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Mental Health Outcomes Among Health Care Workers Exposed to Covid-19 in a Tertiary Government Hospital*

Jaylo G. Abalos, MD[1]

ABSTRACT

BACKGROUND

The Coronavirus disease 2019 (COVID-19) is a major health crisis that affected 32 million people to date and caused death to 990,000 individuals. The impact of this pandemic on the healthcare system took its toll especially to the healthcare workers and its effect on their physical and mental health. We aim to assess severity of generalized anxiety, depression and subjective distress among medical, allied and ancillary healthcare workers (HCWs) who handled COVID-19 patients.

METHODOLOGY

This is a cross sectional, survey based study done from July1 to August 31, 2020 involving healthcare workers who handled COVID-19 patients in a tertiary hospital in Pangasinan. The self-administered questionnaires used were the Generalized Anxiety Disorder- 7 for generalized anxiety, Patient Health Questionnaire (PHQ-9) for depression and Impact of Events Scale–Revised (IES-R) for subjective distress.

RESULTS

A total of 417 of 450 contacted individuals completed the survey, with a participation rate of 92.67%. Majority were women (64.57%) and 53.24% were aged 19 to 30 years old. Sixty percent of the respondents were nurses, 25.9% were physicians and the rest were composed of medical technologists (6.47%), radiologic technologists (5.52%) and respiratory therapists (1.68%). Subjective distress was noted to be present in 253 (60.67%) healthcare workers followed by anxiety 224 (53.72%) and depression 184 (44.12%). Allied health professionals and male participants experienced anxiety the most as well as subjective distress. Depression was more severe among physicians (2 [1.85%]) and women (3 [1.1%]). Physicians and allied health professionals reported more severe degrees of mental health symptoms compared to nurses.

CONCLUSION

In this study, a significant proportion of HCWs especially physicians and allied health professionals involved in handling and treating suspected and confirmed COVID-19 patients experienced generalized anxiety, depression and distress.

Keywords: COVID-19, Coronavirus, Depression, Stress, Anxiety, mental health, healthcare workers (HCWs)

INTRODUCTION

According to Centers for Disease Control and Prevention, pandemic is defined as constant presence and/or usual prevalence of a disease or infectious agent that has spread over several countries or continents, usually affecting a large number of people.[1] The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) outbreak a public health emergency of international concern when all 34 regions of China had cases of infection and the total case count surpassed that for the Severe Acute Respiratory Syndrome (SARS) of 2003.[2] On March 11, 2020, COVID-19 was declared a pandemic. COVID-19 is a major health concern affecting several nations, currently with over 31, 361, 979 cases and 965,

*1 Place, 2021 Philippine Medical Association Original Research Presentation, June 21, 2021
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642confirmed death.[3] To date, there are about 291, 789 confirmed cases and 5, 049 deaths reported in the Philippines.[4] Infection with COVID-19 is characterized by fever, dry cough, sore throat, fatigue and difficulty of breathing. Recent reports have shown that 80% of patients with the disease have mild symptoms and will recover. Mortality rate is low at 2.3%[5], but because of the high transmission rate, total mortality from COVID-19 surpassed that of SARS and Middle East Respiratory Syndrome coronavirus (MERS-CoV) combined.[6]

As COVID-19 pandemic was declared, it brought not only death from the viral infection but also unbearable psychological pressure and mental health problems especially to health care workers.[7] Studies show that the infection rate of medical staff during the SARS and MERS outbreaks reached 21% and 18.6%, respectively, which resulted in adverse psychological effects, including anxiety and depression. [8] The unpredictability and uncertainty of pandemic outbreak of infectious disease from its clinical presentation, rapid transmission pattern, seriousness of public health impact and implication for international public health and underprepared health facilities to address the pandemic outbreak of COVID-19 has considerably high potential for psychological fear contagion. This result in prevalent multitude of psychological problems including fear, anxiety, stigma, prejudice, marginalization towards the disease and its relation to all people ranging from healthy to at-risk individuals to health care workers.[9] It is pivotal therefore not to neglect psychological impact of the outbreak to individuals and society, which is often the limiting factor for the nation to overcome the crisis. Even after the pandemic has ended, psychological ramifications can be long-lasting.[10]

The stress that health care workers are dealing with includes perceived risk of infection to themselves and their families, patient mortality and availability of effective protective equipment as well as clear infection control guidance. Evidence-based evaluations and mental health interventions targeting front-line health care workers are relatively scarce. In the province of Pangasinan, where COVID-19 is being handled by secondary and tertiary hospitals, healthcare workers are faced with the same stressors. To address this gap, this study aims to evaluate the mental health outcomes among healthcare workers exposed to COVID-19 by quantifying the magnitude of symptoms of generalized anxiety, depression and subjective distress in this time of pandemic.

OBJECTIVES

General: To assess mental health outcomes among healthcare workers exposed to COVID-19 in a tertiary hospital in Pangasinan.

Specific:

1. To assess severity of generalized anxiety, depression and subjective distress among medical, allied and ancillary healthcare workers who handled confirmed, suspected and probable COVID-19 patients.
2. To compare the severity of generalized anxiety, depression and subjective distress among medical, allied and ancillary healthcare workers who handled confirmed, suspected and probable COVID-19 patients in a tertiary hospital in Pangasinan.

SIGNIFICANCE OF THE STUDY

This pandemic has highlighted the fragility of mental resilience and the need for the provision of coordinated psychological intervention. Identifying vulnerable groups susceptible to psychological distress and strengthen their psychological defense by counseling services and development of support system among colleagues can aid us in fighting this long-drawn battle and secure success for the future.

Definition of Terms

1. Mental health- a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively, and is able to make a contribution to his or her community.[11]
2. COVID-19- stands for coronavirus disease 2019 caused by the SARS-CoV-2 (2019-nCoV) virus.[12]
3. Confirmed case - A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.[12]

4. Suspected case[12]
   a. Patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath), and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset
   b. Patient with any acute respiratory illness and having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset
   c. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; and requiring hospitalization) and in the absence of an alternative diagnosis that fully explains the clinical presentation.
5. Probable case[12]
   a. A suspect case for whom testing for COVID-19 is inconclusive.
   b. A suspect case for whom testing could not be performed for any reason.
6. Exposed to COVID-19 – healthcare workers who underwent on duty at Isolation/COVID ward, involved in handling suspected and confirmed COVID-19 patients and those involved in the triage areas

REVIEW OF RELATED LITERATURE

Pandemics are large-scale outbreaks of infectious disease that can greatly amplify morbidity and mortality over a wide geographic area. Economic, social, and political disruption are significant effects of the pandemic. [13] Increased global travel and integration, urbanization, changes in land use, and greater exploitation of the natural environment may have contributed to the increased likelihood of pandemics over the past century [14, 15] The world has endured several notable pandemics which include Black Death, Spanish flu, SARS, Zika virus and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and currently the COVID-19.[1]

COVID-19 is an enveloped, positive single-strand RNA virus. It belongs to the Orthocoronavirinae subfamily, with the characteristic crown-like spikes on their surfaces.[16] The mean incubation period is 5.2 days.[17] The most common signs and symptoms are fever (83%–98%), cough (76%–82%), and shortness of breath (31%–55%). It is crucial to trace the travel and exposure history following 14 days before onset of symptoms in diagnosing COVID-19 since the signs and symptoms are non-specific.[18] In a number of patients, there is progression of the condition to acute respiratory distress syndrome wherein patients worsen in a short period of time and die of multiple organ failure.[18,19] Laboratory diagnosis include clinical specimen (nasopharyngeal swab, sputum, or lower respiratory tract aspirates, etc.) that were isolated and identified as 2019-nCoV or a positive RT-PCR. [20, 21]

For COVID-19, fear has promulgated due to its unparalleled magnitude of spread and rate of transmission. There is more intensified psychological fear now as compared to 17 years ago during the SARS period, which may be related to increased air travel and enhanced global connectedness making an effortless spread of the pandemic.[22] Increased propagation of fear potentially leads to erratic behavior among people amidst infectious outbreaks and play a major role on how people respond to such crisis.[23] Extensive media coverage, serving as a tool in boosting precautionary and preventive measures may inevitably amplify the apprehension of the public's physical and psychological response to the infectious disease threat.[24]

Facing this critical situation, front line health care workers who are directly involved in the diagnosis, treatment, and care of patients with COVID-19 are at risk of developing psychological distress and other mental health symptoms. Overwhelming workload, depletion of personal protection equipment, loneliness, separation from family and feelings of being inadequately supported may all contribute to the mental burden of these health care workers.[25]

In a study by Wang et.al. among health workers in China during the initial outbreak of COVID-19, 16.5% reported moderate to severe

depressive symptoms, 28.8% had moderate to severe anxiety symptoms and 8.1% had moderate to severe stress levels.[23] Increased levels of stress and anxiety to health care workers are also related to social stigmatization and contact with infected patients.[26] During the outbreaks of SARS and MERS-CoV, healthcare workers had reported high levels of stress that resulted in post-traumatic stress disorder (PTSD).[26, 27] Risk factors of psychological stress among medical practitioners include perception of their risk of infection, the impact of disease on their work, feelings of depression and working in high-risk medical units.[28]

Mental health problems affecting the decision-making ability of medical workers may have long term detrimental effect on their overall well-being.[29] The long-term mental health impact of COVID- 19 may take weeks or months to become fully apparent, and managing this impact requires concerted effort not just from psychiatrists but from the health care system at large.[30] Stigmatization, discrimination and fear of labeling may potentially hinder healthcare workers to ask for counseling and psychosocial interventions.[31] Working under high stress environment, the emotional and behavioral responses of the health care workers are naturally adaptive in the face of extreme (unpredictable and uncertain) stress, and thus counseling and psychotherapy based on the stress-adaptation model might act as early and prompt intervention. Protecting health care workers is an important component of public health measures for addressing the COVID-19 epidemic.[25]

METHODOLOGY

4.1 Study Design

This is a cross- sectional study which utilized validated and self-administered questionnaires. Data collection was from July 1 to August 31, 2020.

4.2 Participants

417 HCWs (doctors, nurses, respiratory therapists, radiologic and medical technologists) involved in handling suspected and confirmed COVID-19 patients in Region I Medical Center, Dagupan City, Pangasinan were targeted to achieve 5% margin of error at 95% confidence interval. The target sample size of participants was determined using the formula $N = Z\alpha^2 P (1 - P) / d^2$, in which $\alpha = 0.05$ and $Z\alpha = 1.96$, and the estimated acceptable margin of error for proportion d was 0.1. The proportion of health care workers with psychological comorbidities was estimated at 35%, based on a previous study of the SARS outbreak.[32] Informed consent was obtained from health care workers who participated in the survey. This study was approved by the Ethics Review board of Region I Medical Center (R1MC).

4.3 Outcomes

Basic demographic data were gathered which include gender, age, marital status, number of children, educational attainment and occupation. The number of children, senior citizens, pregnant and household members with comorbidities, the number of years of service to the hospital and the length of time in handling suspected and confirmed COVID-19 patients were also obtained.

The questionnaires used include Generalized Anxiety Disorder- 7 for generalized anxiety, Patient Health Questionnaire (PHQ-9) for depression and Impact of Events Scale–Revised (IES-R) for subjective distress.

