present in most reported cases, but for over 30 years now, atypical cases have also been documented.^{3,8} The following report describes one such case posing a diagnostic dilemma.

CASE REPORT

A 35-year-old female presented at the Dermatology Outpatient Department with multiple hyperpigmented, annular and circinate desquamating plaques and coalescing flaccid pustules on erythematous bases on the scalp, neck, trunk, and extremities of ten-days-duration. She has had multiple recurrences of similar lesions over the past 16 years. Lesions would start as multiple erythematous, irregularly shaped plaques developing pustules on the scalp, spreading to the neck, trunk, upper extremities, and lower extremities. There were no associated symptoms such as pruritus and pain, and no

systemic symptoms including fever, joint pains, and photosensitivity. There was no drug intake prior to onset and no personal or family history of psoriasis, lupus, or arthritis. Previous pustular eruptions persisted for a few months and spontaneously resolved despite no physician or dermatologist consult.

Three years prior, the patient sought dermatology consult due to generalized eruption of similar lesions. Skin punch biopsy showed subcorneal pustular dermatitis. Patient was managed with clobetasol propionate ointment, petroleum jelly, and hydroxyzine with note of resolution associated with post-inflammatory pigmentary change. Patient was advised to consult as needed.

At the time of present consult, dermatologic examination showed multiple erythematous to hyperpigmented, irregularly shaped, well-defined, annular and circinate plaques, some topped with scales and some topped with coalescing flaccid pustules on the scalp, neck, trunk, and extremities (Figure 1). There were no lesions on the face, mucosal areas, palms, and soles. Nikolsky sign was negative. Hair and nail findings and general physical examination were unremarkable. The clinical impression was Sneddon-Wilkinson disease. Skin punch biopsies of a lesion and of perilesional skin were done on the left arm.



Figure 1. Multiple erythematous to hyperpigmented, irregularly shaped, well-defined, annular and circinate plaques, some topped with scales and some topped with coalescing flaccid pustules on the scalp, neck, trunk, and extremities.

Histopathologic examination showed subcorneal pustular dermatitis (Figure 2). DIF of perilesional skin revealed granular intercellular deposits of IgG, IgM and IgA in the epidermis and granular deposits of C3, IgM and IgA in the basement membrane zone (Figure 3). Complete blood count, creatinine, alanine transaminase, fasting blood sugar, glucose-6-phosphate dehydrogenase, chest x-ray, and urinalysis were all normal. Erythrocyte sedimentation rate was elevated. Antinuclear antibody (ANA) was negative and complement C3 was normal. Enzyme-linked immunosorbent assay (ELISA) for desmoglein 1 and 3 antibodies were both negative. The provisional diagnosis was Sneddon-Wilkinson disease, rule out IgA pemphigus. The patient was given clobetasol propionate ointment with petroleum jelly, oral antibiotics, tar shampoo, and cetirizine.

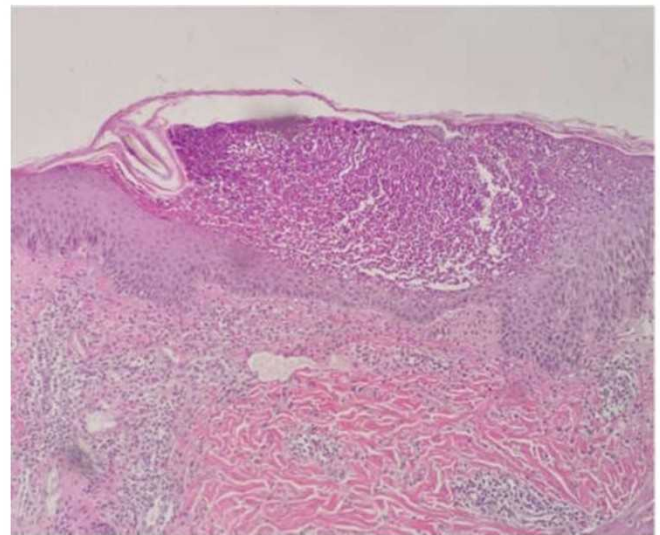


Figure 2. Subcorneal pustular dermatitis described as collections of neutrophils beneath the cornified layer and within the upper spinous cell layer. Perivascular infiltrates of lymphocytes and neutrophils are present in the papillary dermis (Hematoxylin-eosin stain, x100).

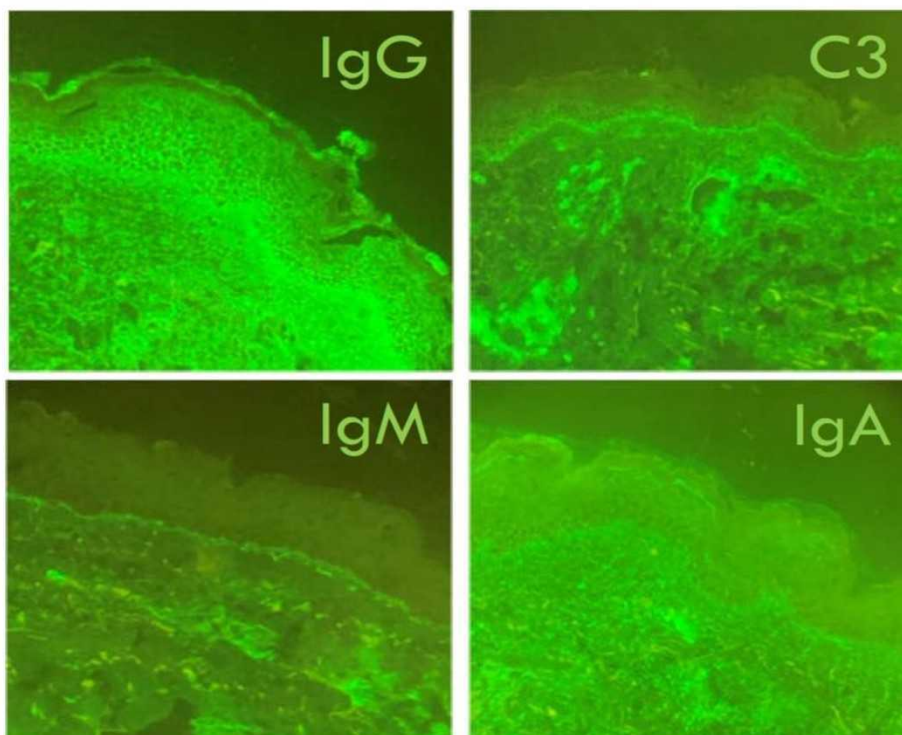


Figure 3. Granular intercellular IgG, IgM and IgA deposits in the epidermis and granular C3, IgM and IgA deposits in the basement membrane zone seen in direct immunofluorescence

After two weeks of topical steroid therapy, the patient presented with only few slightly erythematous patches and thin plaques topped with fine scaling. On the third week, lesions then healed with faintly hyperpigmented, smooth patches on the trunk and extremities (Figure 4). Topical steroid was discontinued. Until the fifth

week, no recurrence was noted. Patient was advised regular monitoring for recurrence of lesions. A summary of the relevant past medical history and series of consults of the patient at the dermatology outpatient department is provided in Table 1.



Figure 4. Few faintly hyperpigmented, smooth patches on the trunk and extremities after three weeks of topical potent corticosteroid therapy.

Table 1. Timeline of the patient's relevant past medical history and series of consults at the dermatology outpatient department (OPD).

Date	Relevant Past Medical History		
16 years prior to consult	Recurrent vesiculopustular eruptions Interventions: traditional healers, unrecalled oils, soaking in seawater, observation only Outcome: spontaneous resolution with/out intervention		
3 years prior to consult	Recurrence of vesiculopustular eruption Interventions: skin punch biopsy, clobetasol ointment, petroleum jelly, hydroxyzine Outcome: resolution of lesions		
Date	Summary of findings	Diagnostics	Management
Initial consult	Multiple erythematous to hyperpigmented, annular and circinate plaques, some topped with scales and some with coalescing flaccid pustules, (-) pruritus/pain	skin punch biopsy, CBC, creatinine, ALT, FBS, ESR	Clobetasol ointment + petroleum jelly Oral antibiotics
1 week after	Few slightly erythematous patches and thin plaques topped with fine scaling Histology: subcorneal pustular dermatitis Normal lab results except ↑ ESR	G6PD	Clobetasol ointment + petroleum jelly Tar shampoo Cetirizine
3 weeks after	Faintly hyperpigmented, smooth patches DIF: (+) epidermal intercellular IgG, IgM, IgA; (+) granular C3, IgM, IgA in BMZ G6PD: not done	G6PD, CXR, urinalysis, ANA, C3, Dsg 1 and 3 ELISA	Emollient
5 weeks after	No recurrence of lesions Normal and negative lab results	None	Advised regular monitoring

CBC = complete blood count; ALT = alanine aminotransferase; FBS = fasting blood sugar; ESR = erythrocyte sedimentation rate; G6PD = glucose-6-phosphate dehydrogenase; DIF = direct immunofluorescence; BMZ = basement membrane zone; CXR = chest x-ray; ANA = antinuclear antibody; Dsg = desmoglein; ELISA = enzyme-linked immunosorbent assay.

DISCUSSION

Based on the clinical history and presentation of the patient at the time of consult, the primary consideration was Sneddon-Wilkinson disease versus subcorneal pustular dermatosis (SPD) type of IgA pemphigus. Both disorders manifest flaccid pustules that coalesce into annular or circinate patterns and desquamating plaques that form from ruptured pustules. The mucous membranes are not affected and systemic symptoms are usually absent,^{6,7,9} as in the patient's case. Meanwhile, the histopathology showing a subcorneal neutrophilic infiltrate and perivascular mixed infiltrates is also compatible with these two conditions. However, as these are nonspecific findings, DIF is essential to establish the diagnosis.

In classic SPD or Sneddon-Wilkinson disease, DIF is negative. In contrast, DIF of IgA pemphigus shows intercellular IgA deposition in the epidermis.^{6,7,10}

DIF of the patient's perilesional skin revealed both intercellular IgG and IgA deposits in the epidermis, with weaker IgA staining compared to IgG. The intercellular IgG pattern is consistent with the pemphigus group of diseases, which includes pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, pemphigus erythematosus, and drug-induced pemphigus.¹¹⁻¹³ Intercellular IgA deposits may be also seen but only as secondary deposits. In IgA pemphigus, typical cases show exclusive IgA

deposition in the epidermis. IgG or C3 may also sometimes be deposited but with weaker staining than IgA.^{3,14} Meanwhile, multiple granular deposits in the basement membrane zone is suggestive of lupus erythematosus (LE) or pemphigus erythematosus.^{11,12} Antibody ELISA for both desmogleins 1 and 3, however, turned out negative, ruling out the classic pemphigus disorders mentioned above. The absence of symptoms and signs of LE, negative ANA, normal C3, and other normal laboratory findings also make the diagnosis of LE or pemphigus erythematosus unlikely.

There are reports of atypical cases of pemphigus with presence of both intercellular IgA and IgG deposits in the epidermis. Some have classified them as IgG/IgA pemphigus, although there is no consensus yet on whether this is a variant of IgA pemphigus or a unique form of pemphigus.^{8,15} On the other hand, IgA pemphigus is considered to be a distinct clinical entity that includes two subtypes, namely subcorneal pustular dermatosis and intraepidermal neutrophilic dermatosis (IEN).¹⁶ Histologically, SPD type shows subcorneal neutrophilic infiltrates while IEN type shows neutrophils mainly in the lower epidermis or throughout the epidermis. Another difference between the two is that the target autoantigen of SPD type is desmocollin 1; while for IEN type, the exact autoantigen is still unknown, but with desmogleins 1 and 3 demonstrated in a few reports.^{2,17} Therefore, for cases of IgA pemphigus, antibody testing for desmocollin should be performed aside from desmoglein antibody tests to elucidate the unique feature of the disease and strengthen the diagnosis. This is ideal but unfortunately, the test is not available in the local setting.

Desmocollin and desmoglein are major desmosomal glycoproteins that belong to the cadherin superfamily of cell adhesion molecules.

They constitute the adhesive core of desmosomes which facilitate adhesion between keratinocyte cell surfaces.^{6,16} In autoimmune blistering disorders of the pemphigus group, autoantibodies preferentially target specific isoforms of these desmosomal proteins. For instance, in pemphigus vulgaris, IgG autoantibodies against desmoglein 3 are present whereas pemphigus foliaceus is characterized by IgG autoantibodies against desmoglein 1.^{18,19} Binding of autoantibodies to their target antigens induces loss of epidermal adhesion, leading to blister formation.^{2,18} In SPD type of IgA pemphigus, antibodies to desmocollin are found instead of antibodies to desmoglein. Desmocollin has three isoforms, desmocollins 1-3, which are expressed in a differentiation-specific manner: desmocollin 1 shows strong expression in the upper spinous layers; desmocollin 2 shows similar expression to desmocollin 1 but is most strongly expressed at the base of the rete ridges; and desmocollin 3 is most strongly expressed in the basal layers.¹⁶ As previously mentioned, desmocollin 1 is the autoantigen of SPD type of IgA pemphigus, which results in the subcorneal blistering and concentration of IgA deposits in the upper epidermis found in histopathology and DIF, respectively.² In the case of the patient, subcorneal pustule formation but with intercellular deposits of IgA throughout the epidermis may be due to the presence of autoantibodies to all three types of desmocollin and not just to desmocollin 1.¹⁶ However, this hypothesis could only be confirmed once testing for these antibodies is done.

Diagnostic dilemmas arise when laboratory results do not correlate with clinical findings. However, considering the clinical presentation of the patient, all the diagnostic and laboratory test results available, and the relatively benign course of the lesions, a diagnosis of SPD type of IgA pemphigus was made.

Unlike classic pemphigus, IgA pemphigus has a milder, limiting clinical course, although it is known to be recurrent and associated with diseases such as monoclonal IgA gammopathy, rheumatoid arthritis, and Sjögren syndrome.^{2,6} With timely and appropriate treatment, IgA pemphigus heals without scarring.

Although dapsone is the treatment of choice,^{2,20} in the patient's case, the current lesions, as well as previous lesions three years ago, successfully resolved with topical corticosteroid alone. One case report cited that the use of topical corticosteroids in a patient with IgA pemphigus provided only slight improvement, and dapsone had to be started to achieve complete remission.¹⁷ If the patient's lesions did not demonstrate a good response to the initial treatment, dapsone may be given at a dose of 50–200 mg daily. Once the disease has been controlled, it is then tapered to the minimum effective dose and usually continued long-term to avoid recurrence.^{7–9} Fortunately, the patient did not require dapsone; hence, potential adverse effects of this drug such as hemolysis and methemoglobinemia were avoided.^{6,10} Few reports also mentioned the use of oral corticosteroids, colchicine, systemic retinoids, adalimumab, mycophenolate mofetil, PUVA, and a combination of these for IgA pemphigus.^{6,21}

In conclusion, IgA pemphigus is a rare, autoimmune blistering disease with epidermal intercellular IgA deposition seen in DIF. Atypical cases with both IgG and IgA antibodies against keratinocyte cell surfaces are more rare, that for over 30 years now, there is still no consensus on how these should be classified. When diagnostic test results are not clear-cut, correlation of the clinical with the laboratory findings is done to commit to a diagnosis and plan the appropriate management of patients. Dapsone is the treatment of choice for IgA

pemphigus, but topical potent corticosteroid alone may also be effective in some cases, thereby avoiding the potential adverse effects of this systemic drug.

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High Grade Spindle Cell Carcinoma of the Ovary Arising in an Endometrioid Cystadenoma: A Case Report*

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ABSTRACT

Spindle Cell Carcinoma of the Ovary is a rare form of cancer with controversial histogenesis. It shares the histologic, cytologic, and molecular properties of both epithelial and mesenchymal differentiation of ovarian neoplasms, which makes diagnosis very challenging among pathologists. Endometrioid cystadenoma is a benign ovarian neoplasms classified under epithelial ovarian tumors. Malignant transformation of benign ovarian neoplasms is known as a rare complication, occurring in approximately 0.9% of patients with ovarian endometriosis. Clear cell adenocarcinoma is the most common endometriosis-associated ovarian cancer followed by endometrioid cancer. This is the case of a 56-year old post-menopausal patient initially presenting with increasing abdominal girth. Whole abdominal ultrasound revealed a large pelvo-abdominal mass. Transvaginal and transabdominal ultrasound findings of bilateral ovarian new growth with benign sonologic features. The patient underwent bilateral salpingo-oophorectomy. Histopathologic findings of the specimen submitted revealed high-grade spindle cell carcinoma arising in an endometrioid cystadenoma of the right ovary, and endometrioid cystadenofibroma with focal epithelial proliferation.

Keywords: ovarian spindle cell carcinoma, sarcomatoid carcinoma, malignant transformation

INTRODUCTION

Ovarian cancer is the second most common malignancy of the lower part of the female genital tract. It is the 10th most common cancer in the Philippines, with the Philippines ranking 16th among the top 25 countries with the highest rates of ovarian cancer. It is considered to be the most common cause of death from gynecologic neoplasm in the United States. It can be classified depending on its specific histologic characteristics.

Endometrioid cystadenoma is a benign ovarian epithelial neoplasm. These are tumors that consist of epithelial cells resembling those of the endometrium, that develop in relation to endometriosis. Endometriosis is a benign condition described with the presence of functioning endometrial glands and stroma outside the uterus, most commonly in the pelvic peritoneum and ovaries. Endometriosis in the ovary, or endometrioma, is known to have an increased risk for developing endometriosis-associated ovarian cancer. Malignant transformation is known as a rare complication occurring in approximately 0.9% of patients with ovarian endometriosis. Clear

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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ovarian endometriosis. Clear cell adenocarcinoma is the most common endometriosis-associated ovarian cancer followed by endometrioid cancer. Further investigation is warranted to understand the mechanisms involved in malignant transformations.

Spindle Cell Carcinoma, also known as Sarcomatoid Carcinoma, is a rare form of cancer with controversial histogenesis. It is a spindle cell neoplasm that simulates a sarcoma and demonstrates epithelial differentiation in both immunohistochemistry and electron microscopy. It shares histologic, cytologic, and molecular properties of both epithelial and mesenchymal differentiation of ovarian neoplasms. It is one of the three subtypes of ovarian anaplastic carcinoma, which is an exceedingly rare ovarian neoplasm. Most cases have unfavorable diagnosis. According to literature, it comprises 3% of all cases of Squamous Cell Carcinoma.