Patient Health Questionnaire (PHQ-9)

The 9- item Patient Health Questionnaire is a self-report measure used to assess the severity of depression. Respondents are asked how much each symptom has bothered them over the past 2 weeks, with response options of "not at all", "several days", "more than half the days", and "nearly every day", scored as 0, 1, 2, and 3, respectively. The total scores are categorized as follows: minimal/no depression (0–4), mild depression (5–9), moderate depression (10–14), moderately severe (15-19) and severe depression (20-27).[33]

The diagnostic validity of the 9-item PHQ-9 was recognized in studies including 8 primary care and 7 obstetrical clinics. PHQ-9 scores > 10 had a sensitivity of 88% and a specificity of 88% for Major Depressive Disorder. Reliability and validity of the tool have indicated it has sound psychometric

properties. Internal consistency of the PHQ-9 has been shown to be high.[34] A study involving two different patient populations produced Cronbach alphas of .86 and .89. Criteria validity was established by conducting 580 structured interviews by a mental health professional. Results from these interviews showed that individuals who scored high (≥ 10) on the PHQ-9 were between 7 to 13.6 times more likely to be diagnosed with depression by the mental health professional. Meanwhile, individuals scoring low (≤ 4) on the PHQ-9 had a less than a 1 in 25 chance of having depression.[35]

Generalized Anxiety Disorder (GAD-7)

The 7- item Generalized Anxiety Disorder is a self-rated scale to evaluate the severity of anxiety and has good reliability and validity. A 7-item questionnaire that asked patients how often, during the last 2 weeks, they were bothered by each symptom. Response options were "not at all," "several days," "more than half the days," and "nearly every day," scored as 0, 1, 2, and 3, respectively. The total scores are categorized as follows: minimal/no anxiety (0–4), mild anxiety (5–9), moderate anxiety (10–14), or severe anxiety (15–21).[36]

The GAD-7 is a valid and efficient tool for screening for general anxiety disorder and assessing its severity in clinical practice and research in the general population. It has a good reliability, as well as criterion, construct, factorial, and procedural validity with sensitivity of 89% and specificity of 82%.[37,38] On the other hand, in a systematic review and diagnostic meta-analysis of five thousand two hundred twenty-three participants, 11 out of 12 samples identified provided data on the accuracy of the GAD-7 for identifying generalized anxiety disorder.[39]

Impact of Event Scale-Revised (IES-R)

The 22- item Impact of Event Scale-Revised is a self-report measure used to assess the degree of subjective distress of the participants in response to a specific traumatic event, especially in the response sets of intrusion (intrusive thoughts, nightmares, intrusive feelings and imagery, dissociative-like re-experiencing), avoidance (numbing of responsiveness, avoidance of feelings, situations, and ideas), and hyperarousal (anger, irritability, hypervigilance, difficulty concentrating, heightened startle). The total scores are categorized as follows: subclinical (0–8), mild distress (9–25), moderate distress (26–43), and severe distress (44–88).[40]

The IES-R was designed and validated using a specific traumatic event as a reference in the directions to the individual while administering the tool and while using a specific time frame of the past seven days. The scale discriminates between different types of traumatized groups from non-traumatized groups in general population studies. The subscales of avoidance and intrusion show good internal consistency. The IES-R has been extensively evaluated in many languages.[41, 42]

4.4 Study Area/ Setting

Region I Medical Center, Dagupan City, Pangasinan a tertiary government hospital catering to confirmed and suspected COVID-19 patients.

4.5 Inclusion Criteria

The following were included in the survey: (1) adults exposed to suspected and confirmed COVID-19 patients; (2) good mental health status

4.6 Exclusion Criteria

(1) HCWs with previous medical history of depression, anxiety, post traumatic disorder and/or under psychotropic medications; (2) HCWs who are stratified as high-risk group (senior citizen, pregnant and with co-morbidities such as diabetes, CAD, cancer, cerebrovascular Disease and chronic respiratory diseases)

4.7 Ethical Considerations

The study was conducted in accordance with the ethical standards of the institution and with Helsinki declaration and its later amendments. Written informed consent was obtained from all participants included in the study. Vulnerable population were protected accordingly. All the information gathered were strictly held confidential by the investigators of the study. There are no risks

of physical injury nor economic risk associated with participation in this study. Inclusion in this study is purely voluntary with no monetary benefit. The primary investigator did not receive any compensation for this study and shouldered all expenses.

4.8 Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) statistical software version 20.0 (IBM Corp). Baseline and demographic descriptive statistics were presented using counts and percentages for categorical variables.

The significance level will be at α = .05, and all tests are 2-tailed. The original scores of the 3 measurement tools were presented as medians interquartile ranges (IQRs). The data collected from the counts of each level for symptoms of depression, generalized anxiety and subjective distress were presented as numbers and percentages. The original scores of the 3 measurement tools were not normally distributed and so are presented as medians with interquartile ranges (IQRs). The nonparametric Mann-Whitney *U* test and Kruskal-Wallis test was applied to compare the severity of each symptom between 2 or more groups.

RESULTS

Demographic Characteristics

In this study, among the 450 HCWs asked to participate, 417 (92.67%) have completed the survey. Characteristics of the participants are presented in Table 1. Most participants were female 273 (64.57%), single (62.59%) and aged 19-30 years old (53.24%). Majority of the respondents were nurses (60.43%) and the rest was comprised of physicians (25.9%) and allied health professionals (13.67%). Fifty three percent lives with senior citizens and have household members with comorbidities, 237 (56.83%). Exposure to confirmed and suspected COVID-19 patients is typically 14 days in 44.84% of the participants.

Severity Level

Table 2 shows the summary of the severity of symptoms of anxiety, depression and distress. Two hundred twenty-four (53.72%) participants had generalized anxiety and was more severe among men and allied health professionals. Off all respondents, 149 (35.73%) had mild symptoms, 47 (11.27%) reported moderate and only 6.71% had severe symptoms. Two hundred sixty-nine or 67.5% answered the last question that it was difficult for them to do their work, take care of things at home and get along with other people this particularly affected more women (174, 43.71%) than men (95, 23.87%).

Depression was present in 44.12% (184) with physicians and women exhibiting the more severe symptoms. Symptoms were mild in 127 (30.46%) participants, moderate in 46 (11.03%) and severe in 4 (0.96%).

Subjective distress was experienced by 253 (60.67%) healthcare workers. Similar to generalized anxiety, symptoms were more severe with men and allied health professionals. Severity was mild in 182 (43.65%), moderate in 59 (14.15%) and severe in 12(2.88%).

Scores of Measurement

Table 3 summarizes the scores for generalized anxiety, depression and distress. The median (IQR) score for GAD-7 was 5, 4 for PHQ-9 and 12 for IES-R. In all 3 scales, there was a significant difference in comparison in terms of occupation with p value 0.011 for anxiety, <0.001 for depression and 0.045 for distress. Pairwise comparison shows that physicians have higher scores than nurses with p value of 0.003 for anxiety and <0.001 for depression. Allied health professionals scored significantly higher than nurses for depression (p value 0. 012) and distress (p value 0.024). No significant difference was observed between physicians and allied health professionals.

TABLE 1. Demographics

Characteristic	Total	Physician	Nurse	Allied Health Professional			
				Total	Medical Technologist	Radiologic Technologist	Respiratory Therapist
Overall	**N = 417**	**108 (25.9%)**	**252 (60.43%)**	**57 (13.67%)**	**27 (6.47%)**	**23 (5.52%)**	**7 (1.68%)**
Gender, n (%)							
• Men	**144 (34.53)**	39 (36.11)	91 (36.11)	14 (24.56)	*4 (14.81)*	*7 (30.43)*	*3 (42.86)*
• Women	**273 (65.47)**	69 (63.89)	161 (63.89)	43 (75.44)	*23 (85.19)*	*16 (69.57)*	*4 (57.14)*
Age, n (%)							
• 19-30	**222 (53.24)**	47 (43.52)	133 (52.78)	42 (73.68)	*21 (77.78)*	*15 (65.22)*	*6 (85.71)*
• 31-40	**147 (35.25)**	50 (46.3)	88 (34.92)	9 (15.79)	*5 (18.52)*	*4 (17.39)*	*0*
• 41-50	**37 (8.87)**	9 (8.33)	22 (8.73)	6 (10.53)	*1 (3.7)*	*4 (17.39)*	*1 (14.29)*
• 51-59	**11 (2.64)**	2 (1.85)	9 (3.57)	0	*0*	*0*	*0*
Marital Status, n (%)							
• Single	**261 (62.59)**	73 (67.59)	145 (57.54)	43 (75.44)	*23 (85.19)*	*15 (65.22)*	*5 (71.43)*
• Married	**152 (36.45)**	34 (31.48)	104 (41.27)	14 (24.56)	*4 (14.81)*	*8 (34.78)*	*2 (28.57)*
• Separated	**1 (0.24)**	0	1 (0.4)	0	*0*	*0*	*0*
• Widowed	**3 (0.72)**	1 (0.93)	2 (0.79)	0	*0*	*0*	*0*
Educational Attainment, n (%)							
• Elementary	**0**	0	0	0	*0*	*0*	*0*
• High School	**0**	0	0	0	*0*	*0*	*0*
• College Graduate	**278 (66.67)**	0	226 (89.68)	51 (89.47)	*22 (81.48)*	*22 (95.65)*	*7 (100)*
• Post Graduate	**139 (33.33)**	108 (100)	25 (9.92)	6 (10.53)	*5 (18.52)*	*1 (4.35)*	*0*
Number of Children, n (%)							
• None	**252 (60.43)**	73 (67.59)	138 (54.76)	41 (71.93)	*19 (70.37)*	*18 (78.26)*	*4 (57.14)*
• 1-2	**135 (32.37)**	33 (30.56)	89 (35.32)	13 (22.81)	*7 (25.93)*	*4 (17.39)*	*2 (28.57)*
• ≥3	**30 (7.19)**	2 (1.85)	25 (9.92)	3 (5.26)	*1 (3.7)*	*1 (4.35)*	*1 (14.29)*
Number of Senior Citizen in the household, n (%)							
• None	**192 (46.04)**	45 (41.67)	119 (47.22)	28 (49.12)	*15 (55.56)*	*10 (43.48)*	*3 (42.86)*
• 1-2	**206 (49.4)**	57 (52.78)	123 (48.81)	26 (45.61)	*12 (44.44)*	*11 (47.83)*	*3 (42.86)*
•≥3	**19 (4.56)**	6 (5.56)	10 (3.97)	3 (5.26)	*0*	*2 (8.7)*	*1 (14.29)*
Number of Household Members with Comorbidities, n (%)							
•None	**180 (43.17)**	32 (29.63)	115 (45.63)	33 (57.89)	*14 (51.85)*	*16 (69.57)*	*3 (42.86)*
•1-2	**197 (47.24)**	65 (60.19)	114 (45.24)	18 (31.58)	*11 (40.74)*	*5 (21.74)*	*2 (28.57)*
• ≥3	**40 (9.59)**	11 (10.19)	23 (9.13)	6 (10.53)	*2 (7.41)*	*2 (8.7)*	*2 (28.57)*
Number of Pregnant in the Household, n (%)							
• None	**391 (93.76)**	102 (94.44)	234 (92.86)	55 (96.49)	*27 (100)*	*21 (91.3)*	*7 (100)*
• ≥1	**26 (6.24)**	6 (5.56)	18 (7.14)	2 (3.51)	*0*	*2 (8.7)*	*0*
Number of Years in Hospital Service, n (%)							
• < 1 year	**39 (9.35)**	17 (15.74)	11 (4.37)	11 (19.3)	*4 (14.81)*	*3 (13.04)*	*4 (57.14)*
• 1-3 years	**111 (26.62)**	62 (57.41)	34 (13.49)	15 (26.32)	*7 (25.93)*	*6 (26.09)*	*2 (28.57)*
• 4-6 years	**129 (30.94)**	12 (11.11)	99 (39.29)	18 (31.58)	*9 (33.33)*	*9 (39.13)*	*0*
• 7-9 years	**70 (16.79)**	7 (6.48)	60 (23.81)	3 (5.26)	*2 (7.41)*	*1 (4.35)*	*0*
• ≥10 years	**68 (16.31)**	10 (9.26)	48 (19.05)	10 (17.54)	*5 (18.52)*	*4 (17.39)*	*1 (14.29)*