OBJECTIVES

Main Objective

To report on the presentation and diagnosis of a rare case of spindle carcinoma of the ovary arising in an endometrioid cystadenoma

Specific Objectives:

1. To report the clinical presentation of a patient with increasing abdominal girth
2. To present the operative diagnosis of malignancy of an ovarian mass with benign sonologic features
3. To describe the histologic diagnosis of malignancy arising in a benign ovarian pathology
4. To describe the role of immunohistochemical staining in obtaining a definitive tissue diagnosis

5. To present the progressively deteriorating course of spindle cell carcinoma

CASE REPORT

This is the case of a 56 y/o post-menopausal patient with a chief complaint of increasing abdominal girth.

History started three months prior to admission when she noted a hypogastric mass, described to be firm and non-tender, accompanied by early satiety. There were no accompanying symptoms of nausea, vomiting, stool changes, or weight loss. No initial consultation was done. Interval history revealed progressive enlargement of the hypogastric mass, persistence of early satiety, and increasing abdominal girth.

Two months prior to admission, the persistence of symptoms prompted consultation with an internist. Whole abdominal ultrasound revealed a huge unilocular pelvoabdominal mass, well-circumscribed, unilocular, measuring 22.62 x 22.67 x 14.52 cm, probably gynecologic in origin. The patient was subsequently advised gynecologic consult prompting consultation at our service. On pelvic examination, the cervix was firm, smooth, closed. The uterus and adnexa was difficult to assess due to abdominal distention. Rectal examination revealed no palpable pole of mass. Transvaginal ultrasound revealed myoma uteri and bilateral ovarian new growth, the right mass measured 21.75 x 21.47 x 14.67 cm, described as unilocular, with medium level echoes, no color on Doppler flow (color score of 1), benign by IOTA simple rules, (Figure 1), and ovarian new growth, left, measuring 6.72 x 6.24 x 5.21 cm, unilocular, with low level echoes, with solid component measuring 3.05 x 2.86 x 3.14 cm, with color score of 2, 96.7% benign by IOTA ADNEX model (Figure 2). CA-125 was elevated at 118 U/mL.

The patient has no known medical comorbidities. There is no family history of malignancy. She is a non-smoker and not an alcoholic beverage drinker. She is regularly menstruating, with complaints of dysmenorrhea on days 1–2 of menses. She is a nulligravid.

The patient was then advised total abdominal hysterectomy with bilateral salpingo-oophorectomy. Intraoperatively, approximately 2 liters of ascitic fluid was drained. The right ovary was cystically enlarged to 20 x 20 cm, highly vascularized, with a point of rupture revealing greenish serous fluid (Figure 3). The left ovary was enlarged to 7 x 5 cm with smooth external surface (Figure 4). The uterus was not enlarged. The appendix was densely adherent to the right ovary. There were dense bowel adhesions posteriorly. Adhesiolysis was attempted by General Surgery but there was no plane of dissection from the adherent bowels were appreciated. Hence, the surgical team did not proceed with performing hysterectomy and the procedure was limited to peritoneal fluid cytology, enterolysis, appendectomy, bilateral salpingo-oophorectomy. The patient tolerated the procedure well and no post-operative complications were noted.

Histopathologic study of the specimens submitted revealed *Endometrioid Cystadenofibroma with Focal Proliferation, Left Ovary* and *Poorly Differentiated Carcinoma, Right Ovary*. Microsections of the right ovarian tumor showed glandular cells of epithelial origin, resembling the endometrium, with cystic structures seen. There are fragments of ovarian tissue infiltrated by cohesive group of spindle-shaped neoplastic cells seen mostly in sheets on a background of extensive necrosis and hemorrhage. The individual neoplastic cells resemble a spindle pattern, containing enlarged, pleomorphic, vesicular to hyperchromic nuclei, with prominent nucleoli exhibiting irregular contour with several

mitotic figures (Figure 5). Additional immunostaining revealed diffusely positive in the neoplastic cells of interest with Vimentin and Pancytokeratin, positive in some atypical cells of interest with Calretinin, and negative expression in the cells of interest with Inhibin, suggesting a combination of mesenchymal and epithelial tumor. The right ovary was then signed out as *High-Grade Spindle Cell Carcinoma arising in an Endometrioid Cystadenoma*.

The patient was subsequently discharged on the 7th hospital day. She was advised to undergo chemotherapy three to four weeks after discharge. However, during the interim, patient developed poor appetite, hematochezia, and generalized weakness. This prompted readmission at our institution. Routine RT-PCR revealed COVID-19 infection. Patient was managed medically by the service of Gastroenterology. However, persistence of gastrointestinal bleeding lead to severe anemia and hypovolemic shock. The patient's condition progressively deteriorated and she ultimately expired at the 40th post-operative day due to hypovolemic shock secondary to the gastrointestinal bleeding.

CASE DISCUSSION

Spindle cell carcinomas, also known as sarcomatoid carcinomas, are rare malignancies that have been reported in many organs such as the breast, urinary bladder, kidneys, and lungs.¹ It comprises of up to 3% of all cases of squamous cell carcinoma.²

In the ovaries, it is one of the subtypes of ovarian anaplastic carcinomas.³ Histologically, it simulates a sarcoma and presents epithelial differentiation in both immunohistochemistry and electron microscopy.² It is characterized by a morphologically biphasic tumor showing a carcinoma with surface epithelial change ranging from dysplasia to invasive carcinoma, and

underlying sarcomatoid proliferation. This makes its diagnosis challenging for pathologists. However, immunohistochemical staining aids in its diagnosis. The co-expression of cytokeratin and vimentin suggests epithelial origin. Metaplasia of squamous cells or multidirectional differentiation of carcinoma cells are indicative of spindle cell transformation.

Endometrioid cystadenoma is a benign ovarian epithelial neoplasm. These are tumors that consist of epithelial cells resembling those of the endometrium.

Endometriosis is a benign condition described with the presence of functioning endometrial glands and stroma outside the uterus, most commonly in the pelvic peritoneum and ovaries. It has been proven to be estrogen-dependent in the reproductive age women. In the ovaries, it is known to have an increased risk for developing endometriosis-associated ovarian cancer. Malignant transformation is known as a rare complication occurring in approximately 0.9% of patients with ovarian endometriosis.⁵ This malignant transformation begins with the development of atypical endometriosis and its subsequent progression to endometriosis-associated ovarian cancer.³ According to one study, the risk factors for malignant transformation include older age (>45 years) and large tumor size (>7 cm).⁵

Endometriosis-associated Ovarian Cancer (EOAC) is thought to develop from ovarian endometrial cysts.⁶ Clear cell adenocarcinoma is the most common endometriosis-associated ovarian cancer followed by endometrioid cancer.⁷ The clinical presentation may not be indicative of a malignancy. Hence, the diagnosis of an Endometriosis-Associated Ovarian Cancer is often done post-operatively with histopathologic findings. However, it is difficult to ascertain the

probability of ovarian cancer being diagnosed in surgical specimens of endometrial cysts. A retrospective single-center study in Taiwan included 7629 surgeries performed following preoperative diagnosis of endometrial cyst and 0.14% (11 cases) were diagnosed with ovarian cancer postoperatively.⁸ Another study in the Taiwan National Health Insurance Research Database showed that among patients diagnosed with endometriosis who underwent surgery from 2000 to 2010, ovarian cancer occurred in 39/5945 cases.⁹ The World Endometriosis Society however stated that the relative and absolute risk of ovarian cancer in women with endometriosis is very low and routine screening for ovarian cancer was not recommended.¹⁰

Clinically, patients may present with abdominal pain, abdominal enlargement, ascites, palpable abdominal mass, or constitutional symptoms of anorexia and weight loss.^{1,11,12} Likewise, some patients may be asymptomatic.² At present, there are no validated clinical or radiological criteria that can be utilized to distinguish benign from malignant tumors.¹³ As such, in malignant cases, the patients are usually diagnosed at an advanced stage.

The management and prognosis of spindle cell carcinoma is not yet well established. Prognosis is seemingly highly dependent on tumor location, depth of invasion, and timing of surgical intervention, but is independent of occurrence of spindle cell transformation.¹² In many organs such as the kidney, the breast, and urinary bladder, the prognosis is poor. There is an ongoing debate on the best management practices for this disease entity. Several case reports on its occurrence in the ovary present good prognosis upon surgical management while some reports also presented unfavorable prognosis despite complete surgery and chemotherapy.^{1,2,11} The role of radiotherapy remains unclear.² The benefits of early diagnosis

and intervention cannot be more emphasized for a better prognosis.²

SUMMARY

Spindle cell carcinoma is a rare type of soft tissue carcinoma. In the ovaries, its incidence is even more rare with less than 10 cases reported in the English medical literature. Hence, diagnosis and management of such cases pose a challenge among pathologists and clinicians. Its pathophysiology is not well understood. One possible mechanism of its development is malignant transformation of a benign ovarian neoplasm. Recognizing the imaging characteristics of such transformations can aid in the diagnosis of rare neoplasms and it is important to recognize radiological mimics of malignant transformation. Unfortunately, current imaging criteria for distinguishing these malignant transformations from their benign counterparts remain largely ill-defined and poorly validated. Likewise, sonologic description may differ from gross findings intraoperatively, and morphologic findings histologically. With the lack of validated guidelines in the management of such cases, prognosis may vary significantly and depend highly on tumor size, location, and involvement of other organs.

CONCLUSION

Endometriosis-associated Ovarian Cancer (EOAC) is thought to develop from ovarian endometrial cysts. The possibility of malignant transformation should always be considered in cases of benign ovarian neoplasms regardless of patient demographics and sonologic description of the tumor. The relative and absolute risk of ovarian cancer in women with endometriosis is very low and routine screening for ovarian cancer is currently not recommended. The importance of timely surgical intervention cannot be overemphasized. However, obtaining a complete histologic diagnosis may be delayed in cases of

rare ovarian neoplasms such as in our patient. In cases of rare ovarian neoplasms, utilization of immunohistochemical staining may aid in obtaining a definitive diagnosis.

Spindle cell carcinoma of the ovary is a rare type of carcinoma. Due to its rare occurrence, there are no standard guidelines or recommendations yet on the management of such cases. A review of available literature suggests beneficial role of surgical intervention. However, prognosis is variable and highly dependent on several factors including tumor location, invasion, and metastasis.

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APPENDICES

Figure 1: Sonographic images of the right ovarian new growth

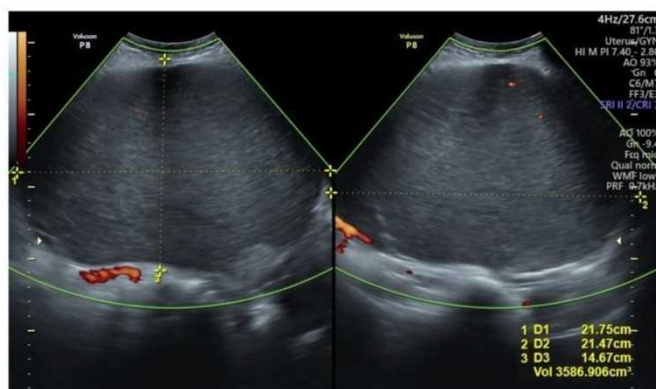


Figure 2: Sonographic images of the left ovarian new growth



Figure 3: Right Ovary

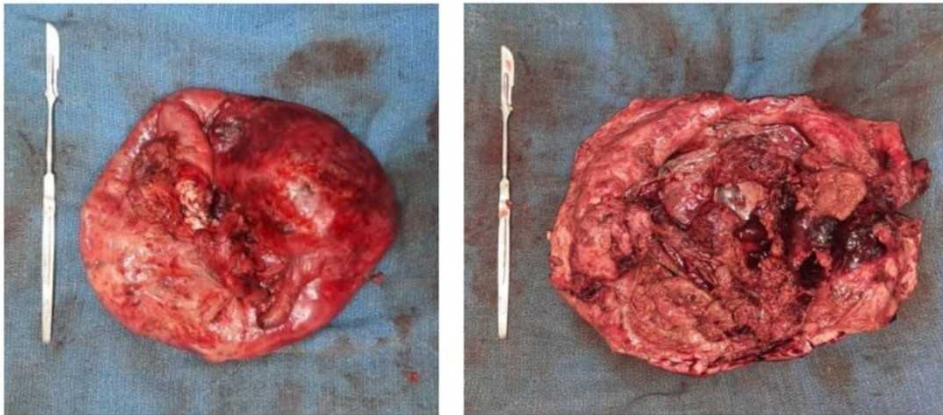


Figure 4: Left Ovary

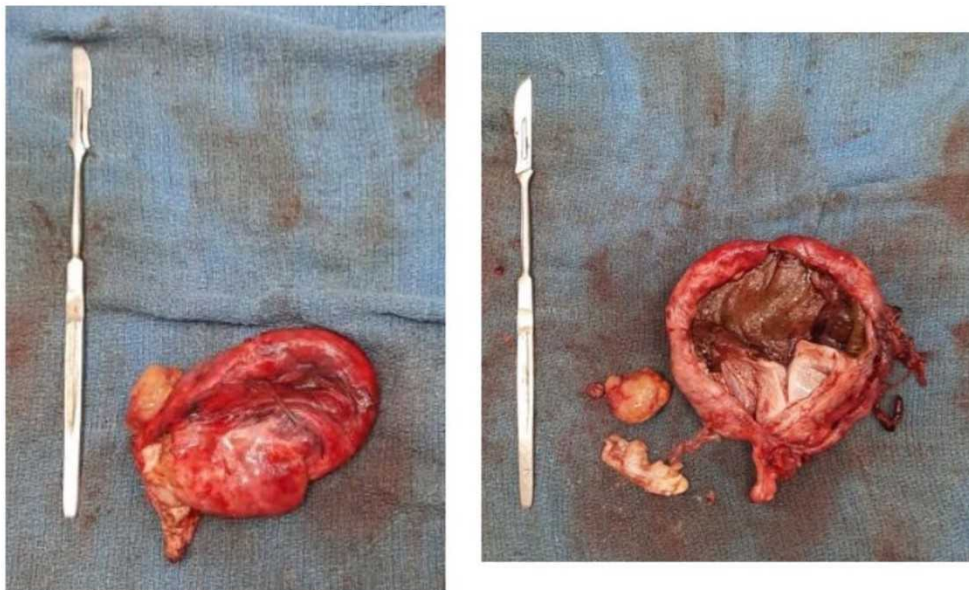
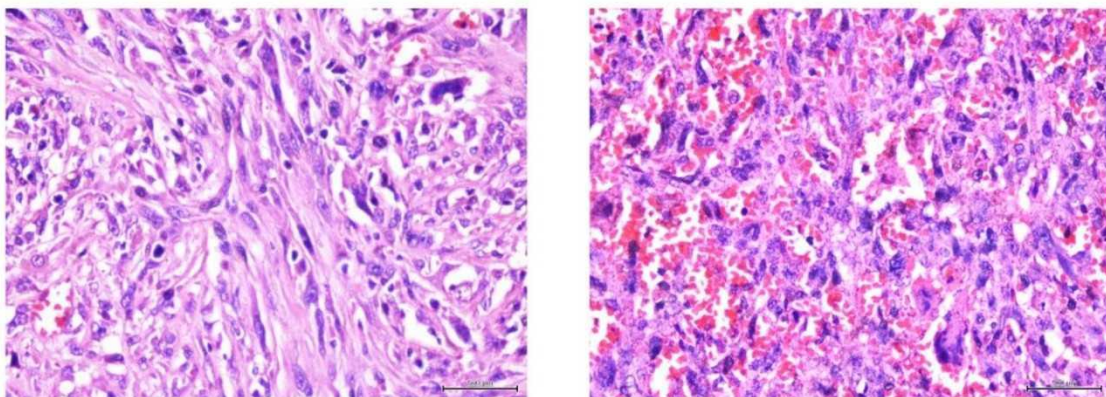


Figure 5: Microsections – Right Ovary



Intraperitoneal Migration of Lippes Loop (Intrauterine Device): A Case Report*

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ABSTRACT

Intrauterine device use as contraception offers the benefits of being affordable, long-acting, highly effective, and reversible. However, like any foreign body, it can be prone to certain complications, at times, with very serious consequences. Migration is the rarest but most feared complication. This is a report of the case of 72-year old woman with a nine-month history of right lower quadrant abdominal pain. Work ups pointed to a migrated intrauterine device. The patient subsequently underwent laparoscopic removal of the foreign body with omental biopsy which later revealed metastatic adenocarcinoma from a primary ovarian malignancy.

INTRODUCTION

Intrauterine Device Insertion the most common contraceptive method used worldwide. In 2019, 23.7 percent of women have been labelled as currently using contraception, that is, 219 million women rely on female sterilisation. Three other methods have more than 100 million users worldwide, male condom (189 million), IUD (159 million) and the pill (151 million). Specific contraceptive methods vary widely across the world. Method mix has shifted over time due to changes in related policies, changes in health-care system, development of new technologies, and changes in access to the various methods.¹

The first Lippes Loop intrauterine device (IUD) was introduced in 1962. It was a plastic double "S" loop, a trapezoid shaped IUD that closely fit around the contours of the uterine cavity, reducing the incidence of expulsion. This IUD was commonly used from the 1960's to the 1980's. Some authors state that the IUD can be left in the uterine cavity for an indefinite amount of time. Prolonged use of this device was common, however, it was associated with some complications like uterine bleeding during post-menopausal period and inflammatory pelvic diseases.¹¹

Perforation is exceptional but one of the most serious complications. Indeed, after a perforation, the IUD can be localized in various neighboring organs. Ectopic localization in the pouch of Douglas, omentum, mesentery, colon and bladder have been described.¹¹ We report a new case of intraperitoneal IUD migration, diagnosed forty six (46) years after its insertion. Laparoscopic surgery was performed to remove the IUD, which was wrapped by omentum at the right lower quadrant of the abdomen.

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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DISCUSSION

A 72 year old G2P2 (2002) presented with colicky right lower quadrant pain radiating to right thigh for nine (9) months. There were no reported fever, anorexia, nausea and vomiting and dysuria. She reported no irregularities in bowel movement. Consultation was done with a General Practitioner who requested complete blood count (CBC) and urinalysis which revealed unremarkable results. She was advised to apply warm compress and take paracetamol tablet as needed for pain. During the interim, the patient noted recurrence of the pain of the same character but decreased in severity. She was then advised to undergo whole abdominal ultrasound, again with unremarkable results. However, pelvic X-ray revealed a radio-opaque foreign body at the right lower quadrant of the abdomen (Fig 1). As the patient recalled, she had an Intrauterine Device inserted way back in 1976 but didn't have any follow up check-up. Also, she had two (2) pregnancies which were both carried to term, all delivered via spontaneous delivery with no fetomaternal complications. The first, was in 1975, a year prior to insertion of Intra Uterine Device (IUD) and then in 1983, seven (7) years after insertion of the IUD.