Length of Time in Handling Confirmed and Suspected COVID-19 Patients, n (%)							
• 1-7 days	**153 (36.69)**	17 (15.74)	132 (52.38)	4 (7.02)	*2 (7.41)*	*1 (4.35)*	*1 (14.29)*
• 8-14 days	**77 (18.47)**	16 (14.81)	59 (23.41)	2 (3.51)	*2 (7.41)*	*0*	*0*
• >14 days	**187 (44.84)**	75 (69.44)	61 (24.21)	51 (89.47)	*23 (85.19)*	*22 (95.65)*	*6 (85.71)*

Table 2. Severity Categories of Anxiety, Depression and Distress Measurements

Severity Category	Overall	Physician	Nurse	Allied Health Professional				Men	Women
				Total	Medical Technologist	Radiologic Technologist	Respiratory Therapist		
	N = 417	n = 108	n = 252	n = 57	n = 27	n = 23	n = 7	n = 144	n = 273
GAD-7, Generalized Anxiety									
• Normal	**193 (46.28)**	40 (37.04)	126 (50)	27 (47.37)	*12 (44.44)*	*8 (34.78)*	*7 (100)*	76 (52.78)	117 (42.86)
• Mild	**149 (35.73)**	41 (37.96)	87 (34.52)	21 (36.84)	*10 (37.04)*	*11 (47.83)*	*0*	46 (31.94)	103 (37.73)
• Moderate	**47 (11.27)**	18 (16.67)	25 (9.92)	4 (7.02)	*1 (3.7)*	*3 (13.04)*	*0*	11 (7.64)	36 (13.19)
• Severe	**28 (6.71)**	9 (8.33)	14 (5.56)	5 (8.77)	*4 (14.81)*	*1 (4.35)*	*0*	11 (7.64)	17 (6.23)
PHQ-9, Depression Symptoms									
• Normal	**233 (55.88)**	37 (34.26)	163 (64.68)	33 (57.89)	*13 (48.15)*	*13 (56.52)*	*7 (100)*	87 (60.42)	146 (53.48)
• Mild	**127 (30.46)**	49 (45.37)	62 (24.6)	16 (28.07)	*10 (37.04)*	*6 (26.09)*	*0*	44 (30.56)	83 (30.4)
• Moderate	**46 (11.03)**	16 (14.81)	24 (9.52)	6 (10.53)	*3 (11.11)*	*3 (13.04)*	*0*	9 (6.25)	37 (13.55)
• Moderately Severe	**7 (1.68)**	4 (3.7)	1 (0.4)	2 (3.51)	*1 (3.7)*	*1 (4.35)*	*0*	3 (2.08)	4 (1.47)
• Severe	**4 (0.96)**	2 (1.85)	2 (0.79)	0	*0*	*0*	*0*	1 (0.69)	3 (1.1)
IES-R, Distress Symptoms									
• Normal	**164 (39.33)**	45 (41.67)	101 (40.08)	18 (31.58)	*8 (29.63)*	*9 (39.13)*	*1 (14.29)*	66 (45.83)	98 (35.9)
• Mild	**182 (43.65)**	41 (37.96)	114 (45.24)	27 (47.37)	*9 (33.33)*	*12 (52.17)*	*6 (85.71)*	57 (39.58)	125 (45.79)
• Moderate	**59 (14.15)**	17 (15.74)	33 (13.1)	9 (15.79)	*8 (29.63)*	*1 (4.35)*	*0*	15 (10.42)	44 (16.12)
• Severe	**12 (2.88)**	5 (4.63)	4 (1.59)	3 (5.26)	*2 (7.41)*	*1 (4.35)*	*0*	6 (4.17)	6 (2.2)

Abbreviations: GAD-7, 7-item Generalized Anxiety Disorder; PHQ-9, 9- item Patient Health Questionnaire; IES-R, 22-item Impact of Event Scale–Revised

Table 3. Scores of Anxiety, Depression and Distress Measurement

		Occupation						P-value	Gender		P-value
		Median (IQR)							Median (IQR)		
	Overall	Physician	Nurse	Allied Health Professional					Men	Women	
	Median (IQR)			Total	Med Tech	Rad Tech	Respiratory Therapist				
GAD-7, Anxiety	5 (2-8)	6.5 (3-10)	4.5 (2-8)	5 (2-7)	5 (2-8)	6 (3-8)	2 (1-4)	.011*	4 (2-8)	5 (2-8)	0.138
PHQ-9, Depression	4 (1-8)	6 (3-9)	3 (1-6)	4 (3-8)	5 (2-9)	4 (3-9)	3 (2-3)	<.001*	3 (1-7)	4 (1.5-8)	0.123
IES-R, Distress	12 (4-23)	14.5 (4-24)	11 (4-22)	17 (6-24)	23 (6-39)	13 (6-20)	14 (9-24)	.045*	11 (3-22.75)	13 (5-23)	0.16

****significant p < .05***

DISCUSSION

The mental well-being of HCWs involved in handling and treating patients with COVID-19 was significantly affected by this pandemic. The occurrence of symptoms of generalized anxiety, depression and distress with the majority of the participants surpassed the 35% prevalence of psychological comorbidities that was seen during the SARS period.[32] Our findings is similar to a recent study by Lai et.al in China wherein the proportions of healthcare workers who experienced anxiety, depression and distress (71%) were 44.6%, 50% and 71% respectively.[25] In contrast to studies done in China, anxiety was more common among the male gender in this study. Depression was more consistent as more women were affected similar to other studies done in Asia.[25, 47,48]

In the Philippines, a study by Tee et al[43] reported low proportions of healthcare providers presenting with symptoms of anxiety, depression and distress however only 32% of their respondents are healthcare professionals which might explain the discrepancy with our results.

Distress seems to be more evident in our results and the variables that can account for it are the following: shortage of supplies of PPE and the increasing influx of suspected and confirmed cases of COVID-19, unsafe working environment, isolation, transmission of the disease to family members which contribute to the pressures and concerns of HCWs. This could, in turn, lead to lack of motivation, desperation and feelings of guilt.[49]

It is noteworthy that in this study, the nurses had the lowest scores in all 3 scales. It can probably be due to the good support of the nursing service to their staff. Other contributing factors since two or more nurses work per shift, would be their ability to talk to someone about their experiences and discuss the emotional and physical challenges of work which could help reduce the feelings of loneliness and stress.[48]

During outbreaks, the HCWs experience considerable stress just like during the MERs outbreak and similar outcome is being expected in COVID-19. There is a need to highlight the need for appropriate psychological support, interventions and staff support measures. Ensuring and protecting the safety of HCWs is a crucial tool in national emergency public health response in fighting this pandemic.

LIMITATIONS

We recognize several limitations of this study which include, first, its limited scope because data collected came from a single tertiary hospital in our region, done in a short period of time with no longitudinal follow-up. Experiences of HCWs from other hospitals might be different thus should be compared especially with the private institutions. Second, there was oversampling of nurses leading to selection bias. As a result, the conclusion might be less generalizable to the entire population. Another limitation is that self-reported levels of psychological impact, anxiety, depression and stress may not always be aligned with assessment by mental health professionals. Third, most of the cases handled were asymptomatic patients or had mild symptoms which can significantly affect the results as compared to other centers wherein severe cases are being handled by healthcare workers. Further studies which can include assessment of post- traumatic stress disorder (PTSD) among health care workers and social support in accordance with existing public health measures is of valuable information and can undoubtedly contribute to literature.

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CONCLUSION

The results of this study established that a significant portion of healthcare workers are suffering from generalized anxiety, depression and distress. Clearly, there is a need to better recognize mental health needs of our health care workers to avert the occurrence of significant mental health problems. They would benefit from personalized care from mental health professionals such as psychiatrists, psychologists and psychotherapists focusing on telehealth measures or providing online or smartphone- based psychoeducation. This may promote mental wellness and may initiate psychotherapeutic treatments and psychosocial interventions like cognitive behavioral therapy, mindfulness-based therapy and mental health and psychosocial support (MHPSS). Moreover, positive working environment with the re-assurance of

personal safety and their family safety can further preserve our health care workers' mental well-being. Public health measures should also include care of the mental health of our front liners.

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APPENDIX

Supplementary Table 1. Level of Difficulty

	Not difficult at all		Somewhat difficult		Very difficult		Extremely difficult		Total	
	GAD-7 (n = 129)	PHQ-9 (n = 157)	GAD-7 (n = 230)	PHQ-9 (n = 190)	GAD-7 (n = 36)	PHQ-9 (n = 17)	GAD-7 (n = 3)	PHQ-9	GAD-7 (n = 398)	PHQ-9 (n = 364)
Gender										
• Men	41 (31.78)	52 (33.12)	81 (35.22)	70 (36.84)	13 (36.11)	5 (29.41)	1 (33.33)	0	136 (34.17)	127 (34.89)
• Women	88 (68.22)	105 (66.88)	149 (64.78)	120 (63.16)	23 (63.89)	12 (70.59)	2 (66.67)	0	262 (65.83)	237 (65.11)
Occupation										
• Physician	22 (17.05)	27 (17.2)	71 (30.87)	69 (36.32)	11 (30.56)	6 (35.29)	0	0	104 (26.13)	102 (28.02)
• Nurse	83 (63.34)	104 (66.24)	136 (59.13)	97 (51.05)	17 (47.22)	6 (35.29)	2 (66.67)	0	238 (59.8)	207 (56.87)
• Allied Health Professional	24 (18.6)	26 (16.56)	23 (10)	24 (12.63)	8 (22.22)	5 (29.41)	1 (33.33)	0	56 (14.07)	55 (15.11)
Medical Technologist	*12 (50)*	*12 (46.15)*	*10 (43.48)*	*12 (50)*	*3 (37.5)*	*3 (60)*	*1 (100)*	*0*	*26 (46.43)*	*27 (49.09)*
Radiologic Technologist	*8 (33.33)*	*8 (30.77)*	*10 (43.48)*	*11 (45.83)*	*5 (62.5)*	*2 (40)*	*0*	*0*	*23 (41.07)*	*21 (38.18)*
Respiratory Therapist	*4 (16.67)*	*6 (23.08)*	*3 (13.04)*	*1 (4.17)*	*0*	*0*	*0*	*0*	*7 (12.5)*	*7 (12.73)*

Supplementary Table 2. Intergroup Comparison of Occupation Differences on Scores of Anxiety, Depression, and Distress

		Occupation			p value	
Scale	**Physician**	**Nurse**	**Allied Health Professionals**	p^a	p^b	p^c
GAD-7, median (IQR)	6.5 (3-10)	4.5 (2-8)	5 (2-7)	.003*	0.066	0.687
PHQ-9, median (IQR)	6 (3-9)	3 (1-6)	4 (3-8)	<.001*	0.076	.012*
IES-R, median (IQR)	14.5 (4-24)	11 (4-22)	17 (6-24)	0.118	0.377	.024*

*significant at p < .05
p^a Physician vs Nurse
p^b Physician vs Allied Health Professionals
p^c Nurse vs Allied Health Professionals

Hepatic Artery Resistive Index (HARI) and Bard Fibrosis Score: Risk Assessment of Advanced Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)*

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ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder with a wide clinical continuum of liver diseases like focal hepatic steatosis, steatohepatitis, advanced fibrosis, and cirrhosis that usually progress in a rectilinear fashion. Through this course, NAFLD endure certain hemodynamic changes in the hepatic arterial blood flow. Thus, identification of patients with advanced liver fibrosis is indispensable.

Purpose: To determine the concordance of Hepatic Artery Resistive Index (HARI) and Bard Fibrosis Score in the assessment of advanced liver fibrosis among patients with NAFLD and across its different disease severity.

Material and Methods: Observational descriptive study design was used. 94 NAFLD patients without history of excessive alcohol consumption were invited and voluntarily participated in the research investigation. Ultrasound scanning of the liver to include color Doppler parameters (Peak systolic volume [PSV], end diastolic volume [EDV] and HAR/) and determination of BARD Fibrosis score (Body mass index [BM/], fasting blood sugar [FBS] and AST/ALT ratio) were done. Different grading across NAFLD was established.

Results: The HARI of NAFLD with BARD Fibrosis scores of 1, 2, 3, and 4 has an average index of 0.84, 0.75 0.54 and 0.52, respectively. There is an unwavering inverse correlation between HARI to BARD Fibrosis scoring system (r=-0.84). Across the different severity of NAFLD, grade III (severe) has the lowest mean HARI at 0.53 followed by grade II (moderate) at 0.76 and grade I (mild) at 0.81. Correspondingly, the BARD Fibrosis score showed inverse ranking pattern across the different severity of NAFLD. Grade I (mild) has the lowest BARD fibrosis score followed by grade II (moderate) and grade III (severe), which yielded having a mean score of 1.00, 3.29 and 3.56, respectively.

Conclusion: The HARI has demonstrated a significant negative correlation with advanced liver fibrosis when correlated with BARD fibrosis score. Thus, this study showed that the conventional Doppler US with hepatic artery indices and laboratory variables are helpful in detecting fibrous tissue accumulation in the course of NAFLD.

Keywords: Non-alcoholic fatty liver disease, hepatic artery resistive index, BARD Fibrosis score, liver fibrosis, ultrasonographic grading.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder with a wide clinical continuum. It is frequently associated with obesity, diabetes mellitus, hyperlipidemia, hypertension and metabolic syndrome[1]. It is characterized by histopathological or imaging that suggests lipid deposition within the hepatocytes and no history of excessive alcohol consumption. NAFLD afflict approximately 1 billion of the general population worldwide and is a burgeoning global health concern[1]. The population prevalence of NAFLD in Asia is around 25%[3]. Data regarding prevalence of NAFLD in the Philippines have been lacking due to limited published peer-reviewed research. NAFLD is

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considered to be benign, but it can progress to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC)[1]. Reported incidence of developing HCC in NAFLD patients with fibrosis/ cirrhosis is between 6.7-15% at 5 to 10 years and 2.7% at 10 years in NAFLD patients without fibrosis/ cirrhosis[31]. Hence, there is an emergent need to assess the presence hepatic fibrosis to prevent mortality. Liver biopsy has been regarded as the gold standard in identifying these liver-related morbidity and mortality, but it has a well-known limitation, including its invasiveness and a rare, but with potential life-threatening complications. Liver ultrasonography (US), an inexpensive and a non-invasive diagnostic modality with 94% sensitivity and 95% specificity becomes popular and is now widely used in detecting NAFLD and other focal liver disorders[21]. Despite advances in its diagnosis, the diagnostic accuracy of conventional US to reveal a sign of progressive fibrosis is low except in advanced stages of disease (e.g. cirrhosis). This has led to host of an innumerable non-invasive approach of assessing hepatic fibrosis in patients with NAFLD. Elastography is the new innovative imaging technique that uses shear wave that assess the degree of hepatic fibrosis. Although the use of elastography has improved the evaluation of liver stiffness in patients with NAFLD, it comes with a finitude use because it requires more specific training and is not readily available in various institutions[2]. Another approached used in the study by Claudio Tana, *et al*., is the measurement of hepatic artery resistive index (HARI), which is significantly altered in patients with NAFLD. It also demonstrated an inverse correlation with US severity of hepatosteatosis and a positive correlation in the degree of fibrosis. However, due to limited target population in the study, the authors recommended a larger sample size and the results were considered only as a preliminary and must be validated by a large study group[2]. The use of different liver fibrosis scoring system garnered relevance in NAFLD that requires serial assessment of fibrosis longitudinally over time. Among the various fibrosis scoring system, NAFLD and BARD fibrosis scores have relatively high sensitivity and specificity. Both scores predict well the presence of significant fibrosis and reducing the need for liver biopsies[7]. In this study, BARD fibrosis score was used because it is more economical and simpler to use. It only requires three serum biomarkers (AST, ALT and FBS) in comparison with the NAFLD fibrosis score which utilizes five serum biomarkers (AST, ALT, FBS, Platelet count and Albumin).

Advanced liver fibrosis in patients with NAFLD are associated with severe hepatic dysfunction and risk for malignant progression. Hepatocellular carcinoma (HCC) which accounts for 70%-85% of the primary liver malignancies is considered the most prevalent histological subtype[2]. in addition, with the advent of potential occurrence of anti-fibrotic drug for the treatment of liver fibrosis, the accurate assessment of fibrous tissue accumulation in NAFLD patients becomes even more relevant, not only for identifying patients for treatment, but also in the evaluation of its efficacy.

In this study, we explore the use of different noninvasive means in assessing liver fibrosis in NAFLD, from serum biomarkers to predictive fibrosis score and imaging measures.

OBJECTIVES

Primary objective: To determine the concordance of Hepatic Artery Resistive index (HARi) and Bard Fibrosis Score in the assessment of advanced liver fibrosis among patients with Non-Alcoholic Fatty Liver Disease (NAFLD).

Secondary objective: To determine the concordance of Hepatic Artery Resistive index (HARi) and Bard Fibrosis Score across different severity of Non-Alcoholic Fatty Liver Disease (NAFLD).

PURPOSE

The goal of this study is to present additional non-invasive and innovative techniques in the assessment of advanced liver fibrosis in the course of NAFLD.

SIGNIFICANCE OF THE STUDY

For the clinicians:

This study will serve as a basis for the clinician to formulate a standardized assessment guideline or tool that will utilize the sonographic

value of hepatic artery resistive index (HARi) through Doppler ultrasound and BARD Fibrosis Score (ie. using clinical and serological methods/markers) in monitoring advanced liver fibrosis for patients with nonalcoholic fatty liver disease (NAFLD).

This study will expedite in the assessment of advanced liver fibrosis in the course of NAFLD which can condense the need for possible biopsy. Through the cutoff value of HARi, it will aid in the selection of NAFLD patients to undergo invasive biopsy for evaluation of the degree of inflammatory activity (grading) and extent of fibrosis (staging).

This study will succor in identifying NAFLD patients to receive management of advanced liver fibrosis (ie. antifibrotic) and in the evaluation of its effectiveness.

For NAFLD patients:

This study will serve as an alternative, non-invasive and cost-effective measure (other than BARD Fibrosis score) that assesses the risk for advanced liver fibrosis. The sonographic value of HARi may help prevent unnecessary follow-up imaging and hence, curtail the diagnostic expenditure on the part of the patient.

This study will minimize patient anxiety (ie. patients with hemophobia and/or with needle phobia) because it will provide an option to lessen serial blood test necessary in the determination of liver function test.

REVIEW OF RELATED LITERATURE AND STUDIES

Non-alcoholic fatty liver disease (NAFLD) is a global disease characterized by an imaging or histological evidence of lipid deposition in the hepatocytes afflicting patients with predisposing risk factors such as diabetes mellitus, hypertension, and hypercholesterolemia[2]. NAFLD is an incipient disease, which remain incognito for years. The majority of patients suffering from NAFLD are asymptomatic[6]. Patients should have no known specific etiology of liver disease such as excessive alcohol consumption, viral hepatitis or neoplasia in diagnosing NAFLD[2]. NAFLD is estimated to afflict 1 billion of world's general population[1]. The population prevalence of NAFLD in Asia is around 25%[3]. it has now become a global burden in NAFLD patients developing complications like nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, hepatocellular carcinoma and other liver related disease[1,4]. Among these complications, advanced hepatic fibrosis has a greatest risk of developing complications of chronic liver disease[1]. Thus, crucial issues in patients with NAFLD are identification of the different complications, most particularly the advanced liver fibrosis.

Conventional ultrasound (US), an inexpensive and with rapid execution for trained radiologist is effective in detecting hepatic steatosis[2]. it is also used to detect several extrahepatic disorders. However, it has its own limitation which yielded low diagnostic accuracy to reveal signs of early hepatic fibrosis except in advanced stages of chronic liver disease, such as cirrhosis. The introduction of elastography has improved the evaluation of liver stiffness which is also used in evaluation of NAFLD patients. This technique led the American Gastroenterological Association which instituted guideline on the role of Elastography in the evaluation of liver fibrosis[32]. There are two different kinds of techniques: ultrasound-based or magnetic resonance- based. Main limitations of elastography are those obese patients, with waist circumference $\geq$102 cm or thick parietal walls which yielded significant failure of measurement of liver stiffness[2]. Although elastography technique has been widely used worldwide, but it is not readily available because it needed an additional equipment that will be installed in the current ultrasound machine or MRi.

There are different approaches that were evaluated to identify patients at high risk of significant fibrosis and one of which, is through measuring the hepatic resistive index (HARi). Measuring HARi is not routinely assessed and evaluated in the routine ultrasound request because many of the clinician has lack of information regarding the importance of the HARi value in clinical practice. in the study of Claudio Tana, *et al*., mentioned that HARi is altered in patients with NAFLD and a reduction in HARi value is inversely

proportional to the severity of diffuse fatty liver disease[4]. The usual range in normal, as well as post-transplant, is between 0.55 and 0.80[22]. it is measured by resistive index (Ri) = (peak systolic velocity [PSV] minus end diastolic velocity [EDV]) divided by PSV. in particular, the detection of low HARi value in NAFLD patients, can predict presence of advanced liver fibrosis[4]. Claudio Tana, *et al*., demonstrated a significant correlation with degree of fibrosis, suggesting that the fibrous tissue accumulation may result in increased in arterial rigidity and, therefore, causing an increase to resistance flow, and that the different tissue composition of liver (adipose and fibrous) can influence HARi[2]. Liver biopsy remains the gold standard technique to detect early liver fibrosis, but it's an invasive procedure and with various complications. Because of its limitation, it leads to the development of different clinical algorithm that is used to assess the risk of NASH evolution and development of early liver fibrosis. Some guidelines suggest the use of non-invasive markers to assess liver fibrosis such as NAFLD fibrosis score, BARD score, fibrosis-4 (FiB-4) calculator, Original European Liver Fibrosis Panel (OELF) score, Enhanced Liver Fibrosis (ELF) score, Palekar's score, BAAT score, Gholam's score and Nippon score?. These markers are based on readily available laboratory tests. Among these scoring systems, NAFLD and BARD fibrosis scores were established specifically for assessing and predicting advanced liver fibrosis which have relatively high sensitivity and specificity. Both scores predict well the presence of advanced fibrosis and reducing the need for liver biopsies?. The main strength of the BARD score over the NAFLD fibrosis score is its simplicity because it utilizes three serum biomarkers: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and fasting blood sugar (FBS). The NAFLD fibrosis score utilizes five serum biomarkers: AST, ALT, FBS, Platelet count and Albumin. Hence, in this study, BARD fibrosis score was used to predict liver fibrosis in NAFLD patients and only requires simple clinical data. in this study, it showed positive correlation of BARD fibrosis scoring system when compared to HARi in assessment of advanced liver fibrosis in the course of NAFLD.