The patient was then advised to observe with serial x-ray monitoring every 3-6 months to monitor the location of the Intrauterine Device (IUD). Five (5) months prior to admission, patient noted recurrence of abdominal pain of the same character. She underwent Triple Phase Whole Abdominal CT Scan with findings of a spiral shaped metallic density which may represent a migrated Intrauterine Device (IUD) (Fig 2). She was advised surgery to remove the IUD. The surgery involving laparoscopy happened 5 months later. Patient tolerated the procedure and was subsequently discharged. However, histopathology report of omental biopsy is consistent with round cell neoplasm. The patient was advised for readmission last August 2022 for further work up. While

admitted, she was referred to Gynecology Oncology service wherein a Transvaginal ultrasound was done which revealed multilocular solid mass in the right adnexa measuring 8 x 7 cms. Positron Emission Tomography/Computed Tomography (PET/CT) was also done with findings of complex cystic and solid mass in the pelvic region which measures 7.7 x 8.3 x 8.7 cms. Tumor marker such as Carcinoembryonic antigen (CEA), CA 125, Alpha Feto Protein (AFP) and CA19-9 are all within normal limits. Patient subsequently underwent exploratory laparotomy and resection of ovarian malignancy with Total abdominal hysterectomy bilateral salphingo-oophorectomy and infracolic omentectomy with post operative diagnosis of Ovarian New Growth, right, malignant, stage IIIC. In addition, histopathology revealed high grade serous carcinoma of the ovary and the omental biopsy done last May 2022 was amended and now with findings consistent with metastatic adenocarcinoma with female genital tract as primary. Patient was subsequently discharged and successfully completed chemotherapy. Patient was subsequently discharged and underwent chemotherapy with Paclitaxel Carboplatin and Bevacizumab from October 2022 to February 2023. A repeat PET CT Scan was done last March 15, 2023 which revealed no evidence of local tumor recurrence and nodal or distant metastasis and resolution pelvic mass and omental node. Tumor markers were also repeated which revealed CEA at 2.03 ng/ml and CA 125 at 6.5 U/ml both were in normal limits.

DISCUSSION

The intrauterine device (IUD) is one of the most widely used methods of long-term reversible contraception in the world^{iv}. Bioactive, copper, copper-silver, or progestin IUDs are the most commonly used because of their better tolerability, but like any foreign body, the IUD can present risks and complications. These include not only abdominal or pelvic pain, abnormal bleeding,

dysmenorrhea, unplanned pregnancy, and spontaneous abortion, especially in the first few months after insertion, but also expulsion, the incidence of which can be as high as 25%, infection, and migration after uterine perforation, which remains rare.^v

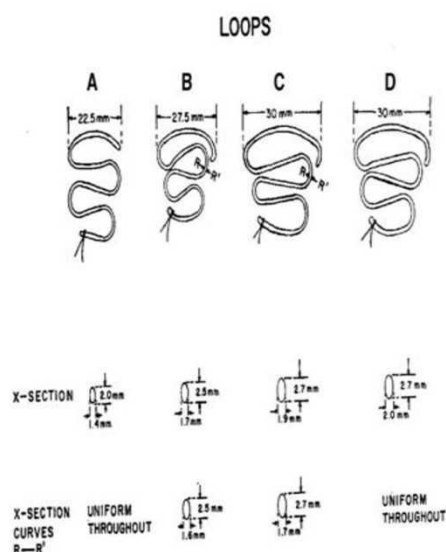


Diagram of the currently available sizes of loops showing differences in over-all dimensions, as well as cross section diameters.
Lippes. The making of the first loop. *Am J Obstet Gynecol* 2018.

A Lippes Loop was inserted in our patient in the late 1975 to early 1976. The double "S" was designed to reduce expulsions and, simultaneously, to accommodate the IUD to the triangular, or some might say trapezoidal, shape of the uterine cavity. The advent of thermoplastics permitted the development of new IUDs. With linear geometric configuration, devices constructed of the right plastic could be straightened to fit into a hollow tube, ejected from the tube and resume the shape in which it was molded. This characteristic of memory for low-density PE was excellent. Measurements of the uterine cavity dictated the dimensions of the loop. Since the internal os of the cervix is 4 mm, the outside diameter (o.d.) of the inserter is also 4 mm. The inside diameter (i.d.) of the inserter barrel is 3.4 mm. For the loop to fit into

the barrel of the inserter, its cross-sectional diameter had to be even smaller. In cross-section, loop D is 2.7 by 2.0 mm, while loop A is 2.4 by 2.0 mm. According to Dickinson, the inside diameter of the uterine fundus varies between 25 and 35 mm while the inside diameter of the lower uterine segment is approximately 6 mm. A double S or loop shape had to be confined with this trapezoid^{vi}

Migration into the surrounding organs is a rare but serious complication after perforation.^{vii} This migration can take several directions; it usually occurs in the peritoneal cavity and rarely in the surrounding pelvic organs, mainly the bladder, rectosigmoid, omentum, peritoneum, bladder, appendix, small intestine, adnexa, and iliac vein^{viii}. Perforation can be primary and occur during insertion, which is usually associated with severe abdominal pain^{ix}. While secondary perforation is a late event, supposedly due to progressive pressure and necrosis of the uterine wall^x.

The exact mechanism by which IUD perforations occur is unclear and various etiologic theories exist. It may occur at the time of insertion (may be from sound dilatation), and the device is released beyond the serosa. Finally, embedment may occur at the time of insertion, which predisposes to trans-mural migration and ultimate perforation^{xi}.

An IUD can penetrate and subsequently perforate the uterine wall. The rate of perforation varies from 0.1 to 3.0 per 1000 applications depending on applicant experience, and is between two and ten times higher for postpartum insertions because of the softening of the uterus. In our case, patient reported had IUD insertion late 1975 to early 1976 few months after giving her first birth on October 1975. We can only assume that IUD migrated from year 1976 to 1982 since she already had her 2nd pregnancy in 1983. Also, 1970s was the year when Philippine Government instituted a

national family planning program to reduce the birth rate. The experience of the Physician inserting the IUD could also be a factor in such cases.

Additionally, it is believed that perforation can occur after insertion. A partial perforation during insertion (i.e. part of the IUD becomes embedded in the cervix or the uterine wall) can eventually lead to a complete migration of the device following repeated uterine contractions. Depending on the location, serious complications (e.g. bladder and bowel damage or peritonitis) occur in about 15% of cases of IUD perforations. Therefore, many clinicians prefer to remove the IUD even if the patients are asymptomatic.^{xii}

Symptomatology varies depending on the site of migration and the type of IUD. In our case, the patient presented with recurrent abdominal pain for almost 9 months. In the literature, 85% of reported cases of perforation were asymptomatic at the time of diagnosis^{xiii}. However, in some cases, the diagnosis may be made by the appearance of clinical signs such as fever, abdominal pain, diarrhea or urinary tract infection, or even serious complications such as occlusive syndrome or peritonitis due to perforation of a hollow organ.

The clinical diagnosis is not always obvious, and further investigations are necessary to locate the device. Imaging has a great advantage in the topographic diagnosis of a migrated IUD. Abdominopelvic ultrasound is then indicated as the first choice. It shows an empty uterine cavity or a parauterine IUD. If the IUD is not seen by ultrasound, a computed tomography (CT) or magnetic resonance imaging (MRI) scan.^{xiv}

The World Health Organization recommends surgical removal of the migrated IUD as soon as possible, even in asymptomatic patients. The recommendation is to use minimally invasive methods if possible, including hysteroscopy, cystoscopy, colonoscopy, or laparoscopy, depending on the location of the IUD. If it is embedded in an organ such as the bladder or bowel, invasive removal is not recommended, but rather an exploratory laparotomy. Similarly, if the device is buried near a blood vessel or is not fully visualized, more invasive methods are recommended by an experienced surgeon.^{xv} Patient underwent laparoscopic removal of intrauterine device and omental biopsy last May 2022. It was also noted during the operation multiple peritoneal implants along the omentum and anterior abdominal wall, hence the decision to do a biopsy (Fig 4)

ILLUSTRATIONS



Fig 1. Pelvic Xray showing a radio opaque foreign body



Fig 2.Triphasic Whole Abdominal CT Scan: A spiral-shaped metallic density is seen in the right lower quadrant of the abdomen anterior to the proximal ascending colon.



Fig 3. 3D reconstructed view of the spiral-shaped metallic density at Right Lower Quadant of the abdomen



Fig 4. Intraoperative view of laparoscopic removal of Intrauterine Device. Lippes Loop can be viewed after careful mobilization of the omentum. The foreign body was safely removed and delivered via umbilical port.

CONCLUSION

The diagnosis of a migrated IUD should be based on a thorough gynecologic and surgical evaluation and appropriate radiologic imaging. Surgical removal is a first-line option via laparoscopy or hysteroscopy can be utilized to avoid serious complications. Encountering a migrated intrauterine device (IUD) forty six (46) years after insertion, might actually be the longest documented retained IUD in the Philippines. A laparoscopic removal which lead to detection of another existing disease in a patient highlights the importance of follow up check up and history taking with complimentary role of advanced imaging which is a key component of patient assessment can enable physicians to provide high-quality and appropriate care.

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Ewing Sarcoma in Pregnancy: A Rare Case Report

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ABSTRACT

This is a case of 34-year-old female Gravida 1 Para 1 37 weeks age of gestation and has been diagnosed as a case of Extraskkeletal Ewing Sarcoma, Right Axillary Mass Grade 3 during the first trimester. Patient had received 4 cycles of Doxorubicin as part of the “Bridging Therapy” and Chemotherapeutic regimen. Chemotherapy has been pursued to this patient, initiated on the 21st week of gestation with hopes to decrease the size of the mass and alleviate the pain during the course of pregnancy. The ethical and therapeutic concerns for both the patient and the physician remains to be a challenge up to this course. A multidisciplinary approach was instigated to weigh risks versus benefit for the expecting mother and the unborn child.

Keywords: Chemotherapy, Cancer, Ewing Sarcoma, Doxorubicin, Pregnancy, Neoadjuvant

INTRODUCTION

Cancer diagnosis and treatment in pregnant women is a challenging situation. A multidisciplinary network of experts is vital to monitor both, the pregnant mother and the fetus through the diagnostic workup and the cytotoxic therapy, by considering the respective risks and benefits. Tumor entity, stage, biology and

gestational week at diagnosis determine the applicable approach. As premature delivery transpired as one of the core risk factors for unfavorable long-term effect of the progeny, it should be avoided, if reasonable from the oncological perspective.

The concurrent incidence of cancer and pregnancy is a rare occurrence and is projected for only 1 to 2 cases per 1000 pregnancies.¹ The numbers have increased in recent years because of the increase in maternal age at the time of the 1st pregnancy.

Chemotherapy during the first trimester of pregnancy is preferably avoided owing to the hazard of several congenital malformations. Conversely, the particular gestational age at which chemotherapy can be introduced safely rests unclear.

Because chemotherapy attacks rapidly multiplying cells and is plainly selective, it also puts the developing fetus at risk of teratogenic effects. Harmful dealings during the periconceptional phase may assume early embryogenesis and end in a miscarriage, though ensuing toxic coverage might hinder with the development of organs,

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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with the most critical periods being the 2nd and 8th week after conception.² There is a comprehensive consensus that chemotherapy should be given until after organogenesis is completed. But since the precise time of conception is undetermined, the crucial question of when to safely administer chemotherapy to pregnant patients to avoid congenital malformations remains an enigma.

9 months prior to consult, patient was noted to have developed a 3 centimeter sized hematoma associated with swelling and palpable mass formation on the right axilla which was tender and warm on palpation after a bicycle accident. A few weeks later, the said hematoma and swelling eventually subsided, however the mass persisted and noted to be increasing in size with noted limitations with range of motion. No numbness, no skin changes, no weight loss, no pins and needles sensation noted. Patient sought consult with a General Physician and was advised to undergo Ultrasound of the Right axilla revealing a well defined, lobular, homogenous, hypoechoic avascular solid mass measuring 5.4 x 6.0 x 4.0 centimeters. Patient underwent Axillary lymphadenectomy as advised by Surgery with additional tests for Immunohistochemical stains due to suspicions of lymphoma. The findings yielded a Fibrocollagenous to Fibroadipose tissues with CD99 Positive Round Cell Malignancy. At this juncture, patient was also noted to be on the first trimester of her first pregnancy specifically at 9 weeks AOG based on Ultrasound. Closer monitoring and surveillance was observed with this patient during the course of the first trimester of pregnancy with aims to treat the said malignancy at a later period.

An MRI of the breast and chest was performed because of the growing size of the said right axillary mass which revealed BIRADS 4: Suspicious for malignancy. Review of slides were then reconducted as recommended which

reviewed Extraskkeletal Ewing Sarcoma FNCLCC Grade 3. The Right axillary lymph node was noted to be negative for metastases.

However, during the interim, patient was noted to have worsening of symptoms such as increased intensity of pain with pins and needles sensation and limitations on ranges of motion. Patient was then referred to a Pain Specialist and was prescribed with Morphine 10mg tab every 12 hours which would provided minimal to no relief.

In line with the persistence of the above mentioned signs and symptoms, patient was then advised to proceed with the planned Chemotherapy even at 21 weeks Age of gestation. Patient was then referred to a Perinatologist and advised to proceed with Chemotherapy after the 24th week of gestation (Age of viability).

A multi disciplinary conference was conducted and a consensus decision was made to begin the Chemotherapy regimen at an earlier week of gestation.

DISCUSSION

Ewing sarcoma (ES) is a rare malignancy that most frequently presents as an undifferentiated primary bone tumor; less commonly, it arises in soft tissue (Extraosseous Ewing Sarcoma). It is an ultra-orphan disease (2/1,000,000/year) which requires a multimodal therapy approach in high-volume centers.

A minority of ES arise in soft tissue. Patients with EES are more often older, likely to be female and arise more often within the axial rather than the appendicular skeleton

Ewing's sarcoma is a highly malignant bone tumor that rapidly metastasizes at an early stage. These tumors have rapid growth and recurrent distant metastasis and individuals present with

chief complaint of persistent pain. Treatment selections include radiation, chemotherapy, and surgery. The combination of chemotherapy with both surgery and radiotherapy increases the survival rate as compared to chemotherapy alone. Prognosis has been developed in recent years. Due to modern-day managements, long-term survival up to 70%-80% can be reached among patients without metastases. Ewing's tumor is favorably chemosensitive and hence treatment of choice is chemotherapy, but sometimes radiotherapy is also given. During pregnancy, chemotherapy is very crucial. In most of the cases, detrimental outcomes were perceived when chemotherapy was given during the 1st trimester have an increased chance of fetal congenital malformations, intrauterine growth restriction (IUGR), or intrauterine fetal death (IUD). When chemotherapy is administered in the 2nd trimester maternal survival rate is much better than delaying the treatment to until after delivery.

Lysyj and Bergquist reported the first case of Ewing's sarcoma in pregnancy in 1963.³ Their patient was at 32nd week of gestation manifested with pain in the right leg.⁴ Cesarean section was performed on the 36th week of gestation but patient did not receive any radiotherapy nor chemotherapy.

Just like Patient MV, patients typically would present with restricted pain or swelling for a few weeks' or months' duration. Trauma, often minor, may be the initiating event that calls attention to the lesion. The pain may be mild at first but intensifies fairly rapidly. A distinct soft tissue mass can sometimes be appreciated.

The diagnostic work-up is usually instigated with a plain radiograph of the affected area. CT scan delineates the extent of the cortical destruction and soft tissue disease better however; MV cannot perform such imaging due to current status. Metastatic work-up is advised including PET

which has a greater utility for surveying the response to chemotherapy and or radiation therapy (particularly neoadjuvant chemotherapy) but all cannot be performed for this patient.

A CT-guided core needle biopsy is also warranted. Adequate amounts of tissue are vital in order to postulate sufficient diagnostic material. The analysis of ES is confirmed using histopathologic evaluation and molecular assessment of malignant tissue obtained via tumor biopsy.⁵

ES seems to advance rapidly during pregnancy. Treatment should consist of therapeutic abortion followed by chemotherapy, radiation therapy, and surgery if discovered early in pregnancy. Controversy exists as to the treatment late in pregnancy. Treatment requires a multimodal therapy approach consisting of pre-operative therapy which patient MV is receiving and post-operative combination of chemo-radiotherapy.

Any pregnant woman suspected with Sarcoma, are mostly subjected with neoadjuvant therapy which are widely accepted and must be started whenever possible during gestation. Radiation therapy is harmful because of the toxic ionizing agents that might scatter to the fetus.

Patient MV received a total of 4 cycles of Doxorubicin 90mg in 200ml PNSS for 30 minutes. Patient stopped chemotherapy sessions on her 32nd week AOG with aims to free her from the side effects of Chemotherapy. Patient gave birth via Cesarean Section due to Breech presentation at 37 weeks AOG to a Term, Appropriate Age of Gestation, Live female neonate with a birth weight of 2.268 kgs (5lbs) with no noted congenital malformations. Patient is set to undergo clearance prior to resuming full doses of Chemotherapy regimen and for metastatic work-up.