In the study of Claudio Tana, *et al*., where the investigators uses NAFLD fibrosis score and when compared to HARI revealed a negative correlation between HARI and NAFLD fibrosis score. Low HARI resulted from high tissue stiffness secondary to fibrous tissue accumulation that can be attributed to increased arterial rigidity and therefore resulted to increase of resistance arterial flow. However, the investigators recommended that it must be validated by large study population before recommending and incorporating into clinical practice. Thus, the present study utilized large population group of NAFLD and exceeded the sample size used by Tana, et al. which aimed to evaluate the concordance between HARI with a simple clinical fibrosis scoring system, the BARD fibrosis score.

Currently, there is no drug treatment available for treating NAFLD. A combination of healthy diet and increased physical activity remains the mainstay of NAFLD management. In order to prevent the hepatic, extra-hepatic, including metabolic complications of NAFLD, it is important to manage the condition early. To date, no drugs has been approved as an antifibrotic drugs however, there are clinical antifibrotic trials currently registered at ClinicalTrials.gov designed for antifibrotic pharmacologic therapies. Since liver fibrosis is the most significant factor for determining the prognosis of NAFLD, therefore it is important to identify early changes of liver parenchyma through routine, inexpensive, readily available ultrasonographic evaluation and more specifically, through determination of HARI value to patients with NALFD. The study provided additional information in the assessment of advanced liver fibrosis in conjunction with the simple, obtainable and validated clinical fibrosis score.

The prevalence of NAFLD has grown correspondingly with the rise of obesity, sedentary lifestyle, unhealthy dietary pattern, and metabolic syndrome [10]. Therefore, a plan should be carried out immediately when NAFLD is diagnosed through dietary modifications and increase exercise activity. Challenges still remain, as noted, including NAFLD that will require pharmacologic intervention to prevent or reverse advanced fibrosis, and the lack of a standardized, and accepted noninvasive endpoints for assessment of fibrosis.

DEFINITION OF TERMS

- Alanine aminotransferase (ALT) test – detects the enzyme alanine aminotransferase in the blood. This enzyme found mainly in the liver. Elevation of which signifies possible liver disease.
- Aspartate aminotransferase (AST) test - detects the enzyme aspartate aminotransferase in the blood. This enzyme found mainly in the liver. Elevation of which signifies possible liver disease.
- AST/ALT ratio – ratio between concentration of the alanine and aspartate aminotransferase enzymes. Normal ratio is approximately 0.80. An elevated ratio is an indication of liver disease.
- Fasting blood glucose (FBS) – a test used to measure level of glucose in the blood.
- Body mass index (BMI) – a value derived from body mass (kilograms) divided by height (meters^2).
- BARD fibrosis score – BARD score will be calculated by assigning points to the following variables: BMI $\geq$28 kg/m2 = 1 point, BMI <28 kg/m2 = 0 point; AST/ALT ratio $\geq$0.8 = 2 points, AST/ALT ratio <0.8 = 0 point; pre-existing type II diabetes mellitus or fasting blood glucose (FBS) of $\geq$126 mg/dl = 1 point. The total possible score ranges from 0 to 4 points. According to the study of Ageely et.al, a score of 2-4 points indicate significant liver fibrosis[5].
- Liver echogenicity – reflects the return echo signal from the liver parenchyma. Liver echogenicity is high when the sound echo reflects increased sound waves, termed as hyperechogenic which is usually represented with lighter colors on medical ultrasonography. An increased lipid deposition in the hepatocytes will reflect hyperechogenic parenchyma.
- Hepatic Artery Resistive index (HARI) – is a sonographic index that assess the systolic and end-diastolic wave of the hepatic artery. Normal range value is between 0.55 to 0.80. Low resistive index is more specific for live disease[22]. It is determined with the following formula:

$$\frac{\text{Peak systolic velocity (PSV)} - \text{End diastolic velocity (EDV)}}{\text{Peak systolic velocity (PSV)}}$$

- Excessive alcohol consumption – an alcohol consumption of more than 20 grams per day for women and more than 30 grams per day for men.

METHODOLOGY

Research Design

An observational descriptive study design was done at Ultrasound Section of QCGH Department of Radiology.

All patients referred to the Ultrasound Section of QCGH Department of Radiology for liver, upper abdomen or whole abdominal ultrasound was evaluated. The ultrasound request was assessed based on the history and physical examination written in the request, along with the initial impression made by the attending physician. All clinical data listed in the request has been validated by the principal investigator.

Data collection Method

Research informed consent to participate voluntarily in the research investigation was discussed to the participant, as per ethics guideline of the Philippines. These include the purpose of the study, duration of research, procedure, potential risks, benefits, compensation of participation and its confidentiality. All participants invited made their informed decision, enrolled and participated in the research investigation. The participants also received their certificate of consent.

Ethics approval with *reference number 2019-0085* for this research investigation was obtained from Far Eastern University – Nicanor Reyes Medical Foundation Institutional Ethics Review Committee (FEU-NRMF IERC), a level III accredited research ethics committee. A letter of intent to conduct research investigation was also secured and was given to the chief of clinics, department chair and training officer of the Department of Radiology.

The duration of the research investigation spanned in less than 36 hours (or 1 ½ day). These involves a 10-15 minutes interview and answering the formulated questionnaire, 8 hours fasting, 5-minute blood extraction, 10-25 minutes ultrasound

examination and 24 hours releasing of the result (*during this time, interpretation and typing of the results are done*).

Additional clinical information (*ex. History of alcohol consumption, past medical history, current medications and exercise pattern*) was extracted and interviewed based on the formulated questionnaire which lasted for about 10-15 minutes. Names of the participant were not placed on the questionnaire and were replaced with a unique identification code for privacy and confidentiality.

The participant was instructed to have 8 hours fasting prior to laboratory and ultrasound procedure. On the day of the scheduled examination, the participant was probed to proceed first to the Clinical Chemistry Section of Department of Pathology for blood extraction (*for determination of ALT, AST and FBS levels*) that took about 5 minutes. Results of ALT, AST and FBS were utilised for BARD fibrosis score.

The sonogram of the liver, upper or whole abdomen was performed by the principal investigator using Philips HD11 XE Ultrasound Machine with a low frequency transducer (3.5MHz). The ultrasound examination took about 10-25 minutes depending on the type of requested procedure (*Liver, upper abdomen or whole abdominal ultrasound*).

Sampling Design Process

Population

Patients with Non-alcoholic fatty liver disease (NAFLD) of both sexes aged 18 years and above were considered eligible for this study.

Sampling Frame

The total number of patients with non-alcoholic fatty liver disease (NAFLD) in the Quezon City General Hospital (QCGH) is 198 and the total number of patients with normal sonogram of the liver is 86 based on the reviewed registry list maintained in the Ultrasound Section of Department of Radiology from February to March 2019.

Sample Size

Using Epi-Info application, the principal investigator arrived at a computed sample size of 81 NAFLD participants with an alpha level of 0.05. In order to account for exclusion due to incomplete information, the principal investigator decided to inflate 20% to the planned sample size which is 16 for NAFLD group. Hence, the total number of sample size are 97 NAFLD participants.

Sampling Technique

The systematic sample technique was utilized in the selection of 97 NAFLD participants with a regular interval of 2 [population size (198) divide by sample size (97)].

Inclusion/Exclusion Criteria

The principal investigator **included** those participants with the following criteria: Liver sonographic findings of fatty liver infiltration, and risk factors for NAFLD (*e.g. body mass index [BMI] ≥30 kg/m2, elevated level of ALT and AST and type 2 diabetes mellitus*).

The principal investigator **excluded** the participants who had fatty liver disease from identifiable cause such as an excessive alcohol consumption (*>20 g/day for women, > 30 g/day for men*), and other causes of liver enzyme elevation (*autoimmune hepatitis, viral hepatitis, Wilson's disease, alpha-1 antitrypsin deficiency, drug induced hepatitis, hemochromatosis and neoplasia*) based on specific clinical and physical findings.

In this study, data collected from three (3) NAFLD participants were not analyzed due to excessive alcohol consumption.

Withdrawal Criteria

Participant who has hemophobia and/or needle phobia may withdraw his or her consent to participate in the research investigation. Blood work-up which include determination of FBS, AST and ALT levels are needed in the computation of BARD Fibrosis score. In this study, there were no documented withdrawals from the NAFLD participants.

Research Instrument

Philips HD11 XE Ultrasound Machine with a low frequency transducer (3.5MHz)

The participant was diagnosed to have fatty liver disease when the echogenicity of the liver was increased than that of the renal cortex. The ultrasound procedure was done by the principal investigator. Sonography findings of fatty infiltration can vary, depending on the amount of fat and whether deposits are diffuse or focal[8]. Participant with evidence of fatty liver disease was assigned to have NAFLD and further subdivided according to grading of fatty liver disease (grade I, II, & III) on the basis of liver parenchymal echogenicity. Severity of the fatty liver was graded based on the US findings into: **Grade I (mild)** – if the echogenicity is slightly increased with normal visualization of the diaphragm and the intrahepatic vessel borders; **Grade II (moderate)** – if the echogenicity is moderately increased with slight impaired visualization of the diaphragm and the intrahepatic vessels and; **Grade III (severe)** – if the echogenicity is markedly increased with poor visualization of the diaphragm, intrahepatic vessels and posterior segment of the right lobe[5].

Other sonographic information documented include liver size (longitudinal diameter of the right hepatic lobe), and color Doppler parameters (using B-mode) such as: resistive index (RI), peak systolic velocity (PSV) and end diastolic velocity (EDV) of hepatic artery.

All sonographic findings assimilated by the principal investigator was verified by the Radiology Consultant on-duty who is a Fellow of Ultrasound Society of the Philippines.

During the entire course of the examination, the participant was instructed that he/she may feel a cold sensation on the abdominal region, which is a normal experience, and ascribed to the ultrasound gel placed on the ultrasound probe.

BARD Fibrosis Scoring System

BARD fibrosis score is a clinically validated scoring system and uses a simple clinical history and serum biomarkers to assess the risk of advanced liver fibrosis for patients with Non-alcoholic fatty liver disease[7]. It utilizes the following parameters: body mass index (BMI), AST/ALT ratio and FBS.

In this study, blood extraction was done for determination of ALT, AST and FBS levels. The participant was instructed that he/she may feel minimal pain or discomfort at the punctured site (mostly at the antecubital fossa), which is a normal sensation during the examination.