Table 1.1 IMAGING

Ultrasound of Right Axilla	<u>05/05/2022</u> - Scanning of the clinically palpable mass in the right axilla shows well defined, lobular, homogenous, hypoechic, avascular solid mass measuring approximately 5.4 x 6.0 x 4.0 cm (l x w x ap). No perilesional hypervascularity. - In light of patient's history, consider hematoma. Neoplastic process not ruled out. Tissue correlation suggested
2D Breast Ultrasound	<u>09/13/2022</u> INTERPRETATION AND FINDINGS Breast ultrasound revealed the following: RIGHT BREAST - Cyst at the 10C position measuring 0.4 x 0.3 x 0.4 cm. LEFT BREAST - Complex nodule at the 2B position measuring 1.2 x 1.0 x 1.0 cm. SHORT INTERVAL FOLLOW-UP is recommended IMPRESSION: SHORT INTERVAL FOLLOW-UP is recommended for the complex nodule in the left breast. Right breast nodule with benign features.
	AXILLARY AREAS: Enlarged lymph node with heterogenous echogenicities at the right axillary area measuring 6.0 x 4.6 x 8.3 cm. TISSUE CORRELATION is recommended.
Second and Third Trimester Ultrasound	<u>10/17/2022</u> IMPRESSION: - Pregnancy uterine 16 weeks 3 days by composite sonar age, live, singleton fetus in cephalic presentation with good cardiac and somatic activities - Placenta anterior, grade 1 - Normohydramnios - Long and closed cervix <u>11/29/2022</u> IMPRESSION: - Pregnancy uterine 21 weeks and 3 days by fetal biometry, live, singleton in CEPHALIC presentation with good cardiac and somatic activities - Right anterior, grade 1 high lying. - Adequate amniotic fluid volume. - EDD by ultrasound: April 08 2023
MRI of the Breast and Chest	<u>10/22/2022</u> IMPRESSION: - Axillary mass, RIGHT, as detailed above. Tissue correlation is suggested. - Irregularly shaped T1W hypointense/SPAIR hyperintense focus, left breast. Due to lack of contrast imaging, enhancement pattern of this focus is not available. A malignant neoplastic process cannot be entirely ruled out. - Breast cysts, bilateral. - No distinct pulmonary or mediastinal mass noted. BIRADS 4: SUSPICIOUS FOR MALIGNANCY Tissue correlation is suggested for the right axillary mass.
Congenital Anomaly Scan	<u>11/18/2022</u> IMPRESSIONS: - Pregnancy uterine 20 weeks and 5 days by average fetal biometry, live, singleton in CEPHALIC presentation, - Placenta anterior, Grade II, High lying, with visualization of subplacental sonolucency adequate amniotic fluid by deepest vertical pocket. - No gross congenital anomalies noted at the time of scan

Pelvic Ultrasound	<u>12/02/2022</u> IMPRESSIONS: • Pregnancy uterine 21 weeks and 4 days age of gestation by average fetal biometry • Live singleton in cephalic presentation with good cardiac and somatic activities. • Placenta anterior, GRADE II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket <u>12/21/2022</u> IMPRESSIONS: • Pregnancy uterine 24 weeks and 5 days age of gestation by average fetal biometry live singleton in BREECH presentation with good cardiac and somatic activities. • Placenta anterior, GRADE II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is appropriate for gestational age <u>01/06/2023</u> IMPRESSIONS: • Pregnancy 25 weeks and 5 days age of gestation by average fetal biometry • Live singleton in breech presentation with good cardiac and somatic activities • Placenta anterior, grade II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is below the 10th percentile for gestational age (at 27 weeks: 850-1450 grams) <u>01/20/2023</u> IMPRESSIONS: • Pregnancy 28 weeks and 1 day age of gestation by average fetal biometry • Live singleton in breech presentation with good cardiac and somatic activities • Placenta anterior, prematurely aged, grade III, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is below the 10th percentile for gestational age (at 29 weeks: 1050-1625 grams)
OB DOPPLER Ultrasound	<u>01/20/2023</u> IMPRESSIONS: • Maternal Doppler study reveal presence of unilateral uterine artery notching suggestive of abnormal trophoblast space invasion of the spiral arterioles, predictive of the development of hypertension later in pregnancy. • Maternal Doppler studies of the uterine arteries reveal unilateral elevation of the indices, suggestive of suboptimal uteroplacental flow • However, all Fetal Doppler indices are within normal limits suggestive of good fetoplacental flow

Pelvic Ultrasound	<u>12/02/2022</u> IMPRESSIONS: • Pregnancy uterine 21 weeks and 4 days age of gestation by average fetal biometry • Live singleton in cephalic presentation with good cardiac and somatic activities. • Placenta anterior, GRADE II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket <u>12/21/2022</u> IMPRESSIONS: • Pregnancy uterine 24 weeks and 5 days age of gestation by average fetal biometry live singleton in BREECH presentation with good cardiac and somatic activities. • Placenta anterior, GRADE II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is appropriate for gestational age <u>01/06/2023</u> IMPRESSIONS: • Pregnancy 25 weeks and 5 days age of gestation by average fetal biometry • Live singleton in breech presentation with good cardiac and somatic activities • Placenta anterior, grade II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is below the 10th percentile for gestational age (at 27 weeks: 850-1450 grams) <u>01/20/2023</u> IMPRESSIONS: • Pregnancy 28 weeks and 1 day age of gestation by average fetal biometry • Live singleton in breech presentation with good cardiac and somatic activities • Placenta anterior, prematurely aged, grade III, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is below the 10th percentile for gestational age (at 29 weeks: 1050-1625 grams)
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	<u>07/13/2022</u> Immunohistochemical Stain Result: OCT2- NEGATIVE REMARK/S: The diagnosis and comments remain unchanged. Dr. Raymundo W. Lo concurs. <u>10/27/2022 (Report date: 11/14/2022)</u> HISTOPATH REVIEW OF SLIDES (SGD22-685 A1-A4 AND B, S-22-0369) (A) RIGHT AXILLARY MASS: EXTRASKELETAL EWING SARCOMA • FNCLCC GRADE 3 ➢ Differentiate score: 3 ➢ Mitotic Score: 3 (25-30/10HPF) ➢ Necrosis Score: 1 (<5%) • TUMOR IS PRESENT ALONG CAUTERIZED EDGE OF SPECIMEN • LYMPHOVASCULAR INVASION IS NO IDENTIFIED • PERINEURAL INVASION IS NOT IDENTIFIED (B) RIGHT AUXILLARY LYMPH NODE: • LYMPHNODE WITH REACTIVE LYMPHOID HYPERLASIA • NEGATIVE FOR METASTASES REMARKS: Correlation with previous histopathology report and radiologic findings is recommended for the tumor size GROSS AND MICROSCOPIC DESCRIPTION Received for review are five H and E slides (labeled SGD22-685 A1-A4 and B) three immunohistochemistry slide (labeled SR-22-0369 for CD99, S100 and cyclin D1 from St. Luke's medical center) and five paraffin blocks stated to be from (A) right axillary mass and (B) right axillary lymph node Immunohistochemical staining was performed on paraffin block A3 with the following results): <table><tr><td>SMA</td><td>- Negative</td><td>Synaptophysic</td><td>- Negative</td></tr><tr><td>Desmin</td><td>- Negative</td><td>Pan-CK</td><td>- Negative</td></tr><tr><td>HMB45</td><td>- Negative</td><td>Desmin</td><td>- Negative</td></tr><tr><td>LCA</td><td>- Negative</td><td>ER</td><td>- Negative</td></tr><tr><td>GATA3</td><td>- Negative</td><td>EMA</td><td>- Negative</td></tr></table>	SMA	- Negative	Synaptophysic	- Negative	Desmin	- Negative	Pan-CK	- Negative	HMB45	- Negative	Desmin	- Negative	LCA	- Negative	ER	- Negative	GATA3	- Negative	EMA	- Negative
SMA	- Negative	Synaptophysic	- Negative																		
Desmin	- Negative	Pan-CK	- Negative																		
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LCA	- Negative	ER	- Negative																		
GATA3	- Negative	EMA	- Negative																		
Immunohistochemistry	<u>10/27/2022 (Report date: 11/14/2022)</u> Chromogranin – negative Review of the immunohistochemical slides done in St. Luke's Medical Center (S-22-0369, done on July 5, 2022) performed on block A1 showed the following results: • CD99 – Positive, strong diffuse membranous • Cyclin D1 – Positive • S100 – Focal Positive The histopathology report form St. Luke's Medical Center (S-22-0369, done on July 5, 2022) also showed the following IHC results: • CD78A – Negative (as per histopathology report) • CD20 - Negative (as per histopathology report) • CD3 - Negative (as per histopathology report) • CD30 - Negative (as per histopathology report) • CD34 - Negative (as per histopathology report) • MPO - Negative (as per histopathology report) • SALL4 - Negative (as per histopathology report) • CD68 - Negative (as per histopathology report) • Ki67 – Positive, 70-80% (as poer histopathology report) • CD5 - Negative (as per histopathology report) • CD10 - Negative (as per histopathology report) • Bcl2 - Negative (as per histopathology report) • SOX11 - Negative (as per histopathology report) • EBERish - Negative (as per histopathology report) Paraffin block A3 was sent to St. Luke's Medical Center for EWSR (22q12) Break Apart by FISH, and showed positive for EWSR break apart by FISH (GC22-FISH-0111F, November 11, 2022) Microscopic examination done.																				

CONCLUSION

The main goal of therapy is to weigh risk and benefit between the mother and the developing fetus. Although there is a very limited guideline and knowledge with ES as of this moment, the diagnosis of a malignant disease during pregnancy remains to be a serious medical as well as ethical, emotional, religious and philosophical questions.

The mother's health and safety as well as the fetal well-being is of equal essence and value. Thus, in favorable prognosis, multi-agent chemotherapy should be administered early in the course of malignant sarcomas since the risk of metastasis occurrence is high.

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Reliability of Surgical Apgar Score (SAS) in Predicting Immediate Post-Operative Extubation and Intensive Care Unit Admission After Major Abdominal Surgeries: A Single Center Three-Year Retrospective Study*

Allen Rey A. Alipen, MD¹

ABSTRACT

Background: Surgical Apgar Score (SAS) is a simple, inexpensive, and readily available ten-point scoring system using patient's parameters which include surgical blood loss, lowest recorded mean arterial pressure (MAP) and lowest intraoperative heart rate in predicting 30-day post-operative morbidities. This study determined the reliability of SAS in predicting immediate post-operative extubation and immediate intensive care unit (ICU) admission among patients who underwent major abdominal surgeries in a tertiary hospital in Iloilo City.

Methods: A descriptive retrospective cross-sectional study conducted in a tertiary hospital in Iloilo City included patients aged 19 and above who underwent major abdominal surgery from January 1, 2017 to December 31, 2019, and met the study's inclusion criteria. Purposive sampling was utilized. Demographics, clinical data, intraoperative data, management as well as treatment course, post-operative course and patient outcome were extracted, and data collected were utilized for data processing and analysis. Frequency count, mean and standard deviation were utilized for descriptive statistics; T- test and One-way Analysis of Variance (ANOVA) were utilized to determine statistical

difference among groups. Logistic regression analysis was employed to assess association between SAS and immediate extubation and post-op ICU admission. Statistical Package of the Social Sciences (SPSS) software version 23.0 was utilized for statistical computations. A probability level of $p < 0.05$ was utilized to determine statistical significance.

Results: The study consisted of 221 patients predominantly female 64.3 % ($n=142$) with the mean age of 55.80 ± 17.53 . Mean SAS was 6.79 ± 1.3 with a total of 13 (5.9%) patients who were classified as high risk (SAS 0-4), 152 (68.8%) patients as medium risk (SAS 5-7) and 56 (25.3%) patients as low risk with SAS 8-10. On logistic regression analysis, mean arterial pressure (MAP), lowest heart rate and estimated blood loss were significantly associated with decision to do immediate post-operative extubation and immediate ICU admission ($p < 0.001$). Those with higher MAP were 1.19 times more likely to be extubated (OR 1.199, CI: 1.078-1.334, $p < 0.001$) and higher estimated blood loss more likely to be admitted in the ICU (OR 1.006, CI: 1.004-1.009, $p < 0.001$). Lastly, those with higher heart rates were 1.2 times more likely to be admitted in the ICU post-

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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operatively. Low-Risk SAS (Score of 8-10) is predictive of immediate post-operative extubation with 97.7% sensitivity and 75.6% specificity. High Risk SAS (score of 0-4) is predictive of immediate post-operative ICU admission with a sensitivity of 76.1% and 98.3% specificity.⁶

Conclusion: SAS is a reliable and valid predictive tool in determining immediate post-operative extubation and ICU admission among patients undergoing major abdominal surgeries. Multicentric, longitudinal and prospective studies are further required to confirm results.

Keywords: Surgical Apgar Score (SAS), extubation, intensive care, critical care, abdominal surgery

INTRODUCTION

Major intra-abdominal surgeries include surgeries involving manipulation of the gut either by resection, stoma formation and/or anastomosis¹ are associated with high rates of post-operative complications.² International studies showed that emergency laparotomy is a common procedure with a high risk for morbidity and mortality. In a study done in UK by Barrow, et al., in 2013, laparotomy carries a 30-day mortality rate of 14.9%.³ Various complications following these surgeries are very common to see and may require invasive treatment and intensive care management.¹ Meanwhile, tracheal extubation in anesthesia and in the critical care setting is an important milestone for patient recovery but carries a considerable risk of complication or failure.⁴ Extubation at the end of anesthesia may be associated with complications which may be transient and easily corrected or may be persistent and require intubation.⁵ Anesthesia practitioners need to stratify extubation risk pre-emptively and establish an extubation plan.⁶ If a patient has had a labile intraoperative course, extubation in the operating room immediately at the end of surgery should be delayed and taken into the Post-

anesthesia Care Unit (PACU) or Intensive Care Unit (ICU) for further stabilization prior to extubation.⁴ Thus, extubation at the end of surgery and anesthesia is always elective, planned and executed when physiologic, pharmacologic and contextual conditions are optimal.⁷

Admission of post-operative surgical patients to Intensive Care Unit may affect outcomes and prevent post-operative complications and death. Timely ICU admission of high-risk patients improved survival. Tharusan et al., in 2018 found out that a large proportion of post-operative mortality occurs in a small, distinct group of patients with high-risk characteristics, and <15% were admitted to ICU post-operatively.⁸ In a study, the overall mortality rate for patients with direct to ICU admission after surgery was 19%, while the initial admission to the ward with ICU transfer had nearly twice the mortality rate (39%).⁹ In another study by Sobol, et al., in 2013 of the total cohort, 8.7% were transferred directly from operating room to the ICU after surgery with 8.4% of these patients with immediate ICU admission died during hospitalization.¹⁰ The capability to predict ICU admission for more than 24 hours after operation would help physicians to define the post-operative patient disposition plan prior to surgery and therefore healthcare resource allocation. This could improve patient's outcome by reducing failure to rescue events and improve efficiency of the valuable ICU bed allocation.⁸ With limited resources and increase in demand of ICU admission, the need for precise identification of patients requiring intensive care after surgery may facilitate proper allocation of resources and improve post-operative outcomes.¹⁰ Appropriate triaging of patients is an imperative step in the management of surgical patients. Therefore, intensivists, surgeons, and anesthesiologists must make post-operative triage decisions on whether a patient should need and intensive care, and identify high-risk patients appropriate for ICU admission by the end of surgery.¹⁰

Pre-operative and intraoperative factors play an important part of the post-operative outcomes of surgical patients. Despite advancement in technology, and various predictive scoring systems to prognosticate post-operative outcomes, the perioperative period still poses an increased risk among patients undergoing major surgery. A surgical risk scoring is a vital parameter in predicting post-operative outcomes in planning admission to the intensive care unit (ICU), to prognosticate general condition of a surgical patient and to plan specific interventions postoperatively.¹¹ The APACHE and POSSUM scoring systems have been used as clinical measures to predict patient risks. These models are noted to provide adequate predictions. But the numerous data elements needed, and laboratory make these models complex. Surgical Apgar Score (SAS) by Gawande et al., in 2007 is a ten-point scoring system relying on the following patient's parameters: surgical blood loss, lowest recorded mean arterial pressure (MAP) and lowest intraoperative heart rate. This scoring system is simple, inexpensive, and readily available even in low resource settings which can reliably predict post-operative outcomes using only three variables and has been used to accurately predict early and 30-day post-operative complications in major surgeries¹² with scores of 0-4 at high risk, scores 5-7 medium risk and scores of 8-10 as low risk.¹³ This study sought to determine the reliability of the Surgical Apgar Score (SAS) as a predictive scoring system in determining immediate post-operative intensive care unit admission and further validate the utilization of SAS as an additional criterion in guiding immediate post-operative extubation.

Materials and Methods

This descriptive retrospective cross-sectional study utilized primary data from the medical records section of a tertiary hospital in Iloilo City. In this study, data of patients who

underwent major abdominal surgery between January 1, 2017 to December 31, 2019 who met the inclusion criteria were collected from the medical records section of a tertiary hospital in Iloilo City.

All patients who underwent major abdominal surgery as identified in the study and who met the study's inclusion criteria were included. Purposive sampling was utilized. Relevant patient data were utilized for the study.

Inclusion and Exclusion Criteria

Adult patients 19 years old and above who underwent major abdominal surgery under general anesthesia (intravenous or inhalational) and/or combined general and regional anesthesia. Major abdominal operations as defined in the study include operations done using midline abdominal incision which may include the following: gastric, small and large intestinal surgery, hepatobiliary and pancreatic surgeries, exploratory laparotomies. Only patients with medical records documented in the medical records section of the tertiary hospital in Iloilo City from January 1, 2017 to December 31, 2019 were included.

Patients less than 19 years old, those who underwent surgeries under regional anesthesia were excluded from the study. Patients who underwent exploratory laparotomies for multiple trauma (gunshot, etc), abdominal surgeries for vascular or renal or urologic procedures and those who had abdominal surgeries done using incision other than midline abdominal incision as well as gynecologic abdominal surgeries were not included in the study. Furthermore, patients who were initially admitted to the ICU complex or was planned to be admitted at the ICU complex prior to the surgery and those who were intubated outside of the operating room prior to surgery were not included in the study.

Data Collection Procedure / Maneuver

A descriptive retrospective cross-sectional study was conducted in a tertiary hospital in Iloilo City. The proposal was submitted for evaluation and approval by the Unified Research Ethics Review Committee (URERC). Upon approval, a letter of request was sent to the Department of Surgery to obtain a copy of yearly census of surgical cases from 2017 to 2019. A letter of request was sent to the medical records section head of the tertiary hospital in Iloilo City to authorize the researcher to use and obtain the medical records of the patient.

ICD code and/or RVU code of cases were generated from the medical records section. Patients who qualify with the study's inclusion criteria were identified. Individual patient chart was reviewed, and the clinical and laboratory data were extracted for analysis. Demographics, clinical data, intraoperative data, management as well as treatment course, post-operative course, and patient outcome were extracted from the medical records. Data collected was utilized for data processing and analysis. Only the records allowed for disclosure were utilized in the study.

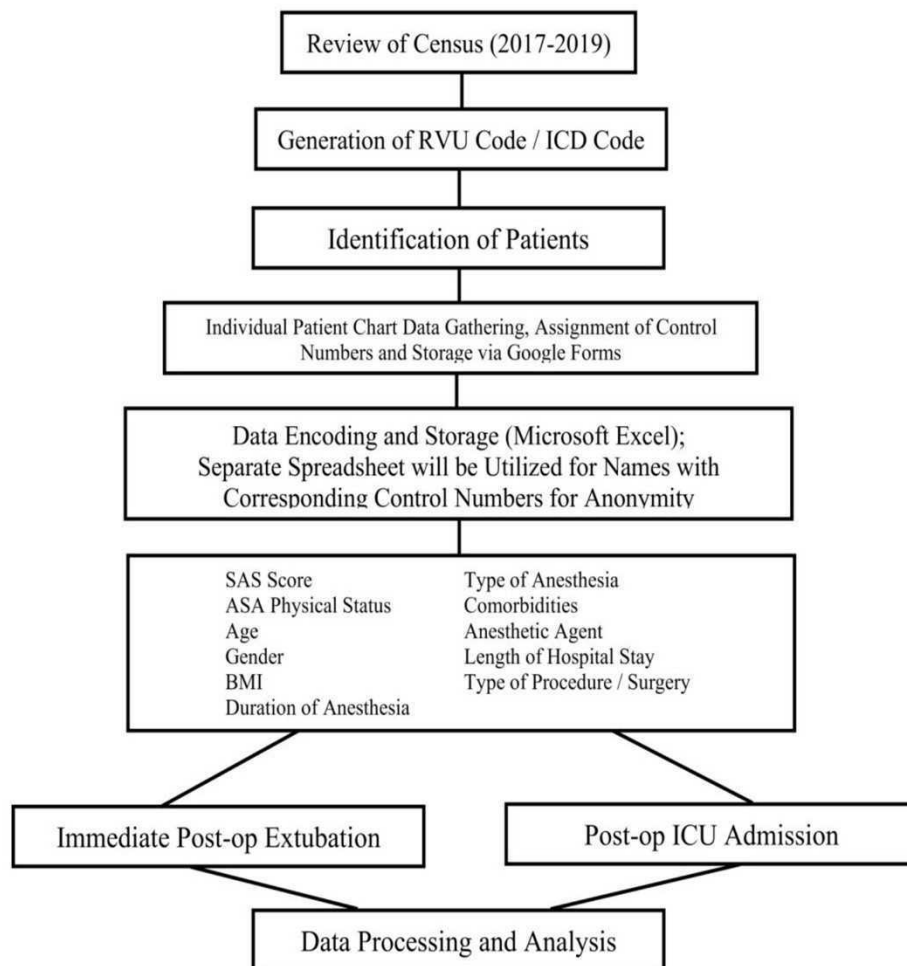


Figure 1. Data gathering algorithm

Data Processing and Analysis

Descriptive statistics was reported as means with standard deviations for continuous quantitative variables while frequency counts and percentages for categorical qualitative variables.

Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate, and continuous variables were compared using Student's t-test and the Mann-Whitney U test when applicable. For variables with more than 3 groups, one-way ANOVA was utilized. Logistic regression was employed to predict immediate post-operative extubation and ICU admission. Variables with a p value of < 0.05 on univariate analysis were entered into a multivariate logistic regression analysis using backward elimination, with 95% confidence intervals calculated using Bonferroni correction to account for multiple comparisons.

A probability level of $p < 0.05$ was considered to be statistically significant and all tests were two-sided. All statistical analyses and graphs were generated using SPSS 23.0 and GraphPad Prism 5.

RESULTS

Table 1. Clinicodemographic profile of patients who underwent major abdominal surgeries (N=221).

	n	mean±SD or %
Gender		
Male	79	35.7%
Female	142	64.3%
Age	55.80 ± 17.537	
Weight (kgs)	54.68 ± 11.78	
Height (cm)	159.03 ± 7.63	
BMI (kg/m²)	21.14 ± 3.75	
ASA Physical Status		
II	126	57.0%
III	82	37.1%
IV	13	5.9%
Urgency of Procedure		
Elective	164	74.2%
Emergency	57	25.8%
Comorbidities		
Hypertension/CAD	22	10.0%
CHF/MI/Ischemic HD	12	5.4%
Diabetes/Obesity/Dyslipidemia	14	6.3%
Respiratory (pneumonia, asthma, tuberculosis, etc.)	28	12.7%
Smoking / Alcohol Use	17	7.7%
Infection / Sepsis	41	18.6%
Anemia/Coagulopathy	4	1.8%

Table 1. Clinicodemographic profile of patients who underwent major abdominal surgeries (N=221).

Comorbidities	n	mean±SD or %
Malignancy	28	12.7%
Malignancy + Hypertension/CAD	12	5.4%
Malignancy + Respiratory	17	7.7%
Malignancy + Anemia /Coagulopathy	17	7.7%
Malignancy + Infection	9	4.1%
Anesthesia Duration		
<2	18	8.1%
2-6	184	83.3%
≥6	19	8.6%
Type of Anesthesia Used		
General (Intravenous)	14	6.3%
General (Inhalational)	97	43.9%
General – Spinal	8	3.6%
General – Epidural	102	46.2%
Anesthetic Agent Used		
Fentanyl+Midazolam+Atracurium	13	5.9%
Sevoflurane + Oxygen	98	44.3%
Ropivacaine + sevoflurane + oxygen	96	43.4%
Bupivacaine + sevoflurane + oxygen	14	6.3%
Length of Hospital Stay		
<7	18	8.1%
7-14	82	37.1%
>14	121	54.8%
Types of Surgery		
Adhesiolysis/Lavage/ Enterolysis	56	25.3%
Small Bowel Surgery	78	35.3%
Large Bowel Surgery	46	20.8%
Omental Biopsy / Patching	19	8.6%
Pancreatic Surgery	4	1.8%
Gastric Surgery	16	7.2%
Splenic Surgery	2	0.9%
SAS Group / Score		
High Risk (0-4)	13	5.9%
Medium Risk (5-7)	152	68.8%
Low Risk (8-10)	56	25.3%
Estimated Blood Loss	268.24 ± 254.32	
Lowest MAP	68.25 ± 7.00	
Lowest Heart Rate	74.92 ± 14.47	
Surgical Apgar Score / SAS	6.79 ± 1.3	

This study aimed to determine the reliability of SAS in predicting immediate post-operative extubation and ICU admission in the perioperative setting in a tertiary hospital in Iloilo City. A total of 221 patients met the study's inclusion criteria. All individual patient records were reviewed and necessary data were extracted.

Demographic profile of the patients in the study showed a total of 35.7% (n=79) male and 64.3 % (n=142) female with the mean age of 55.80 ± 17.53 . Majority of the patients (46.6%) had an ideal body weight (18.5-22.9). Mean BMI of the total study sample is 21.14 ± 3.75 which is within the ideal body weight category.

According to ASA Physical Status Score, a total of 126 (57%) were classified as ASA-PS II, 37.1% (n=82) and 5.9% (n=13) were classified as ASA-PS III and IV respectively. A total of 57 (25.8%) patients had emergency surgeries while most of the patients had elective surgery (74.2%).

Patients who have sepsis comprised majority of the patients when grouped according to their comorbidities (n=41 or 18.6%). A large portion of the population had a duration of surgery of two to six hours (83.3%) while 8.1% and 8.6% had a surgical duration of <2 hours and >6 hours respectively.

Small bowel surgeries (n=78, 35.3%) followed by adhesiolysis/lavage (n=56, 25.3%) and large bowel surgeries (n=46, 20.8%) were the top three surgery done to the patients. A small portion of the population had splenic (n=2, 0.9%) and pancreatic (n=4, 1.8%) surgeries. As for the length of hospital stay, majority of the patients were hospitalized for >14 days (n=121, 54.8%) while 18 patients (8.1%) had less than seven day

hospitalization and 82 patients (37.1%) had 7-14 days of hospital stay.

A total of 102 (46.2%) patients had combined general-epidural anesthetic technique with ropivacaine - sevoflurane - oxygen as anesthetic used for maintenance (n=96, 43.4%). Meanwhile, 97 (43.9%) and 13 (5.9%) patients had general inhalational and general intravenous anesthetic technique respectively using sevoflurane-oxygen as maintenance gas (n=98, 44.3%) and fentanyl-midazolam-atracurium as maintenance intravenous anesthetic (n=13, 5.9%).

When grouped according to Surgical Apgar Score, a total of 13 (5.9%) patients were high risk (SAS 0-4), 152 (68.8%) patients as medium risk (SAS 5-7) and 56 (25.3%) patients were low risk with SAS 8-10.

Estimated blood loss is 268.24 ± 254.32 , with mean lowest heart rate and mean lowest MAP of 74.92 ± 14.47 and 68.25 ± 7.00 , respectively. Mean surgical apgar score in the study is 6.79 ± 1.3 .

Table 2. Patient characteristics as stratified according to SAS category.

Variable	High Risk (SAS 0-4)	Medium Risk (SAS 5-7)	Low Risk (SAS 8-10)	p value
Sex				
Male	5	54	20	0.978
Female	8	98	36	
BMI (kg/m²)				
Underweight (<18.5)	0	37	12	0.337
Normal (18.5-22.9)	9	66	28	
Overweight (23.0-24.9)	1	28	9	
Obese (≥25)	3	21	7	
ASA Physical Status				
II	1	85	40	<0.001
III	10	56	16	
IV	2	11	0	
Urgency of Surgery				
Emergency	11	119	34	0.025
Elective	2	33	22	
Comorbidities				
Hypertension/CAD	0	12	10	0.031
CHF/MI/Ischemic HD	1	8	3	
Diabetes/Obesity/Dyslipidemia	0	10	4	
Respiratory (Pneumonia, asthma, tuberculosis, etc.)	1	25	2	
Smoking / Alcohol use	0	9	8	
Infection / Sepsis	8	25	8	
Anemia / Coagulopathy	0	4	0	
Malignancy	0	21	7	
Malignancy + Hypertension/CAD	0	8	4	
Malignancy + Respiratory	1	12	4	
Malignancy + Anemia	1	12	4	
Malignancy + Infection	1	6	2	
Anesthesia Duration				
<2 hours	0	11	7	0.409
2-6 hours	11	127	46	
>6 hours	2	14	3	
Type of Anesthesia				
General (Intravenous)	5	9	0	<0.001
General (Inhalational)	6	75	16	
General – Epidural	1	63	38	
General – Spinal	1	5	2	
Anesthetic Agent Used				
Fentanyl + Midazolam + Atracurium	5	8	0	<0.001
Sevoflurane + oxygen	6	76	16	
Ropivacaine + sevoflurane + oxygen	2	57	37	
Bupivacaine + sevoflurane + oxygen	0	11	3	
	0	11	3	
Length of Hospital Stay				
<7	2	13	3	0.030
7-14	2	50	30	
>14	9	89	23	
Type of Surgery				
Adhesiolysis/Lavage/ Enterolysis	1	38	17	0.020
Small Bowel Surgery	7	47	24	
Large Bowel Surgery	3	37	6	
Omental Biopsy / Patching	0	16	3	
Pancreatic Surgery	1	3	0	
Gastric Surgery	0	10	6	
Splenic Surgery	1	1	0	
Immediate Post-op Extubation				
No	13	32	0	<0.001
Yes	0	120	56	
Post-op ICU Admission				
No	0	119	56	<0.001
Yes	13	33	0	

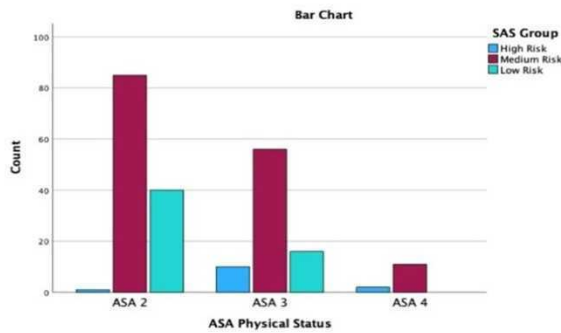


Figure 2. Distribution of patients according to ASA Physical Status and SAS Category.

Of the 221 patients, 126 (57%) were scored as ASA 2, 82 (37.1%) under ASA 3 and 13 (5.9%) as ASA 4. When stratified according to SAS group, ASA score is significantly different between the groups ($p < 0.001$) such that, the higher the ASA score the lower the SAS or categorized as High risk.

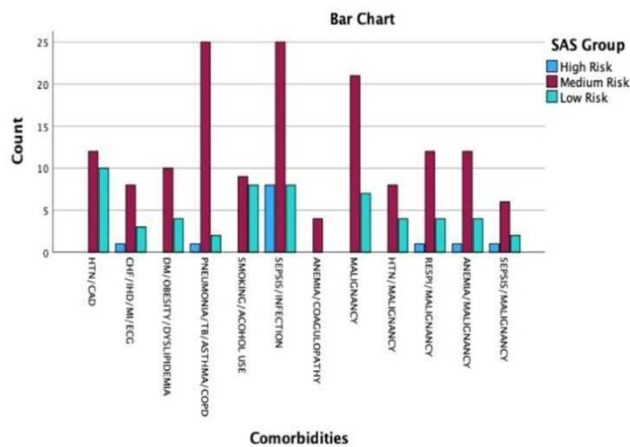


Figure 3. Distribution of patients according to comorbidities and SAS Category.

Stratifying the patients according to comorbidities showed significant difference between the groups ($p = 0.031$) with sepsis more likely associated with high risk SAS.

Furthermore, stratifying the SAS group as to the urgency of surgery revealed a significant difference ($p = 0.025$) showing that Emergency Surgeries have lower SAS (Figure 4.).

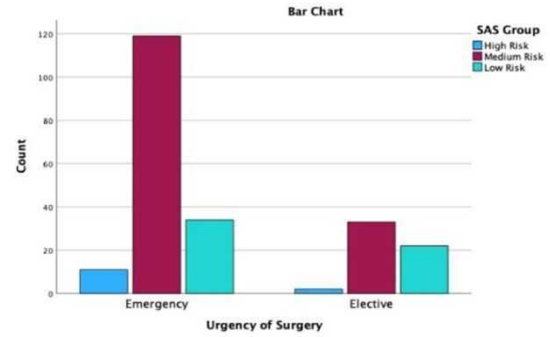


Figure 4. Distribution of patients according to urgency of surgery and SAS category.

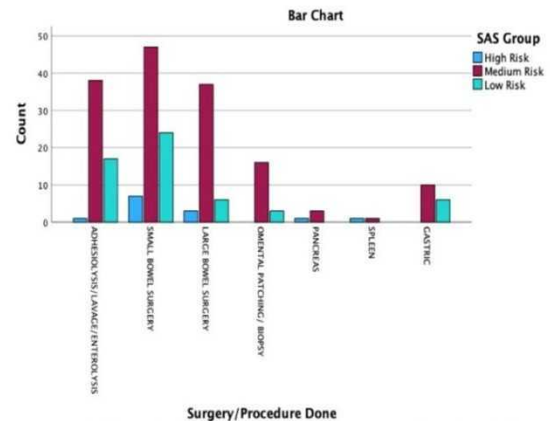


Figure 5. Patient distribution according to procedure and SAS category.

Classifying SAS group as to the type of surgery showed significant difference ($p = 0.020$) with small and large bowel surgeries more likely associated with low surgical apgar score (high risk).

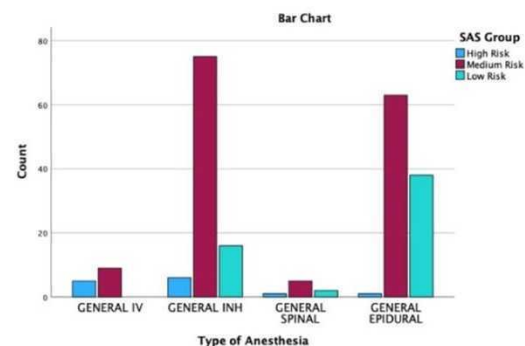


Figure 6. Patient distribution according to type of anesthesia and SAS category.

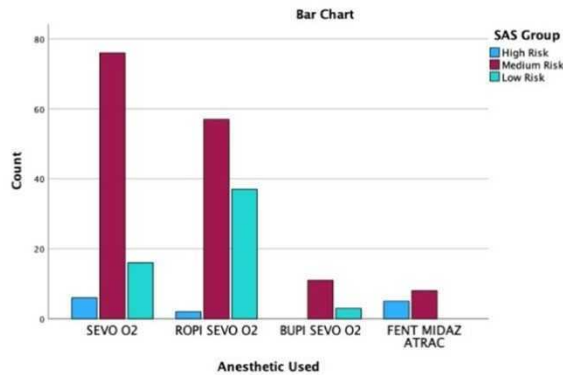


Figure 7. Distribution of patients according to anesthetic agent used and SAS category.

Consequently, the type of anesthetic technique and anesthetic agents used are significantly different between groups ($p<0.01$). Consistently, High Risk SAS is associated with

General Intravenous and General Inhalational anesthetic technique with fentanyl-midazolam- atracurium and sevoflurane-oxygen anesthetic agents as maintenance, respectively.

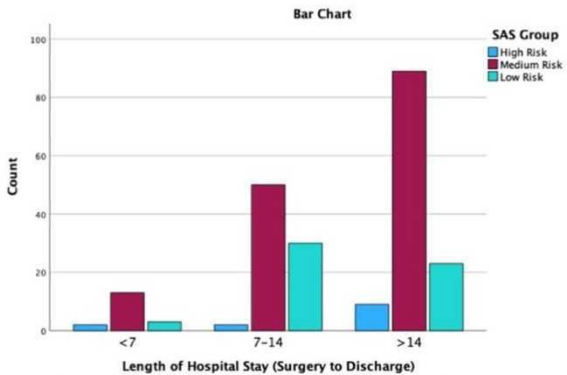


Figure 8. Patient distribution according to length of hospital stay (surgery to discharge).

Stratifying SAS groups further revealed that length of hospital stay is significantly different between groups, with longer hospital stay (>14 days) linked with high risk SAS (SAS of 0-4).

Variables such as gender, BMI, age as well surgical duration showed no significant difference between groups.

Table 3. Variables when classified according to SAS category.

Variable	High Risk (mean±SD)	Medium Risk (mean±SD)	Low Risk (mean±SD)	p value
Age	46.85 ± 19.39	55.94 ± 17.36	57.50 ± 17.27	0.114
Weight	58.85 ± 9.31	54.44 ± 12.14	54.37 ± 11.27	0.276
Height	159.77 ± 7.15	158.68 ± 7.64	159.80 ± 7.77	0.678
BMI	22.43 ± 3.27	21.21 ± 3.88	20.64 ± 3.47	0.283
Estimated Blood Loss	761.54 ± 459.23	271.51 ± 215.45	144.82 ± 110.43	<0.001
Lowest MAP	59.08 ± 8.48	68.70 ± 6.97	69.16 ± 5.055	<0.001
Lowest Heart Rate	101.15 ± 10.03	76.76 ± 13.35	63.84 ± 5.39	<0.001

Surgical Apgar Score relies on three intraoperative factors: lowest heart rate, lowest mean arterial pressure and estimated blood loss. When stratified according to SAS group, estimated blood loss, lowest MAP and lowest heart rate significantly differed between groups ($p<0.001$).

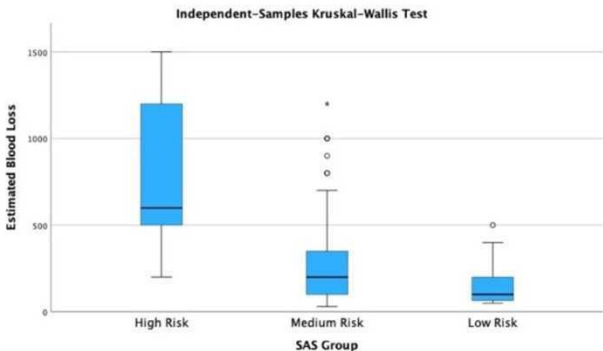


Figure 9. Box plot of Estimated blood loss across SAS group.