Body mass index (BMI) is determined through the standard formula of weight in kilograms divided by height in meters squared [kg/m2]. Computed value of BMI was used as one of the variables in determining fibrosis score.

Alcohol Consumption (grams/day) Questionnaire

A standard questionnaire by *Poikolainen and Vartiainen 1997* that determines the average daily alcohol consumption was applied in this study. The questionnaire was utilized to exclude those participants diagnosed to have fatty liver disease from identifiable cause and one of which is excessive alcohol consumption (>20 g/day for women, > 30 g/day for men). In this study, data collected from three (3) NAFLD participants were not analyzed due to chronic alcohol consumption.

Participant's Data Sheet

All gathered questionnaires, laboratory and ultrasound results are recorded in the subject data sheet formulated by the principal investigator for easy collection and access of participant's data (*See appendices*). Participants' recorded data sheet was kept on locked files at all time. At the end of the research investigation, all gathered data from the participants' data sheet was destroyed after it was analyzed.

Statistical Method

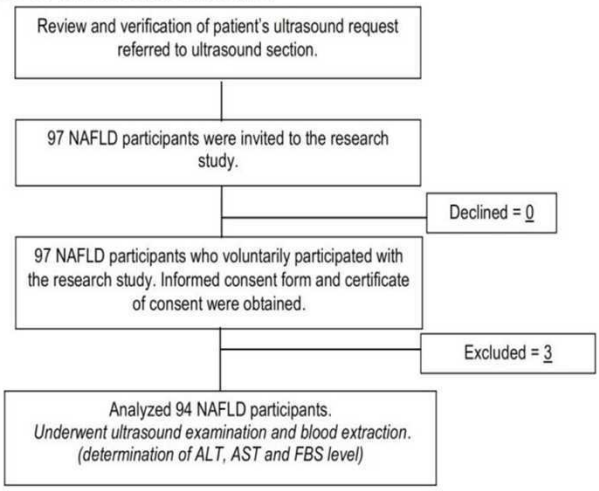
The number of retrieved, reviewed, selected and rejected clinical information was presented as a flowchart (Figure 1). The statistical analysis and tables were done using, Microsoft Excel Data Analysis ToolPak. The baseline characteristics of NAFLD participants are presented as tables of

frequencies, means and standard deviations. Determination of the concordance of the Hepatic Artery Resistive Index (HARI) with BARD Fibrosis score, both measured qualitatively was analyzed using correlation coefficient. Determination of the concordance across the different levels of severity of nonalcoholic fatty liver disease was done using analysis of variance. A statistically significant difference was considered if the p value is less than 0.05.

Cost Analysis

Cost for the procedure will depend on the request of the attending physician. It varies from liver, upper abdomen and whole abdomen ultrasound. The principal investigator's interest focused on the liver size, its corresponding echogenicity and Doppler Ultrasound parameters (RI, PSV, EDV) of hepatic artery, and the latter is not routinely included in the requested procedure. Hence, these additional parameters will not be charged to the participant. The principal investigator shouldered 50% as to the total cost of the ultrasound procedure of the NAFLD participant. Cost for laboratory (ALT, AST and FBS) was also shouldered by the principal investigator. The pricing of laboratory and ultrasound procedure fee was adopted from Quezon City General Hospital information system (HIS). Total cost of this study was highlighted on the appendices.

Figure 1. Flowchart of Data Collection



RESULTS

Baseline Characteristics of the NAFLD Participants

There is a total of 94 participants (66 males, 28 females) with mean age of 44.6 participated in the research investigation. The sample comprised of participants of both sexes aged 18 years and above who were diagnosed with nonalcoholic fatty liver disease (NAFLD) through sonographic features with no history of excessive alcohol consumption and other known history of liver enzyme elevation (eg. Hepatitis, drug-induced hepatitis, neoplasia, etc) based on clinical and physical examination. It was found that most of the participants with NAFLD had Grade II (moderate) fatty liver changes (51.1%), followed by Grade III (severe) fatty liver changes (26.6%), and Grade I (mild) fatty liver changes (22.3%) [Table 1]. The majority of the NAFLD participants have no history of alcohol consumption (67.0%) [Table 1]. Only 33.0% has a history of mild alcohol consumption with male preponderance (71.0%). Both sexes have an average daily alcohol consumption of 19.91 grams/day for male and 14.56 grams/day for female (Table 1). The age distribution and demographics of the participants is shown in Table 1. Most of the NAFLD participants are predominantly male (70.2 %). The mean age from both sexes is 44.6 and mostly in the 4th decade of life.

Table 1 also showed the risk factors for NAFLD. Majority of the participants are overweight (61.7%) followed by obese group (8.5%). It was also observed that 31.9% has pre-existing or newly diagnosed with diabetes mellitus (DM) type II who is currently taking oral anti-diabetic medications (29.7%). Upon checking their fasting blood sugar (FBS) level, it showed that 76.7 % of the NAFLD participants with pre-existing diabetes are compliant with maintenance medication since their FBS are within normal level ($\leq$125 mg/dl) with a mean value of 110.2 mg/dl (Table 2). However, 50.0 % of the NAFLD participants who are undetected with DM or having an unknown status of FBS level, showed elevated (>125 mg/dl) level with a mean value of 128.5 mg/dl (Table 2).

Sonographic features of the liver with NAFLD are reported in Table 1. It was found that 42.6% of the participants with NAFLD have a longitudinal liver diameter (midclavicular) ranging from 14.0-14.9 cm (42.6 %) followed by 15.0-15.9 cm (23.4%) with a mean liver size of 14.46 cm and 15.38 cm, respectively. Using the B-mode scan of Philips HD11 XE ultrasound machine, hepatic artery resistive index (HARI) was calculated among NAFLD participants and found that 45.7 % had a normal HARI value followed by 44.7% who have low value, with mean HARI of 0.68 and 0.45, respectively.

Markers used for BARD fibrosis scoring system are also shown in Table 1. It showed that 72.3% of the NAFLD participants have increased (>0.80) in AST/ALT ratio with mean value of 0.88. The fasting blood sugar (FBS) level was also determined and showed that 55.3% has increased (>125 mg/dl) in FBS level with mean value of 128.24 mg/dl.

HARI of NAFLD participants with different BARD Fibrosis scores

Table 3 shows the correlation of HARI and BARD fibrosis score. The correlation coefficient was -0.84 which showed strong negative relationship between the Hepatic Artery Resistive Index and Bard Fibrosis Score. This indicates that yielding a higher BARD Fibrosis score, the HARI equates to a lower value. The HARI of NAFLD with BARD Fibrosis scores of 1 and 2 ranges from 0.80 to 0.88 and 0.69 to 0.88 with an average index of 0.84 and 0.75, respectively. The HARI of NAFLD with BARD Fibrosis scores of 3 and 4 ranges from 0.42 to 0.69 and 0.39 to 0.70 with an average index of 0.54 and 0.52, respectively. Thus, Table 3 showed that there is an unwavering inverse correlation between HARI to BARD Fibrosis scoring system.

HARI and BARD Fibrosis score across different severity of NAFLD

Based on the p-values under Table 4 using analysis of variance, Hepatic Artery Resistive Index (HARI), EDV (cm/s), Bard Fibrosis Score, BMI (kg/m2), and AST/ALT Ratio have significant difference across the different severity or grading of NAFLD participants. Meanwhile, PSV (cm/s) and FBS (mg/dl) do not indicate any significant difference among the grading of fatty liver disease.

Grade III (severe) nonalcoholic fatty liver disease has the lowest mean HARI at 0.53 followed by grade II (moderate) at 0.76 and grade I (mild) at 0.81. Mean HARI value for grades I (mild) and grade III (severe) are not within the normal limits. Correspondingly, the BARD Fibrosis Score showed inverse ranking pattern across the different severity of NAFLD, grade I (mild) has the lowest score followed by grade II (moderate) and grade III (severe), which yielded having a mean score of 1.00, 3.29 and 3.56, respectively.

Table 4 showed that across the different severity of NAFLD, those who had grade III (severe) fatty liver disease commensurate to a higher BARD Fibrosis score and lowest Hepatic artery resistive index (HARI). And those who had grade I (mild) fatty liver disease corresponds with lower BARD Fibrosis score and highest HARI.

Table 1. Baseline Characteristics of the NAFLD participants (*n*=94)

	Frequency (%)	Mean	*SD*
CHARACTERISTICS			
Sex			
Male	70.2 %	NA	*NA*
Female	29.8 %	NA	*NA*
Age (years)		**44.670**	***9.24***
18-29	3.4 %	26.00	*4.20*
30-39	18.1 %	34.82	*2.92*
40-49	47.8 %	44.51	*2.49*
50-59	23.4 %	54.27	*3.40*
60-69	4.3 %	63.5	*3.08*
BMI (kg/m2)**		**27.254**	***2.95***
>40 kg/m2 (Extremely obese)	0	NA	*NA*
30-39.9 kg/m2 (Obese)	8.5 %	30.15	*0.14*
25-29.9 kg/m2 (Overweight)	61.7 %	28.92	*0.56*
18.5-24.9 kg/m2 (Normal)	29.7 %	22.98	*1.42*
<18.5 kg/m2 (Underweight)	0	NA	*NA*
Alcohol consumption			
None	67.0 % (63/94)		
With history of mild to moderate alcohol consumption	33.0% (31/94)		
Male	71.0 %	NA	*NA*
Female	29.0 %	NA	*NA*
Average mild-moderate alcohol consumption (g/day)***		**6.054**	*9.15*
Male	NA	19.91	*5.21*
Female	NA	14.56	*2.18*
Pre-existing or newly diagnosed DM	**31.9 %**	NA	*NA*
Pre-existing or newly diagnosed HPN	**11.7 %**	NA	*NA*
Medication History			
1. No medication intake	60.6 %	NA	*NA*
2. Multivitamins	21.3 %	NA	*NA*
3. Anti-hypertensive (*Losartan, Amlodipine, others*)	10.6 %	NA	*NA*
4. Anti-diabetic (*Metformin, others*)	29.7 %	NA	*NA*
5. Anti-dyslipidemic (*Rosuvastatin, others*)	14.9 %	NA	*NA*
Physical activity (with exercise)	**34.0 %**	**-**	*NA*

ULTRASOUND PARAMETER			
Liver size (cm)		**14.25**	*0.96*
10.0-10.9	0	NA	*NA*
11.0-11.9	1.1 %	11.90	*NA*
12.0-12.9	12.8 %	12.66	*0.17*
13.0-13.9	19.1 %	13.52	*0.28*
14.0-14.9	42.6 %	14.46	*0.30*
15.0-15.9	23.4 %	15.38	*0.27*
16.0-16.9	1.1 %	16.00	*NA*
HARI			
>0.80	9.6 %	0.84	***0.02***
0.55 – 0.80	45.7 %	0.68	***0.08***
<0.55	44.7 %	0.45	*0.05*
LABORATORY TESTS			
AST (U/L)	*NA*	37.794	*5.86*
ALT (U/L)	*NA*	46.165	*8.27*
AST/ALT ratio	*NA*	0.833	*0.12*
≤ 0.80	27.7 %	0.70	*0.07*
>0.80	72.3 %	0.88	*0.09*
FBS (mg/dl)****	-	117.330	*11.12*
< 125	44.7 %	109.00	*7.22*
> 125	55.3 %	128.24	*2.24*