Figure 9 revealed that on post hoc analysis, High Risk SAS has higher estimated blood loss than Medium Risk SAS ($p<0.001$) and Medium Risk SAS has higher estimated blood loss than Low Risk SAS ($p<0.001$).

Furthermore, post hoc analysis of SAS groups and lowest mean arterial pressure revealed that, High Risk SAS has lower MAP when compared to Medium and Low Risk SAS ($p<0.001$) but Low Risk to Medium Risk SAS has no significant difference ($p=0.582$) as shown in Figure 10.

Consistently, post hoc analysis of SAS group and Lowest Heart Rate showed that High Risk SAS has higher heart rate than both Medium and Low Risk SAS ($p<0.001$) and Medium Risk SAS has higher heart rate when compared to Low Risk SAS ($p<0.001$) as seen in Figure 11.

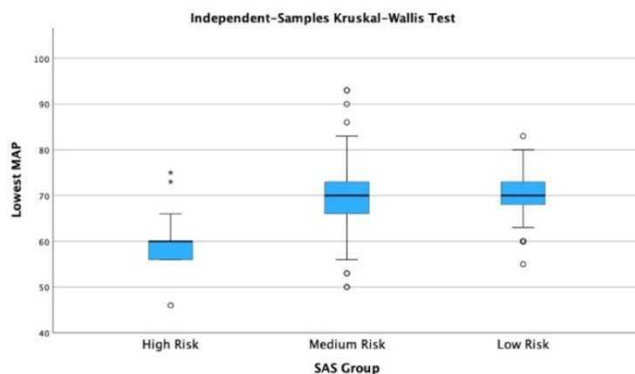


Figure 10. Box plot of Lowest MAP across SAS group.

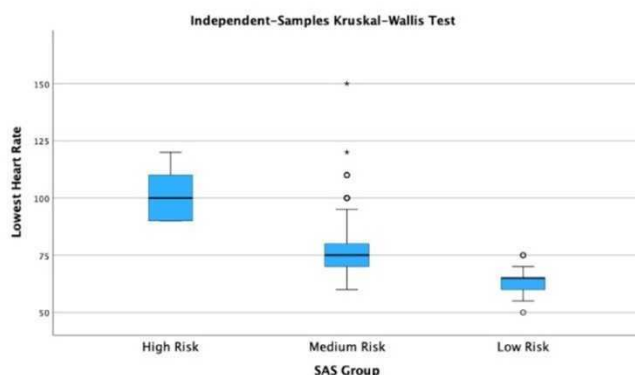


Figure 11. Box plot of Lowest heart rate across SAS group.

Table 4. Variables Associated with Immediate Post-op Extubation by Logistic Regression with Odds Ratio and 95% Confidence Interval (CI).

Variable	Odds Ratio (CI 95%)	p value
Estimated Blood Loss	0.994 (0.991-0.996)	<0.001
Lowest MAP	1.199 (1.078-1.334)	<0.001
Lowest Heart Rate	0.807 (0.754-0.864)	<0.001

Patients with higher mean arterial pressure (MAP) is 1.19 times more likely to be extubated immediately post-op (OR 1.199, CI: 1.078-1.334, $p<0.001$).

Table 5. Variables Associated with Immediate ICU Admission by Logistic Regression with Odds Ratio and 95% Confidence Interval (CI).

Variable	Odds Ratio (CI 95%)	p value
Estimated Blood Loss	1.006 (1.004-1.009)	<0.001
Lowest MAP	0.809 (0.724-0.902)	<0.001
Lowest Heart Rate	1.247 (1.162-1.338)	<0.001

Patients with higher estimated blood loss more likely to be admitted in the ICU (OR 1.006, CI: 1.004-1.009, $p<0.001$). Those patients with higher heart rates are 1.2 times more likely to be admitted in the ICU post-operatively.

Table 6. Sensitivity and specificity of SAS in predicting immediate post-op extubation and ICU admission.

Outcome	Sensitivity	Specificity
Immediate Post-op Extubation	97.7%	75.6%
Post-op ICU Admission	76.1%	98.3%

The study revealed that Low Risk SAS (SAS of 8-10) predicts immediate post-operative extubation. This has a 97.7% sensitivity and 75.6% specificity with a positive predictive value of 93.98% and a negative predictive value of 89.47%.

High Risk SAS (score of 0-4) predicts immediate post-operative admission with a sensitivity of 76.1% and 98.3% specificity with a positive predictive value of 92.10% and a negative predictive value of 93.98%.

DISCUSSION

Almost 250 million surgeries are performed worldwide annually and this number is rapidly increasing. With the increasing trend in access to

surgery, the rates of post-operative complications increases as well, making delivery of safe surgical care a public health concern. Identifying patients at high risk for morbidity and mortality leads to changes in management and outcome improvements.^{14,15}

An ideal scoring system in predicting post-operative outcomes should be simple and readily applicable to all surgical patients.¹³ Several risk scoring systems exist in predicting surgical outcomes. Accurate surgical risk prediction is paramount in shared decision making in the clinical setting.¹⁴

Multiple studies internationally validated the use of SAS as a predictor of 30-day mortality and morbidity among various surgical specialties and subspecialties such as gynecologic, orthopaedic, neurologic and major general surgeries among others. In a local study by Santos, et al., in 2011, SAS is a simple scoring system derived from readily available intraoperative data which can predict high risk patient groups for major post-operative complications among patients who underwent major surgeries.¹⁶

In the study presented, patients who underwent major abdominal surgeries/laparotomies using midline incision were included with malignancy and post operative adhesions as the most common indication for surgery. Small and large bowel surgeries such as resection and diversion procedures are among the most common surgery performed.

This study utilized the SAS as a predictor of immediate ICU admission and an adjunct in deciding immediate post-operative extubation and revealed that SAS is a reliable predictive tool in prognosticating immediate post-operative extubation and ICU admission among patients who underwent major abdominal surgeries.

Furthermore, it can be used as an additional parameter in decision-making regarding extubation.

Logistic regression analysis of the study revealed that SAS is associated with immediate post-operative extubation and ICU admission such that, low SAS (0-4) or High Risk category is more likely to be admitted in the ICU and warrants the use of ventilator post-operatively. This is consistent with the study of Yusufali, et al., in 2016 citing that low SAS are associated with post-operative complications such as ICU care as well as ventilator use. Furthermore, mortality as well as post-operative need of ICU care was associated with high risk SAS category demonstrating the ability of SAS to predict post-operative ICU admission and ventilator use.¹³

ASA physical status score is a classification system developed by the American Society of Anesthesiologists to offer clinicians a simple categorization of a patient's physiological status that can be helpful in predicting operative risk.¹⁷ This study showed that higher ASA score is likely associated with low SAS score. This is consistent with a study by Sobol, et al., wherein higher ASA physical status score were 8 times more likely to go to ICU after surgery.¹⁰

The presence of comorbidity was found to have association with SAS and adverse outcome post-operatively. This is consistent with Zara Ali's study showing that the presence of comorbidity is likely associated with post-operative complications.¹⁸ As seen in the results, the presence of sepsis among other comorbidities is associated with High Risk SAS category ($p=0.031$).

Emergency surgeries in the study were found out to be associated with low SAS. This is consistent with previous studies: emergency procedures were almost 5 times as likely to be admitted to ICU 3 and sustain post-operative morbidity and mortality.¹⁵

In the study, type of surgery (small and large bowel surgeries) were associated with low SAS. This is consistent with the previous study of Sobol et al., stating that the type of surgery was associated with higher probability of ICU admission (esophagectomy, Whipple and hepatectomy among others) as compared to bowel surgery. However in the present study, bowel surgeries (large and small bowel) were more likely associated with high SAS category mainly because the study limited the type of surgery into midline abdominal surgeries and that a smaller sample size was included as compared to the study by Sobol et al.

In the study presented, gender, BMI as well as age were found out to show no significant differences between groups. This finding is somehow in line with a 2016 study by Ali et al., on SAS as a predictor of postoperative complications in gynecologic surgery revealing that age ($p=0.114$) and BMI ($p=0.337$) are not associated with the likelihood of postoperative complications.¹⁸ A study by Kinoshita et al., also agreed with the findings in the study: age, gender and BMI are not associated with postoperative events.¹⁹ These findings however are in contrast with Ngarambe, et al., revealing that age is associated with higher mortality risk¹⁵. This may be due to the association of various comorbidities with older age group.

Various relative indications for intensive care unit admission exists which explain variations in utilization of intensive care unit resources and post-operative admission criteria across institutions. In the surgical populations, initial post-operative triage has important implications for clinical outcomes.⁸ Predicting the risk for ICU admission post-operatively aids in determining post-operative disposition and healthcare resource allocation.¹⁴ Objective variables such as mean arterial pressure, lowest heart rate and estimated blood loss intraoperatively among others help in the anesthesiologists and surgeons' clinical judgment on ICU resource allocation and decision

on extubation immediately post-op. Surgical risk scoring is important in predicting post-operative outcomes, prognosticate patients' general conditions and plan out specific interventions post-operatively.¹¹ Surgical Apgar Score is a simple risk scoring system easily applicable in low resource setting that can predict post-operative outcomes. In the study presented, SAS is a reliable predictor of immediate post-operative extubation and ICU admission.

Previous studies are consistent with the study's findings. In-hospital mortality and complications increased as SAS decreased with high risk categories more likely associated to sustain morbidity and mortality post-operatively.¹⁵ A SAS of 0-4 was associated with immediate admission to critical care unit.²⁰ Moreover, a Philippine study by Santos, et al., in 2011 showed that major complications were associated with SAS of less than 6.¹⁶ Sobol et al., further supports the study findings stating that there was a clear association between SAS and the decision to admit to ICU. Patients with SAS of 0-2 were 14 times more likely to be admitted to ICU compared with SAS 7-8.¹⁰ This is consistent with the present study showing that a SAS of 0-4 (High Risk SAS) is more likely to be admitted in the ICU. Factors such as MAP, intraoperative estimated blood loss and heart rate were the factors noted to increase the likelihood of ICU admission.

This present study revealed that Low Risk SAS (Score of 8-10) predicts immediate post-operative extubation with 97.7% sensitivity and 75.6% specificity. High Risk SAS (score of 0-4) predicts immediate post-operative admission with a sensitivity of 76.1% and 98.3% specificity.

The following conclusions were made after conducting the study: First, the Surgical Apgar Score (SAS) is a simple, readily applicable and reliable predictive tool in determining immediate post-operative extubation and Intensive Care Unit (ICU) admission after major abdominal surgeries in a

tertiary hospital in Iloilo City. SAS relies on three intraoperative factors: lowest heart rate, lowest mean arterial pressure and estimated blood loss and when grouped according to SAS category these variables significantly differed between groups. High Risk SAS category (SAS of 0-4) is associated with delayed extubation and post-operative ventilator use and immediate post-operative ICU admission. Low Risk SAS category (SAS of 8-10) is associated with immediate extubation post-operatively and ward admission. On the other hand, further correlation with other parameters such as comorbidities, hemodynamic status, extent and complexity of surgical procedure among others, in deciding for immediate extubation and ICU admission is warranted for patients under Medium Risk SAS Category (SAS of 5-7).

Second, Low SAS corresponds to High Risk SAS category which is predictive in prognosticating immediate post-operative ICU admission. The predictive model achieved a sensitivity of 97.7% and a specificity of 75.6%. Third, Low SAS score (High Risk SAS) was also a valid parameter in deciding whether patients can be extubated immediately post-operation. SAS can be utilized in conjunction with other extubation criteria/parameters as an adjunct in determining extubation.

Lastly, SAS is an acceptable tool in predicting post-operative outcomes using intraoperative objective parameters: heart rate, blood loss and mean arterial pressure. SAS is a simple, readily applicable and reliable tool that can be an additional parameter to guide anesthesiologists and surgeons in guiding perioperative decision-making.

In low resource settings, the use of SAS as a predictive tool in guiding extubation and triaging patients in ICU can help mitigate the burden on prioritizing and proper allocation of healthcare resources. Additional studies can be done to further validate the use of SAS in predicting post-operative

outcomes in various demographic, clinical and time periods in a prospective study design. Moreover, it is necessary that the tool should be utilized and validated in larger samples and various populations.

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Effectiveness of Lung Recruitment Maneuver in the Oxygenation, Hemodynamics and Post-Operative Pain of Patients Undergoing Laparoscopic Cholecystectomy*

Eunice Heincy H. Aguda, MD¹

ABSTRACT

Introduction: Laparoscopic Cholecystectomy uses carbon dioxide (CO₂) which affects the respiratory, cardiovascular and renal system. The residual CO₂ induces phrenic nerve irritation, manifesting as shoulder and abdominal pain. Recruitment maneuvers opens the lungs and helps expelling this residual carbon dioxide. However, there are limited studies on its role to hemodynamics especially in patients undergoing abdominal laparoscopic procedures.

Methods: Sixty patients (51 ± 15.1) scheduled for laparoscopic cholecystectomy under General Endotracheal Anesthesia were randomly allocated to two groups. The control group (Group C) underwent standard laparoscopic cholecystectomy procedures. The experimental group (Group R) was placed in a Trendelenburg and was given 4–5 manual pulmonary inflations at a pressure of 40cmH₂O. The blood pressure, heart rate, respiratory rate and oxygen saturation, as well as the post operative site pain and shoulder pain were measured using the Numerical Pain Scale (NPS) were monitored at 0, 1 and 2 hours post operatively.

Results: The demographics and preoperative vital signs were comparable. The mean systolic blood pressure [119.5 vs 131.5 ; $p=0.002$], mean arterial pressure [91.8 vs 95.3 ; $p=0.049$], heart rate [74.9 vs 87.5 ; $p<0.001$] and respiratory rate [15.7 vs 16.2 ; $p=0.02$] were all different only during the immediate post operative period. The mean shoulder pain was lower in Group R immediately [1.9 ± 1.2 ; $p=0.07$] and 1 hour after surgery [0.7 ± 0.8 ; $p=0.01$].

Conclusion: Recruitment maneuver significantly reduces the shoulder pain scores after laparoscopic cholecystectomy. It causes a decrease in blood pressure, heart rate and mean arterial pressure in the immediate post operative period.

Keywords: Recruitment Maneuver; Laparoscopic Cholecystectomy; Shoulder Pain; Hemodynamics; Carbon Dioxide

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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¹2nd Place, PSA Residents' Research Oral Presentation 2023

INTRODUCTION

Laparoscopic Cholecystectomy is currently the gold standard in the treatment of cholelithiasis or gallstones¹. This minimally invasive procedure involves small incisions where the tools can be inserted and carbon dioxide insufflation. Carbon dioxide (CO₂) is a gas that affects the respiratory, cardiovascular and renal system. Increase in intraabdominal pressure leads to compression of inferior vena cava, which can increase venous return and venous resistance. This can increase the cardiac output initially, but as the intraabdominal pressure rises, it eventually decreases the cardiac output, venous return and hepatic blood flow. The residual carbon dioxide during laparoscopic surgery maybe trapped between the liver and diaphragm. This may induce phrenic nerve irritation which manifests as shoulder and abdominal pain². Shoulder pain is said to occur more intensely as compared to post operative site pain in 40% of patients³.

Lung Recruitment maneuvers, also known as pulmonary recruitment or alveolar recruitment, is a strategy, that improves oxygenation in different ways. This provides a high peak airway pressure for a sustained length of time to open up collapsed alveoli. Many studies show its positive effects on oxygenation especially in preventing complications such as atelectasis, pneumothorax and pulmonary edema⁴. There are also reports of decreased shoulder and abdominal pain because of reduction in residual carbon dioxide¹. There are many ways to provide recruitment maneuvers^{4,5}. Cinella et al in 2013 used increasing peak inspiratory pressure (PIP) to 40cm H₂O with or without peak end expiratory pressure (PEEP) of 20cmH₂O for 5-10 respiratory cycles.⁴ Another method used by Kyoungcho R. et al in 2016 wherein a series of three short inflations to reach an inspiratory pressure of 40-55cmH₂O. The last method known was using a volume-controlled ventilation with a low tidal volume computed at

5ml/kg, PEEP of 30 cmH₂O and inspiratory plateau pressure of 15cmH₂O above PEEP for two minutes immediately after desufflation⁷. Different studies showed the maximal airway pressure needed in order to open the lungs. However, there are limited studies on its role to hemodynamics especially to patients undergoing abdominal laparoscopic procedures.³

This study aims to determine the effectiveness of Recruitment maneuver in terms of oxygenation status, hemodynamic stability and post operative pain of patients undergoing laparoscopic cholecystectomy.

RESEARCH OBJECTIVES

A. General Objective

To determine the effectiveness of Recruitment maneuver in the oxygenation, hemodynamic status and post-operative pain of patients who undergoing laparoscopic cholecystectomy

B. Specific Objectives:

1. To determine the effectiveness of Recruitment Maneuver in the oxygenation status (oxygen saturation) of the patient intraoperatively and post operatively
2. To determine if Recruitment Maneuver will affect the hemodynamics (blood pressure, heart rate and respiratory rate) of the patient intraoperatively and post operatively
3. To determine if the Recruitment Maneuver will reduce the post operative site pain of patients undergoing Laparoscopic Cholecystectomy using Numerical Pain Score (NPS)
4. To determine if the Recruitment Maneuver will reduce the post operative shoulder pain of patients undergoing Laparoscopic Cholecystectomy using Numerical Pain Score (NPS)

RESEARCH METHODOLOGY

Following the approval from the Institutional Review Board, this single blinded randomized control trial was conducted at a government hospital Quezon City from December 2020 to November 2022. There were 61 patients scheduled for laparoscopic cholecystectomy under General Endotracheal Anesthesia (GETA) with the following inclusion and exclusion criteria.

Inclusion criteria:

1. Admitted at the hospital who underwent proper pre-operative protocols.
2. Age 30 years old and above.
3. Body Mass Index (BMI) <35kg/m²
4. ASA physical status I and II.
5. Able to verbalize pain

Exclusion criteria:

1. Poorly controlled cardiac and respiratory pathology
2. Emergency surgery

These patients were visited pre-operatively for a standard assessment by the principal investigator. Explanation of the study were done and written consent for the procedure and the study were obtained. All eligible patients were allocated into control and experiment group using a computer-generated random number table. The demographics and the baseline vital signs were also gathered. Following the fasting guidelines, all patients were given Omeprazole 40mg/IV and were started on fluid management at maintenance rate.

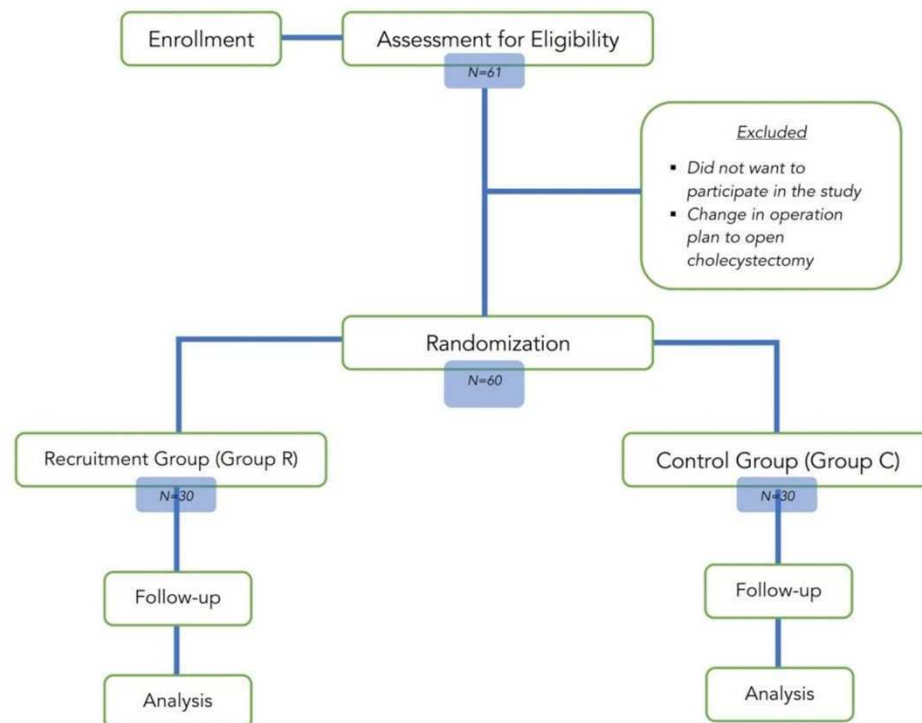
Upon arrival at the operating room, standard monitors were applied on all patients to obtain the baseline non-invasive blood pressure (BP), heart rate (HR), respiratory rate (RR) and oxygen saturation (SaO₂). Anesthesia induction were conducted using Fentanyl 1mcg/kg/IV, Propofol 1-2mg/kg/IV and Rocuronium

0.6mg/kg/IV. Anesthesia was maintained using Sevoflurane and adjusted accordingly. During the course of anesthesia, continued monitoring of vital signs were done.

Laparoscopic cholecystectomy for all patients was done by an attending or resident in charge. Insufflation using carbon dioxide (CO₂) and intraabdominal pressure was maintained <15mmHg throughout the surgery. Prior to the removal of the probes, the experimental group (Group R) received the Recruitment maneuver. This was done by asking the surgeon to fully open the sleeve valve to allow carbon dioxide (CO₂) escape. The patient was placed in a Trendelenburg position and was given 4-5 manual pulmonary inflations at a pressure of 40cmH₂O. After this, the patient was placed into a level position to facilitate removal of the probes and wound closure. Patients were extubated after muscle relaxant reversal using Sugammadex 2mg/kg/IV. For the control group (Group C), standard extubation procedures were also done.

Post operatively, patients were transferred at the Post Anesthesia Care Unit (PACU). They were given oxygen supplementation at 2-3 liters per minute (LPM) via nasal cannula, fluid management at maintenance rate and pain medications. Both groups were given Paracetamol 1g intravenously every 8 hours for 48 hours, Ketorolac 30mg intravenously every 6 hours for 24 hours and Tramadol 50mg intravenously every 8 hours as needed for pain. The blood pressure, heart rate, respiratory rate and oxygen saturation were monitored and recorded upon the arrival at the PACU, 1 hour and 2 hours post operatively. Post operative site pain and shoulder pain were also be recorded and measured using the Numerical Pain Scale (NPS) at 0h (upon arrival) and at 1, 2, 24 and 48 hours after the surgery.

Figure 1. Research flowchart



The data gathered from the participants were recorded, organized and summarized using Medcalc Statistical Software version 20.216 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2023). Calculation of sample size was adopted from Khanna et al in 2013, wherein the sample size was based on the presumption that postoperative pain scores after recruitment maneuver would be 3 when compared with 4.5 in the control group with a standard deviation of 2 at all time points.¹ Thus, accepting a level of significance of 5% and a power of 80%, a sample size of 60 patients was required to obtain statistically significant differences between the two assessment groups. Patient characteristic data were organized and analyzed as mean and standard deviation, while qualitative variables were tallied as frequency and percentages. Intraoperative and post operative changes in the blood pressure, heart rate, respiratory rate and

oxygen saturation as well as the post operative site pain and shoulder pain scores were analyzed using independent t-test at the significant level of 5%. A *P* value of < 0.050 was considered statistically significant.

RESULTS

A total of sixty two (61) patients were initially recruited for the study. However, one from the experimental group (Group R) was excluded from the analysis due to a change in the surgical plan to open cholecystectomy. Thirty (30) patients from the experimental group (Group R) and thirty (30) patients from the control group (Group C) were included in this study.

Table 1. Demographics of patients undergoing laparoscopic cholecystectomy

	Group R n=30	Group C n=30	p value
Age (years)	50.1 ± 14.7	51.7 ± 15.6	0.6845
Gender			
Male	17 (56.7)	12 (40.0)	0.2002
Female	13 (43.3)	18 (60.0)	
Weight (kg)	64.17 ± 9.8	65.0 ± 10.17	0.17
Height (cm)	1.60 ± 0.06	1.61 ± 0.07	0.07
BMI	25.1 ± 2.6	25 ± 3	0.9871
ASA			
1	4 (13.3)	5 (16.6)	0.6006
2	26 (86.7)	25 (83.3)	

Table 1 shows no significant difference in the demographic profile of the patients in both groups, specifically average age of patients from experimental group is 50 years old while around 52 for control. There were 57% males and 40% females under ASA 1-2 classification. Other demographic variables such as weight, height, body mass index (BMI) and ASA physical status were comparable between these groups ($p>0.05$)

Table 2. Pre-operative Vital Signs of Recruitment Maneuver Group (Group R) and Control Group (Group C) undergoing laparoscopic cholecystectomy.

Pre-operative parameters	Group R n=30	Group C n=30	P value
Systolic blood pressure	117.3 ± 6.4	117 ± 7.5	0.8537
Diastolic blood pressure	76 ± 5.6	76 ± 5.6	1.0000
Mean Arterial Pressure	89.9 ± 4.8	89.7 ± 4.4	0.8529
Heart rate	79.9 ± 7.7	80.1 ± 6.8	0.9295
Respiratory rate	18 ± 0.5	18.2 ± 0.5	0.1904
O2 Saturation	98.3 ± 0.6	98.1 ± 0.5	0.1040

The mean blood pressure (BP), pulse rate (PR), respiratory rate and oxygen saturation (SaO₂) were not significantly different between the two groups as shown in Table 2.

Table 3. Hemodynamic Parameters of Recruitment Maneuver Group (Group R) and Control Group (Group C) undergoing laparoscopic cholecystectomy

	Group R n=30	Group C n=30	p value
Systolic blood pressure			
Pre-Induction	118.4 ± 8.2	121.5 ± 15.3	0.3369
Induction	118.9 ± 10.6	118.9 ± 12.1	0.9820
Intraoperative	118.4 ± 11.7	115.4 ± 9.6	0.2935
Extubation	119.8 ± 10.5	118.7 ± 12	0.7025
Immediate Post-Op	119.5 ± 14	131.5 ± 14.2	0.0020**
1 hour Post op	120.4 ± 10.6	118.1 ± 10.1	0.3950
2 hour post op	121.1 ± 11.1	119.7 ± 11.9	0.6500
24 hour post op	118.6 ± 8.7	116.7 ± 7.6	0.3870
48 hour post op	117.2 ± 6.5	117 ± 7.5	0.8900
Diastolic blood pressure			
Pre-Induction	76.8 ± 6.4	78.5 ± 7.2	0.3370
Induction	76.4 ± 7.8	77 ± 10	0.7855
Intraoperative	77.1 ± 6.8	76.2 ± 6.9	0.6110
Extubation	77.1 ± 6.5	75.5 ± 7.2	0.3843
Immediate Post-Op	77.9 ± 7.7	77.2 ± 6.8	0.7275
1 hour Post op	76.1 ± 7.7	79 ± 7.9	0.1642
2 hour post op	77.2 ± 5.6	77.7 ± 6.5	0.7412
24 hour post op	78.2 ± 5	76.5 ± 7.1	0.3016
48 hour post op	76.2 ± 6.2	77.7 ± 6.3	0.3728
Mean Arterial Pressure (MAP)			
Pre-Induction	90.6 ± 4.7	92.8 ± 8.2	0.2186
Induction	90.6 ± 5.6	91 ± 8.2	0.8269
Intraoperative	90.9 ± 5.6	89.3 ± 6.3	0.3076
Extubation	91.3 ± 5.9	89.9 ± 7.3	0.4136
Immediate Post-Op	91.8 ± 6.3	95.3 ± 7.2	0.0488**
1 hour Post op	90.9 ± 6.5	92 ± 5.6	0.4715
2 hour post op	91.8 ± 6.2	91.7 ± 5.6	0.9579
24 hour post op	91.6 ± 4.8	89.9 ± 5.2	0.1911
48 hour post op	86.9 ± 17.4	90.8 ± 4.3	0.2419
Heart Rate (HR)			
Pre-Induction	70.6 ± 7.2	74.1 ± 8.5	0.0963
Induction	72.3 ± 8.8	76.7 ± 8.9	0.0572
Intraoperative	78.6 ± 9.1	77.4 ± 7.6	0.5814
Extubation	72.1 ± 9.4	73.1 ± 8.7	0.6522
Immediate Post-Op	74.9 ± 8.4	87.5 ± 8.3	<0.0001**
1 hour Post op	73.8 ± 18.9	75.3 ± 8.4	0.6789
2 hour post op	74.8 ± 10.2	74.6 ± 10.1	0.9520
24 hour post op	74 ± 7.5	75.6 ± 8.3	0.4309
48 hour post op	74.4 ± 10	74 ± 8.4	0.8414
Respiratory Rate (RR)			
Pre-Induction	15.7 ± 1	15.9 ± 1.1	0.5406
Induction	15.7 ± 1.1	15.5 ± 0.9	0.5203
Intraoperative	15.7 ± 1.1	15.8 ± 1	0.8133
Extubation	15.6 ± 0.9	16.1 ± 1	0.0674
Immediate Post-Op	15.7 ± 0.8	16.2 ± 1.1	0.0236*
1 hour Post op	21.7 ± 21.2	15.9 ± 1.1	0.1353
2 hour post op	15.8 ± 1.1	16 ± 0.9	0.4410
24 hour post op	16 ± 1.1	15.6 ± 0.8	0.1121
48 hour post op	15.9 ± 1	15.8 ± 0.9	0.9043
O2 Saturation (SaO₂)			
Pre-Induction	98.9 ± 1.3	98.3 ± 1.5	0.1036
Induction	99.8 ± 1.3	99.5 ± 0.8	0.1084
Intraoperative	99.4 ± 1	99.7 ± 0.5	0.0720
Extubation	99.2 ± 1.1	99.5 ± 0.9	0.2200
Immediate Post-Op	99 ± 1.4	98.9 ± 1.4	0.7797
1 hour Post op	99.4 ± 1	99.3 ± 0.8	0.8473
2 hour post op	99.4 ± 0.8	99.2 ± 1	0.4356
24 hour post op	98.1 ± 0.9	98.3 ± 1.2	0.4137
48 hour post op	98.8 ± 1	98.4 ± 1.1	0.2310

Table 3 shows that the parameters mean systolic blood pressure, mean arterial pressure (MAP), heart rate and respiratory rate were all statistically significantly different only during the immediate post operative period. These were all lower in the recruitment maneuver group (119.5 vs 131.5) as compared to the control group. Mean diastolic blood pressure was not significantly difference across all periods. Mean arterial pressure was also significantly different during immediate post op where mean of experimental group was lower (91.8) as compared to 95.3 of control. Similarly, significant difference also existed during immediate op for heart rate where it was lower for experimental group (74.9) as compared to 87.5 of control (Figure 2). Respiratory rate was also significantly lower during immediate post op (15.7) as compared to 16.2 for control (Figure 3). On the other hand, O₂ saturation was not significantly different from pre-induction to post-operative period (Figure 4).



Figure 2. Pulse Rate of the Recruitment Maneuver Group (Group R) and Control Group (Group C) during the post operative course



Figure 3. Respiratory Rate of the Recruitment Maneuver Group (Group R) and Control Group (Group C) during the post operative course.

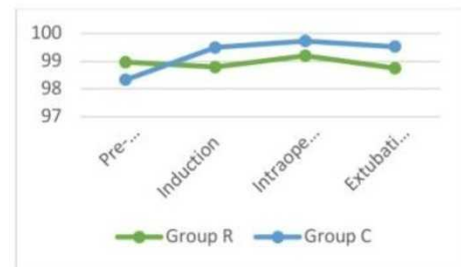


Figure 4. Respiratory Rate of the Recruitment Maneuver Group (Group R) and Control Group (Group C) during the post operative course.

Table 4. Post operative Site Pain of the Recruitment Maneuver Group (Group R) and Control Group (Group C) using Numerical Analog Scores

	Group R n=30	Group C n=30	p value
Immediate Post-Op	6.1 ± 2.6	7 ± 2.1	0.1319
1 hour Post op	5.4 ± 2.6	5.4 ± 2.3	0.9741
2 hour post op	2.6 ± 1.5	3.3 ± 1.9	0.1277
12 hour post op	1.9 ± 1.6	1.7 ± 1	0.7200
24 hour post op	0.7 ± 0.9	0.6 ± 0.6	0.4445
48 hour post op	0.3 ± 0.5	0.3 ± 0.5	0.8412



Figure 5. Post operative Site Pain of the Recruitment Maneuver Group (Group R) and Control Group (Group C) using Numerical Analog Scores

The overall postoperative site pain scores did not differ significantly between the groups during the 48 hours of monitoring. Both groups showed moderate to severe pain (pain score 5-7/10) during the immediate to 1-hour post-operative period. Whereas, both groups showed mild pain (score 0-3) from 2 hours to 48 hours after the surgery as shown in Table 4 and Figure 5.

Table 5. Post Operative Shoulder Pain Score of the Recruitment Maneuver Group (Group R) and Control Group (Group C) using Numerical analog scores

	Group R n=30	Group C n=30	p value
Immediate Post-Op	1.9 ± 1.2	3.4 ± 1	0.0001*
1 hour Post op	0.7 ± 0.8	2.5 ± 2	0.0001*
2 hour post op	0.3 ± 0.5	0.5 ± 0.5	0.1343
12 hour post op	1.8 ± 2	1.2 ± 1.3	0.1822
24 hour post op	0.1 ± 0.4	0.3 ± 0.5	0.1379
48 hour post op	0.1 ± 0.4	0.2 ± 0.4	0.5334

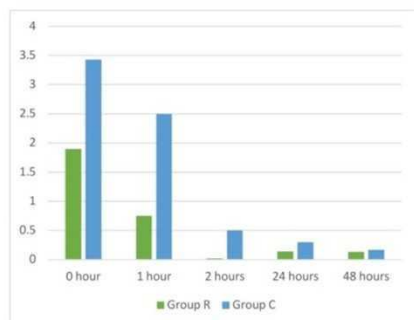


Figure 6. Post Operative Shoulder Score of the Recruitment Maneuver Group (Group R) and Control Group (Group C) during the postoperative course.

On the other hand, Table 5 shows a significant difference was found for mean shoulder pain, where it is lower among experimental group immediately after surgery (1.9 ± 1.2) and 1 hour after surgery (0.7 ± 0.8). No significant difference was noted from two hours, twelve hours, twenty four hours and forty eight hours post operatively.

DISCUSSION

The results of the study showed that there was a decrease in the hemodynamic parameters of systolic blood pressure, mean arterial pressure (MAP), heart rate (HR) and respiratory rate (RR) in the experimental group immediately post-operatively as compared to the control group. This may be attributed to the mechanism of the recruitment maneuver of using high inspiratory

pressure that causes hemodynamic instability that was also shown in previous studies.⁴ The increase in the lung volume from the recruitment maneuver may increase intrathoracic pressures, impeding the venous return and may result to the reduction of cardiac output.

The decrease in heart rate in the recruitment group was also found in different studies, but there was no noted significant hemodynamic instability was noted.⁷ The mean arterial pressure was 91.04mmHg from the pre induction to immediate post operative period in the experimental group. This was consistent with the study of Jo et al, who found that there are higher incidence of decrease in heart rate and blood pressure postoperatively may require vasopressor use in the recruitment group (Group R).¹

Tusman et al. also noted that cardiac output always decreases for a few seconds or a few minutes at the start of the maneuver, and then normalizes within 15-20 minutes of reducing opening pressure. The use of Recruitment maneuver in pressure control mode provides constant driving pressure and step-wise increments in PEEP so the blood pressure changes does not fall below 20%.⁸

From one hour post-operatively to the second day of surgery, the mean hemodynamic scores were the same among both groups. There were also no cases of cardiovascular and pulmonary problems reported for both groups. However, these finding warrants caution especially for patients with cardiovascular disease, pulmonary disease and elderly patients.