NAFLD non-alcoholic fatty liver disease; *BMI* Body mass index; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase; *FBS* fasting blood sugar; *HARI* hepatic artery resistive index; *SD* standard deviation; DM *diabetes mellitus*; HPN *hypertension*;
**significant values at α = 0.05 are shown in bold text*
***Average Body Mass Index for both sexes*
****Average mild to moderate alcohol consumption for both sexes*
*****FBS of all NAFLD participants*

Table 2. FBS among NAFLD participants with Pre-existing or newly diagnosed DM and undiagnosed DM

FBS (mg/dl)	Pre-existing or newly diagnosed (*n=30*)		Undiagnosed (*n=64*)	
	Frequency (%)	Mean	Frequency (%)	Mean
>125	23.3 %	128.43	50.0 %	128.50
≤125	76.7 %	110.26	50.0 %	109.59

NAFLD non-alcoholic fatty liver disease; *FBS* fasting blood sugar; DM *diabetes mellitus*

Table 3. Correlation of Hepatic Artery Resistive Index (HARI) and Bard Fibrosis Score

BARD Fibrosis Score	Hepatic Artery Resistive Index (HARI) Average index	*Lowest index*	*Highest index*
1	0.84	0.80	0.88
2	0.75	0.69	0.82
3	0.54	0.42	0.69
4	0.52	0.39	0.70
Correlation Coefficient is **-0.84**			

Table 4. Hepatic artery resistive index (HARI) and BARD Fibrosis Score across different severity of Non-Alcoholic Fatty Liver Disease (NAFLD) (*n* = 94, means ± SD)

	Different severity of Non-Alcoholic Fatty Liver Disease						
	Grade I (Mild) (*n* = 21)		**Grade II (Moderate)** (*n* = 48)		**Grade III (Severe)** (*n* = 25)		*p**
Hepatic Artery Resistive Index (HARI)	0.81	(±0.058)	0.76	(±0.106)	0.53	(±0.098)	**0.000**
PSV (cm/s)	54.92	(±12.212)	57.97	(±12.786)	55.86	(±13.755)	0.607
EDV (cm/s)	11.42	(±4.22)	12.44	(±5.112)	23.33	(±5.503)	**0.000**
Bard Fibrosis Score	1.00	(±0.755)	3.29	(±0.865)	3.56	(±0.571)	**0.000**
BMI (kg/m2)	24.62	(±3.022)	28.21	(±2.351)	27.62	(±2.541)	**0.000**
FBS (mg/dl)	117.33	(±9.843)	116.95	(±11.25)	119.04	(±11.515)	0.748
AST/ALT Ratio	0.72	(±0.088)	0.81	(±0.069)	0.94	(±0.121)	**0.000**

PSV peak systolic velocity, *EDV* end diastolic velocity, *BMI* Body mass index, *FBS* fasting blood sugar, *AST* aspartate aminotransferase; *ALT* alanine aminotransferase
**significant values at α = 0.05 are shown in bold text*

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Non-alcoholic fatty liver disease (NAFLD) is characterized by imaging or histological evidence of steatosis in patients with predisposing factors such as obesity, diabetes, hypertension, and hypercholesterolemia. NAFLD patients should have no specific etiology of liver disease such as hepatitis or excessive alcohol abuse. Instrumental evaluation of NAFLD is made with conventional ultrasound (US), with 94% sensitivity and 95% specificity in the detecting of fatty liver disease [21]. Because of its low cost, simple and rapid performance by skilled radiologist, it is more commonly requested imaging procedure in diagnosing NAFLD. Though histopathology is considered the gold standard for the diagnosis of NAFLD, it is not practically possible to perform biopsy for the colossal population of NAFLD and taking consideration of its various complication.

Baseline Characteristics of the NAFLD Participants

Among 94 participants diagnosed with non-alcoholic fatty liver disease (NAFLD), the study showed 70.2% cases were found in males. Similar results found by some investigators (Shivram Prasad, *et al.*, and Jen Jung Pen *et al.*,) who found that it has a male predominance among patients with NAFLD. In the article of Jen Jung Pen *et.al.*, this was attributable to the difference in body fat composition, lifestyle, and sex hormone metabolism.

It was also found in this study that the mean age for both sexes diagnosed with NAFLD is 44.6 years old. One study (Dhumal *et al.*,) showed similar findings where the prevalent fraction of people with fatty liver was in the age group of 4th to 5th decade. This is also showed in this study where 47.8% of the NAFLD participants belonged to the age group of 4th to 5th decade with a prevalence of 47.8% and 23.4%, respectively. This can possibly be attributed to the sedentary lifestyle and less engagement in physical activity in this age group[27].

In this study, only 29.7% had normal body mass index (BMI), 61.7% are overweight, and 8.5% are obese. In the study of Ghobad *et al.*, showed that most of the NAFLD patients are overweight and obese. In the study done by Mohammad Aleem *et*

al., showed that increasing weight was associated with increasing grades or severity of fatty liver.

Sonographic liver size of 75.6% NAFLD participants are within normal limits, on which 42.6% ranges from 14.0-14.9 cm with mean size of 14.46 cm. On the contrary, 24.5% is considered to have slight hepatomegaly, on which 23.4% ranges from 15.0-15.9 cm with mean size of 15.38 cm. The average sonographic liver size through midclavicular line is 10.0-12.5 cm in craniocaudal length. A liver that is longer than 15.5-16.0 cm in the midclavicular line (MCL) is considered enlarged [25]. There is lack of consensus on standard reference values for sonographic measurement of the liver [37]. There have been quite a few previous reports giving the standard sizes of liver through ultrasound in general adult population, but none has been done in Asian populace, and in particular with NAFLD patient. In this study, the liver span of the NAFLD patient was found to be significantly higher or within the upper margin when compared with the average liver size. In the study of Khanal, *et al*., showed increasing grades of NAFLD were significantly associated with increasing levels of serum cholesterol, LDL, *liver size* and BMI. There is moderate positive correlation seen between increasing severity of fatty liver and increasing liver size (r=0.405). In the study of Tana *et al*., the possible explanation would be as the severity of the fatty infiltration increases there is more deposition of fat in the liver, causing increase in the liver span. It is plausible that when NAFLD patients with reduced liver span, the clinician must suspect and must adequately evaluate to rule out the possibility of fibrous tissue accumulation. However, due to paucity of literature regarding liver span in various severity of NAFLD (histologically diagnosed), validation of our remark needs furthermore studies in this concern.

Concordance of HARI and BARD Fibrosis score across different severity of NAFLD

Although ultrasound can demonstrate fatty liver, however its reliability to predict fibrous tissue in NAFLD is not well established. The recent development of novel techniques, such as elastography, has led to great advances in the assessment of liver fibrosis, but these methods are not readily available, are expensive, need additional US equipment and have significant limitations in obese patients[5,6,7]. The failure rate is 2-10% of patients with BMI >30 kg/m^2 [2, 7]. Liver biopsy remains the gold standard in the assessment of advanced liver fibrosis in the course of NAFLD; therefore, identification of these patients is with prodigious importance[14]. Various simple, non-invasive methods have been established as an alternative to liver biopsy. Among the serological tests that could be expedient, the BARD fibrosis scoring system, a simple, readily available and, has been corroborated in several studies which give auspicious results.

The BARD fibrosis score is easily calculated, and requires clinical and laboratory parameters such as BMI, fasting blood sugar and AST/ALT ratio. It represents a simple method of assessing the presence of advanced liver fibrosis in NALFD patients [6]. The BARD Fibrosis scoring system has been validated by liver biopsy. A recent study found that the BARD fibrosis score has a negative predictive value (NPV) of 94% [15]. Similar study validated 126 patients with biopsy proven NALFD reported the sensitivity, specificity, PPV and NPV of 88.89, 88.89, 68.57 and 96.70%, respectively [8]. The total possible score ranges from 0-4. In this study, it revealed contrasting BARD fibrosis score across different severity of NAFLD with mean scores of 1.0, 3.3 and 3.6 for grades I (mild), II (moderate) and III (severe) fatty liver disease, respectively. In the study of Harrison *et al*., found high values of NPV (96%) in patients with low BARD score (0-1), which enabled identification of patients without advanced liver fibrosis and a higher score (2–4) was associated with advanced liver fibrosis. The findings of this study are similar with the study of Hussein Ageely, *et al*., which revealed that grade 3 fatty liver disease is associated with high BARD fibrosis score, and hence correlated significantly with advanced fibrosis. Thus, it can deduce in this study that those with grade III fatty liver disease having BARD fibrosis scores of 3-4 are associated with advanced liver fibrosis. The result gathered can be a parameter in the primary health care, since it provides positive data necessary for identification of those patients with NAFLD who require liver biopsy for histologic diagnosis of advanced liver fibrosis and assessment of its severity. Liver biopsy is the most sensitive and specific to establish and assess the degree of inflammatory activity (grading) and extent of fibrosis (staging), but in general it

should be weighed against the small, but not negligible, risk of a various complication. Hence, imaging modalities (ie. Ultrasonogram, computed tomography, magnetic resonance imaging) are now becoming reasonable and acceptable alternative for diagnosing NAFLD.

Literature shown that as the disease progresses from isolated fatty liver disease to NAFLD to cirrhosis, the hemodynamics of the vascular components passing thru the portal triad (portal vein and hepatic artery) also changes, the resistance to the blood flow in these vessels increases secondary to changes occurring in the liver (ex. inflammation, fatty accumulation, inflammation with or without fibrosis) [16-19]. Of the total hepatic blood flow, one third is supplied by the hepatic artery and about two thirds is supplied by portal venous blood [30]. Erdogmus *et al*., and Balci *et al*., hypothesized that the fatty liver infiltration causes increased resistance to the portal vein flow thereby reducing the portal blood flow to the liver. However, some studies disputed this hypothesis. In the study of Oguzkurt *et al*., reported no correlation between the degree of fat infiltration and the hepatic vein waveform pattern. Ehsan Solhjoo *et al*., found no correlation between the severity of fat deposition and portal vein pulsatility index (VPI), Mean flow velocity (MPF), or rate of abnormal hepatic vein waveform patterns. Because of these contrasting findings, the present study opted not to utilize portal vein indices as a variable for assessment of advance liver fibrosis. Interestingly, there are only few studies have correlated the hepatic artery indices with the different grades of severity of the NAFLD. Hence, this study was done to observe whether there is significant hemodynamic changes in the HARI of NAFLD patients and whether the hemodynamic changes correlates with the different severity assessed thru US grading.

In this study, it showed that there is a significant difference in the HARI across different severity of NAFLD. The study revealed that grade III (severe) NAFLD has the lowest mean HARI value (0.53±0.09) when compared to grades II (moderate) and I (mild) yielding 0.76 and 0.81, respectively. Similar findings reported by Tana, *et al*., and Padhmini B, *et al*., showed variations in HARI value of patients with different severity of NAFLD, diagnosed based on ultrasonography. The research investigators concluded that HARI was found to be significantly lower in the NAFLD when compared to healthy group. When compared to the different grading of NAFLD, they found that Grade III (severe) fatty liver disease has the lowest HARI value followed by grade II (moderate) and grade I (mild), on which similar ranking pattern is established to this present study[2, 4]. The usual range of HARI in normal, as well as post-transplant patient, is between 0.55 and 0.80[22]. Surprisingly, among the two studies mentioned previously, this present study documented the lowest HARI value for grade III (severe) NAFLD (vs 0.61±0.10 and 0.61±0.05, respectively). This study when compared to the investigation done by Padhmini B, *et al*. documented a strong negative relationship (r=-0.84) between the Hepatic Artery Resistive Index and Fibrosis Score (vs r=-0.51). The lower value of HARI can be attributed that as the fatty infiltration progresses, it causes increase in resistance to blood flow and as a compensatory, the hepatic artery blood flow increases thereby reducing its HARI[20,23,24]. In this study, the total hepatic blood volume is not estimated because of the intricate visualization of other arteries (ex. Common hepatic artery).