For the oxygen saturation, there was no noted significant difference between the two groups. Lee et al also found no significant postoperative pulmonary complications following

pulmonary recruitment maneuver among patients who underwent laparoscopic gynecologic surgery.⁵ There were many previous studies that used different maximal inspiratory pressures. Recruitment Maneuvers in a level of 40 cmH₂O were safe, effective and even improved the arterial oxygenation during anesthesia. This airway pressure reduces the risk of barotrauma and hemodynamic instability.⁵

Khanna et al. showed that early pain after laparoscopic procedures is multifactorial and complex, resulting from a variety of different mechanisms such as abdominal wall penetration by trocar placement for somatic component, rapid insufflation of the peritoneum by carbon dioxide may cause tearing of blood vessels, traction of nerves and release of proinflammatory cytokines accounts for the visceral pain and inflammation and local irritation subsequent to peritoneal and visceral manipulation.¹

This study showed that the overall scores of post operative site pain has no significant difference between the two groups. Ryu et al. also noted no significant difference on the post operative wound pain scores at 24 to 48 hours after the surgery when the maximal pressures of 40cmH₂O, 50cm H₂O and 60cmH₂O for the recruitment maneuver were compared.⁵

However, the mean scores of the post operative shoulder pain were reduced after the recruitment maneuver (Group R) ($p=0.0001$). Recruitment group reduced median Numerical Pain Scale scores of shoulder pain from 2 to 0. Post operative shoulder pain is defined as referred pain to the corresponding dermatome (C3-5) due to carbon dioxide insufflation.⁹

During a laparoscopic surgery, pneumoperitoneum is induced using carbon dioxide because of its safety, higher solubility in the

blood and rapid pulmonary clearance. Phelps et al. initially showed that Pulmonary Recruitment Maneuvers (PRM) facilitates the removal of CO₂ gas from the peritoneal cavity by opening the alveoli which increases the intrapulmonary pressure allowing the increase in the intraperitoneal pressure. This expulsion of carbon dioxide allows less irritation to the phrenic nerve by 61% to 31%, hence decreasing the incidence of shoulder pain in laparoscopic surgeries.⁶

Post operative shoulder pain scores were considered mild to severe, but was noted to be lower than the post operative site pain. This is in contrast to Kyoungcho et al finding that the shoulder pain was more severe than the wound pain at 24 hours post surgery for the control group (70%) and the experimental group (20-21%).⁶ This also supports the study done by Gungorduk et. al in 2018, which revealed that the postoperative shoulder pain scores were significantly lower in the maneuver group (2.2 ± 0.5 vs. 4.0 ± 0.5 ; $p < 0.001$).¹⁰ Both studies also showed no significant difference in post operative shoulder pain observed between the groups at 48 hours (1.7 ± 0.5 and 1.9 ± 0.4 ; $p = 0.115$). The degrees of the pain score reduction were similar in this study. To reduce the risk of barotrauma and hemodynamic deterioration, a low airway pressure of 40 cmH₂O was used. This was supported by the randomized controlled study by Kyoungcho, R. in 2016 who compared low pressure (40 cmH₂O) vs high-pressure (60 cmH₂O) recruitment maneuver for removing CO₂ gas from the peritoneal cavity. Low pressure PRM is safe and efficacious for the reduction of post laparoscopic shoulder pain.⁵

In studies investigating shoulder pain after laparoscopic cholecystectomy, the prevalence has been 36–80% (control populations).⁶ There seems to be a positive correlation between volume of sub-diaphragmatic gas and intensity in shoulder pain. Also, longer exposure to carbon dioxide will

lead to the increase in incidence of pain in laparoscopic surgeries. The duration and level of insufflation and over all duration of the surgery may play a great role in the severity of both post-operative site and post-operative shoulder pain.¹¹

This study has several limitations. First, it did not monitor the use of postoperative supplemental analgesics, such as weak opioids. Second, the monitoring of the insufflation flow, intra-abdominal pressure and length of the surgery were not included. Many studies have shown that these factors might affect pain scores. Finally, the use of automated recruitment maneuver may also be explored since most of the anesthesia machines in tertiary hospital are already equipped with different ventilation strategies. Manual hyperinflation using a bag valve mask or bagging was used in these study, but volume controlled ventilation or pressure controlled ventilation along with increasing peak end expiratory pressure (PEEP) may also be used to provide more accurate and timely recruitment maneuver.

CONCLUSION

This study showed that Recruitment maneuver significantly reduces the shoulder pain scores after laparoscopic cholecystectomy. Also, the use of this strategy causes a decrease in blood pressure, heart rate and mean arterial pressure in the immediate post operative period. Overall, this may translate to faster recovery, improved patient satisfaction and faster hospital discharge. Since this is a simple and safe procedure, this may be included by the surgeon and anesthesiologist in the Enhanced Recovery After Surgery (ERAS) protocol.

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Drastic Times, Drastic Measures: A Case Report on Massive Transfusion*

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ABSTRACT

Massive intraoperative bloodloss requires expectant measures, efficient coordination among providers, and timely feedback to optimize outcomes. In the Philippines, case reports on massive blood loss and transfusion are lacking. This report describes a 67-year-old female who underwent elective adrenalectomy, nephrectomy, and hepatic resection, with a total intraoperative blood loss of 20 liters in a 13-hour surgery. Efficient conduct of the institution's massive transfusion protocol, multiple pressor support, electrolyte and glucose correction, and anticipatory management of associated complications of hypovolemia and transfusion were important elements to successful management. The patient tolerated the surgery and was discharged well after 12 days. In the absence of more sophisticated monitoring and management options in a low-resource setting, maximizing available means and anticipatory interventions is key.

Keywords: massive transfusion, hemorrhage, coagulopathy

INTRODUCTION

In the face of extensive and life-threatening hemorrhage, massive transfusion aims to maintain oxygen supply and circulating volume as well as to minimize complications of dilutional coagulopathy and hypovolemia, all while source control is being carried out. While massive transfusion may be arbitrarily defined, it is traditionally the transfusion of 10 or more units of whole blood (WB) or red blood cells (RBC) in 24 hours, the transfusion of more than 4 RBCs in 1 hour with the anticipation of continued need for blood product support, or the replacement of greater than 50% of total blood volume by blood products within 3 hours¹. A massive transfusion protocol (MTP) serves to delegate tasks and streamline workflow once it is activated, predefine ratios of different blood products for transfusion, and set subjective and objective goals to continue or hold transfusion.

In the index hospital, MTP is triggered following (1) Assessment of Blood Consumption (ABC) score ≥ 2 , (2) persistent hemodynamic instability, or (3) active bleeding requiring surgery or angioembolization². The first round of blood products made available within 15 minutes

Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

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¹1st Place, PSA Interesting Case Oral Presentation 2023

of activating MTP consists of 4 units packed RBC (type O), 4 units plasma (type AB or A with low anti-B), and 4 units platelet concentrate. Type and match tailors blood product provisions for succeeding rounds. Transfusion is held once bleeding is controlled via clinical assessment and once specific laboratory parameters are met. a series of three short inflations to reach an inspiratory pressure of 40–55cmH2O6. The last method known was using a volume-controlled ventilation with a low tidal volume computed at 5ml/kg, PEEP of 30 cmH2O and inspiratory plateau pressure of 15cmH2O above PEEP for two minutes immediately after desufflation⁷. Different studies showed the maximal airway pressure needed in order to open the lungs. However, there are limited studies on its role to hemodynamics especially to patients undergoing abdominal laparoscopic procedures.³

This study aims to determine the effectiveness of Recruitment maneuver in terms of oxygenation status, hemodynamic stability and post operative pain of patients undergoing laparoscopic cholecystectomy.

CASE DESCRIPTION

A 67-year-old female, categorized under the American Society of Anesthesiologists Physical Status Classification 3 for malignancy, metabolic syndrome, and pulmonary tuberculosis, presented for elective excision of a retroperitoneal mass, probably renal versus adrenal cancer.

The mass had been increasing in size for the past 2 months, accompanied by a 10-kilogram weight loss, right flank pain, and postprandial vomiting. The patient is also a known hypertensive for the past 25 years with poor compliance to medications. She was also previously diagnosed with impaired fasting glucose and dyslipidemia. From another wise unremarkable physical examination is a finding of a large, firm, palpable mass occupying the right hemi abdomen. Bloodtests showed mild anemia at 106 g/L (normal

range 120–160 g/L). Chest x-ray showed suspicious densities on bilateral upper lung lobes; chest CT showed calcified granulomata for which pulmonary tuberculosis was suspected. Abdominal CT showed a circumscribed mass in the right upper abdomen measuring 16 x 14.5 x 16.5 cm, accompanied by caudal displacement of normal renal parenchyma, compression of the liver, anteromedial displacement of the inferior vena cava, and antero caudal displacement of the hepatic flexure.

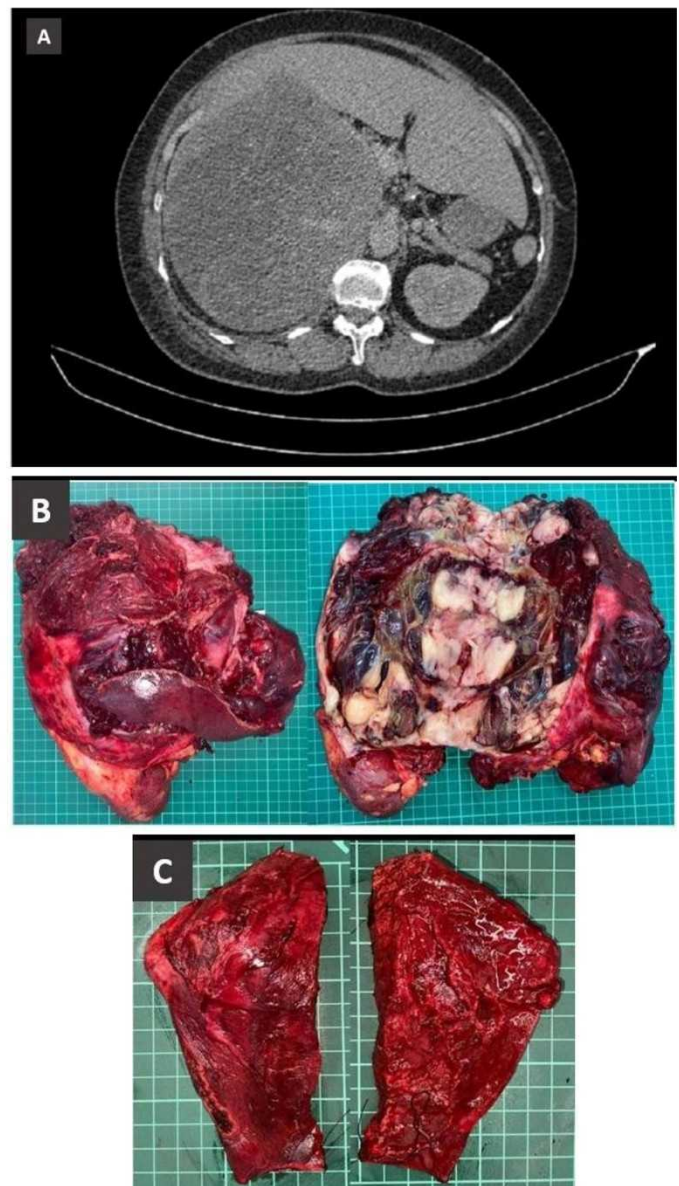


Figure 1. A) Cross-sectional CT of the circumscribed renal mass, B) Adrenal en bloc nephrectomy en bloc non anatomic hepatic resection, C) liver segment.

Preoperatively, bilateral quadrates lumborum block was done. ASA standard monitors, arterial and central venous access were inserted, and forced air warming was employed. Intubation was done via standard sequence, using the following intravenous medications: fentanyl 100 mcg, propofol 120 mg, and atracurium 40 mg. This was followed by placing the patient on right soft flank position. General anesthesia was initially maintained with sevoflurane and neuromuscular blockade with atracurium boluses. A loading dose of tranexamic acid was given at 10mg/kg, then an infusion was run at 2 mg/kg/hour intraoperatively. Packed red blood cells (RBC), frozen fresh plasma (FFP), and platelet concentrate (PC) were transfused starting 2 hours into the surgery. Norepinephrine and epinephrine infusion were also started subsequently, following decreasing blood pressure trends.

Four hours into the operation, anesthetic management was shifted to total intravenous anesthesia due to hemodynamic instability. This was done using intermittent midazolam and fentanyl boluses. At this time, blood loss was at 3,700mL and still rising. Vital signs were as follows: blood pressure 90/50, heart rate 80s-90s, oxygen saturation 100%, and computed pulse pressure variation at 22. At this time, all the blood products prepared for the surgery, namely 10 units each of RBC, FFP, and PC, were already given.

MTP was triggered after all 30 units of blood products were exhausted, 5 hours into the surgery. A total of 3 rounds were called, with the first and second rounds consisting of 4-4-4 (RBC-FFP-PC), and the third round consisting of 4-4-0 due to unavailability of platelet concentrate at the time. MTP was terminated 3 hours after activation. Point-of-care testing was done at multiple points during the procedure to evaluate adequacy of transfusion and correct other derangements, with results as detailed below:

Table1. Laboratory parameters taking before, at various points during, and after surgery.

	Baseline	1100H	1354H	1515H	1641H	1700H	1746H	1827H	2000H	2058H	Postop
<i>pH</i>	-	7.415	7.333	7.150	7.149	7.303	7.158	7.26	7.146	7.197	7.244
<i>pO2</i>	-	254.5	242.9	246.9	320	318.0	257.1	284	248	224.6	260.9
<i>pCO2</i>	-	39.3	42.0	54.3	43.3	38.5	36.3	43.2	49.8	52.8	50.8
<i>HCO3</i>	-	25.2	22.3	18.9	15.1	19.1	12.9	19.4	17.2	19.7	21.9
<i>Be(b)</i>	-	0.6	-3.4	-9.4	-12.9	-6.6	-14	-7.3	-10.9	-8.2	-5.3
<i>O2sat</i>	-	99.9	99.9	99.7	99.9	99.9	99.7	99.8	99.7	99.6	99.8
<i>Hgb</i>	106	92	75	74	81	67	79	96	71	86	89
<i>Hct</i>	0.34	0.27	0.22	0.22	0.24	0.14	0.29	0.24	0.21	0.24	0.26
<i>Na</i>	134	139	136	140	141	148	147	149	143	152	155
<i>K</i>	3.7	3.6	4.1	3.9	3.4	3.1	2.9	2.7	3.6	3.7	3.1
<i>iCa</i>	2.21	1.27	1.14	1.01	0.72	0.49	0.68	2.23	1.22	1.26	1.28
<i>Cl</i>	100	-	-	106	108	103	111	107	108	107	111
<i>Glu</i>	-	155	228	357	302	281	240	271	201	216	179
<i>Lac</i>	-	0.56	2.49	6.97	8.45	12.04	12.48	12.54	15.6	18.0	14.32
<i>Crea</i>	70	0.93	0.89	1.0	1.12	1.24	0.96	1.04	1.17	1.08	1.07

Other interventions intra operatively included electrolyte corrections (sodium bicarbonate, potassium chloride, and calcium gluconate) and glucose correction with insulin as guided by the point-of-care test results. Hydrocortisone was also given to address adrenalin sufficiency from the adrenalectomy, noting increasing press or requirements. Vasopressin infusion for hemo dynamic support on top of the norepinephrine and epinephrine infusions was started 10 hours into the surgery; both vasopressin and epinephrine were discontinued by the end of the surgery.

Total operating time was 11 hours and 47 minutes. The complete surgical procedure done was laparotomy, adrenalectomy right, en bloc nephrectomy right, enblochon-anatomic hepatic resection (segments V and VI), segmentectomy VI, cholecystectomy, tube thoracostomy right, and JP drain insertion. A 18 x 17 cm adrenal mass, grossly adherent to the right kidney and inferior border of the right liver lobe, was removed. Estimated blood loss was 20liters.

Fluid balance is detailed as follows:

Input	Output	Fluid balance
21,150mL	23,600mL	-2450mL
RBC6600mL(22units)	EBL20000mL	
FFP3300mL(22units)	UO100mL	
PC900mL(18units)	MF+RF3500mL	
Crystalloids10350mL		

RBC: redbloodcells; FFP: fresh frozen plasma; PC: platelet concentrate; EB: estimated blood loss; UO: urine output; MF: maintenance fluid; RF: replacement fluid

Postoperatively, the patient was monitored in the surgical intensive care unit, still intubated and on sedation with fentanyl infusion 1 mcg/kg/hr, as well as press or support. Norepinephrine was discontinued the following day; she was arousable and able to follow commands by the second day postoperatively. She was monitored for

complications of massive blood transfusion such as coagulopathy and transfusion-related lung injury using serial blood gas and chest radiographs. She was extubated 8 days after surgery, and was discharged well after another 4 days. She was on regular outpatient follow-up consultations with the urology service afterwards.

DISCUSSION

A protocol for massive transfusion is grounded not only on evidence but also the logistics of the institution using it. As the development of the MTP was initially grounded on trauma surgery principles, the index hospital uses the Assessment of Blood Consumption Score (ABC)². Unlike several other scoring systems, the ABC score relies only on clinical parameters (heart rate >120, systolic blood pressure <90, FAST-positive, and presence of penetrating chest injury) to determine if MTP is warranted. This scoring system by passes the need to collect laboratory data and wait for results prior to using the system, which is advantageous for more resource-limited institutions like the index hospital, where laboratory turnaround times may take longer.

Blood product ratios and the availability of certain blood products are also areas of continued research. Review of literature shows conflicting evidence, with some studies citing FFP, platelet, and RBC ratio to 1:1:1 as conferring survival advantage. Other studies found no benefit to balanced transfusion with regards to either survival or morbidity outcomes³. Moreover, the use of whole blood in transfusion therapy has been associated with less total blood products received and increased survival in some studies⁴. In this institution, a pool of RBC, platelet concentrates, and FFP is reserved from the blood bags collected daily by the blood bank for exclusive use of MTP. Whole blood, however, is not available in the institution.

Any delay in the timing of blood transfusion can lead to unfavorable outcomes, such as poor tissue oxygenation, acidosis, coagulopathy, dysfunction in homeostasis and increased mortality. The index hospital algorithm dictates the availability of the first round (4-4-4) within 15 minutes of calling the MTP. While no definitive record was made, a group chat in the messaging app Telegram made specifically for correspondence concerning MTP provides

approximations. Acknowledgment of MTP by the transfusion service was made within 1 minute of TP activation. Four units each of RBC and FFP were available 15 minutes after activation, and 4 units platelet followed after another 11 minutes of activating MTP. It must be noted that the operating rooms in the hospital are on a separate floor from the blood bank (approximately 1.5 kilometer away), and thus delivery of the blood products is limited by the designated runner.



Figure 2. Screenshots of the Telegram group chat from when the MTP was activated until termination.

After control of bleeding and resuscitation, adequacy of transfusion is ultimately determined by laboratory parameters. In the operating room, the most accessible means is with repeated point-of-care testing. Towards the end of the surgery, the index case showed an increase in hemoglobin to greater than 70g/dL, blood pressure and heart rate stability, as well as decreasing press or requirement. Standard and rapid thromboelastography as well as rotational thromboelastometry were also discussed in the MTP guidelines but are not readily available in the

institution's setting. All blood products brought from the MTP were used for the patient, with no products wasted. As discussed by Paganini and colleagues⁵, timely updates among the different services ensures efficient transfusion and minimal wastage. In this case, providers are prompted every 10 minutes whether to continue or terminate MTP. Blood products are not released until the referring service indicates so explicitly via the MTP chat, minimizing wastage.

CONCLUSION

The approach to massive blood loss and conduct of MTP in a low-resource setting, while lacking the sophistication and accuracy present in more well-equipped institutions, does not drastically differ from international standards. Rapid determination of the need for MTP, efficient response and delivery, moment to moment feedback on adequacy of transfusion, and timely termination are key elements to maximize proper execution of the protocol. Along with anticipatory interventions for hypovolemia, blood loss, and complications of transfusion, anesthetic management becomes proactive rather than reactive.

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