Concordance of HARI and BARD Fibrosis Score in the Assessment of Advanced Liver Fibrosis Among NAFLD Patients

With the use of HARI value thru B-mode technique on ultrasonography, the assessment of advanced liver fibrosis in the course of NAFLD can be established readily. Although its accuracy is not well established because there are no reports that correlated HARI value with the biopsy proven advanced liver fibrosis in the course of NAFLD. Since the BARD Fibrosis scoring system has been validated by liver biopsy, the present study correlated the HARI value with the BARD Fibrosis score in the assessment of advanced fibrosis among NAFLD patients.

This study showed inverse correlation between HARI and BARD fibrosis score (r=-0.84). The HARI of NAFLD in this study with BARD Fibrosis score of 1 to 4 has an average index of 0.84, 0.75, 0.54 and 0.52, respectively. This indicates that yielding a higher BARD Fibrosis score, the HARI equates to a lower value. According to the study of Ageely et.al, a BARD Fibrosis score of 2-4 points

indicate significant liver fibrosis[5]. In this study, the mean HARI value of grade III (severe) NAFLD is 0.53±0.09 with a mean BARD fibrosis score of 3.56. These finding suggest fibrous tissue accumulation and maybe attributed in increased arterial rigidity, and that the different tissue composition of the liver (adipose or fibrous) can influence HARI [2, 4]. The HARI has demonstrated a significant negative correlation with advanced liver fibrosis when correlated with BARD fibrosis score.

The cutoff HARI values may be helpful in the selection of NAFLD patients to undergo liver biopsy for histologic diagnosis of advanced liver fibrosis. Another major benefit of noninvasive ultrasound HARI determination is that the examinations can be readily repeated; a method helpful for the long-term monitoring of liver fibrosis.

Lastly, the study also supports the hypothesis that there are different physiopathological mechanisms influencing the hepatic arterial resistance in the different severity of NAFLD [2, 4]. Thus, this study showed that the conventional Doppler US with hepatic artery indices and laboratory variables can be helpful to detect fibrous tissue accumulation in the course of NAFLD.

LIMITATIONS OF THE STUDY

The present study has three limitations. First, the sample may not be a representation of NAFLD population of the Philippines, since it was conducted in only one tertiary government hospital in Quezon City, Metro Manila, Philippines. This study should be corroborated by larger NAFLD population from other hospital to estimate the prevalence of NAFLD in the country. Second, assessment of fibrous tissue accumulation was done through correlation between HARI and BARD fibrosis score, parameters determined on clinical, laboratory and imaging variables, and not with the histopatholic results. If correlated with the biopsy proven advance liver fibrosis in the course of NAFLD, the cutoff HARI value can be a sole indicator and may integrate in the clinical practice guideline as a non-invasive alterative imaging technique in the assessment for advanced hepatic fibrosis. Thus, treatment plan can be planned to prevent from progression into liver cirrhosis and evaluation of its effectiveness. Lastly, the diagnosis of NAFLD was based on correlation of clinical and ultrasonographic findings. The grading gives an indirect estimation of the quantification of fat deposition in the liver [27]. Radiologist observation is a major variability of US, however, it has been shown to have satisfactory sensitivity and specificity for identifying moderate to severe hepatic steatosis. Though it was not confirmed by liver biopsy, ultrasonography is by far the most common imaging modality of diagnosis NAFLD in clinical practice. Quantification of fat content using CT scan or MRI may be more reliable for estimation of fat deposition in the liver. Quantification of fat using CT and MRI with lipid correlation can be done in the future.

RECOMMENDATIONS

The present study has the following recommendations: First, further studies to look for the exact physiopathological event on hemodynamic changes (ie. Hepatic artery resistive index) like positive feedback mechanism and role of possible mediators, which might be tangled in the proposed increase in hepatic arterial blood flow. These changes might be important for prognosticating advanced hepatic fibrosis in the course of NAFLD because if the cutoff of HARI value when used alone, or in combination with other fibrosis score can detect early cirrhosis with a higher sensitivity and specificity, then it will be a better noninvasive and cost effective method for risk assessment. Second, further studies to look whether medication intake, lifestyle modifications and exercise affects the hemodynamic changes (ie. Hepatic artery resistive index) in hepatic arterial blood flow. HARI can be used as a noninvasive diagnostic value for monitoring treatment response.

Declaration of Conflict of Interests

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Comparison of Post-Operative Outcomes Between Enhanced Recovery After Surgery Versus Standard Operative Protocol Among Cesarean Delivery Mothers at a Tertiary Hospital*

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ABSTRACT

This Randomized Controlled Trial sought to determine whether mothers who underwent Cesarean delivery had better postoperative outcomes when subjected to the Enhanced Recovery After Surgery (ERAS) protocol compared to mothers who also underwent Cesarean section as a mode of delivery but were under the Standard operative protocol.

The research concentrated on evaluating the postoperative outcomes of the patients in the study through the following factors: length of hospitalization, efficiency and cost-effectiveness of hospital expenses, early resumption of diet and early ambulation, breastfeeding initiation and continuation.

A total of 72 subjects were included in the study. Two were not included due to conversion to general anesthesia. Thirty two (44.4%) were randomized to the ERAS protocol while 40 (55.6%) patients were randomized to Standard postoperative procedure. Demographic characteristics were recorded and comparable between the two groups. Mothers randomized to the ERAS protocol had significantly shorter length of stay compared to mothers in the standard operative procedure with a mean of 53.01 hours (2.21 days) and 78.86 hours (3.29 days) respectively. Mothers randomized to the ERAS protocol spent significantly lower hospitalization cost compared to mothers in the standard operative procedure. There was no significant difference noted in the proportion of mothers with fever between the two groups (p=0.25). Mothers randomized to the ERAS protocol had significantly lower post-operative pain compared to mothers in the standard operative procedure. The time from end of OR until general liquids was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure. Similarly, the time from end of OR to flatus and bowel movement was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure. The time from end of OR to removal of foley catheter and time to void after foley catheter removal was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure. Finally, there was a significant difference noted in the length of time from end of OR to breastfeeding as proven by all p value of 0.02. Mothers randomized to the ERAS protocol had significantly shorter length of time from end of OR to breastfeeding compared to mothers in the standard operative procedure with a mean of 30.67 hours and 43.09 hours respectively.

Ultimately, the study concentrated on Emergency or Elective Cesarean deliveries of Low risk patients as well as patients with controlled gestational or overt diabetes mellitus, thyroid disorders in euthyroid state, and hypertensive disorders not complicated with eclampsia. This study did not seek to generalize the benefit of ERAS protocol on all Cesarean deliveries.

ERAS protocol showed better post-operative outcomes compared to the Standard operative protocol in terms of shorter length of hospital confinement, lower cost of hospitalization, no occurrence of post-operative infections and complications, shorter length of time from operation

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to diet progression tolerance, passage of flatus, bowel movement, shorter length of time from end of OR to removal of foley catheter and time to void and finally shorter time from operation to initiation of breastfeeding and continuation.

Keywords: Enhanced Recovery After Surgery, ERAS protocol, Cesarean delivery

INTRODUCTION

Enhanced recovery after surgery (ERAS) is a concept that combines evidence-based aspects of peri-operative care which aims to accelerate patient recovery. It had been developed for patients undergoing colorectal surgery but was adopted by other surgical specialties with similar positive outcomes. [1]

The principles of ERAS protocol involve interventions that span the pre-operative, intraoperative and post-operative periods. It addresses the common reasons why there is delay in patient recovery from surgery and prolonged hospital stay due to inadequate analgesia slow return of bowel function, and delayed ambulation.[1]
According to an article entitled Rising Rate of Cesarean section- A Year-end review, there is a rising trend of Cesarean section in modern obstetrics which is a major concern in the Health Care system all over the world. With all the limited health care resources in developing countries like the Philippines, the national CS rate is now at 22.7%.[3] In addition, the World Health Organization states that no region in the world is justified in having a Cesarean rate greater than 10-15% and this rising trend definitely has major implications.[4]

Financial burden is also a major consideration during childbirth. The cost of Cesarean delivery in over 40 maternity hospitals in Manila ranges from 20,000 to 100,000 (with or without Philhealth coverage)[2] During a five-year period from 2013-2017, Philippine Obstetrical and Gynecological Society Annual Census reported approximately 30% Elective or Emergency Cesarean Section which corresponded to 145,647 Cesarean deliveries from a total of 447,614 deliveries.

Due to the rising trend of Cesarean section rate, the ERAS protocol will serve to address the common reasons that delay recovery of the mother (inadequate analgesia, slow return of bowel function and delayed ambulation) which will shorten the hospital stay and the cost of hospitalization.

The significance of this study is to determine whether women randomized to an enhanced recovery program will have improved post-operative outcomes, including reduction in length of hospital stay, lower hospital bill, early resumption of diet and early ambulation, improved breastfeeding initiation and continuation without compromising the satisfaction of patients compared to the standard postoperative recovery interventions.

If this study will seek to prove whether ERAS protocol is superior than the Standard Operative Care in terms of post-operative outcomes, it will serve as a reference for probable implementation and support of ERAS protocol in all Cesarean deliveries at MCU-FDTMF Hospital and other Hospitals in the Philippines. This research may also promote modifications in the ERAS protocol suited for the needs of each individual Hospital and may be used for further studies.

The ERAS society was founded in 2010 which aims to develop international consensus guidelines and resources for the implementation of ERAS bundles. This consensus outlined techniques to decrease perioperative physiologic stress to reduce perioperative morbidity and mortality, accelerate recovery, and decrease cost of care. [6] This research protocol has been patterned from the guidelines for Antenatal and Pre-operative care in Cesarean Delivery recommendations of the ERAS society.

Enhanced Recovery After Surgery, also known as "Enhanced Recovery Protocols" (ERP) or "Fast-track surgery" is a multidisciplinary approach aimed to enhance recovery and preserve immune function.[5,6] Its effectiveness in reducing hospital stay is well described in literature and mostly in colorectal surgery. No mechanical bowel preparation, no preoperative fasting, early postoperative feeding, avoidance of opiates and avoidance of fluid overload.

In one study, it was demonstrated that there was surgical stress reduction in elderly patients undergoing elective colorectal laparoscopic surgery

in an ERAS protocol. In the postoperative period, ERAS group patients returned faster to a normal bowel function. Passage of flatus and return to a solid meal was evident in the ERAS group (EG) and was statistically significant [5]. First flatus occurred on 1.5 +/- 0.6 versus 2.4 +/- 0.9 days in the Standard group (SG). However, there was no difference between groups for passage of stool. Solid meal was tolerated at day 1.2 +/- 0.8 in EG versus 2.9 +/- 0.3 days in the SG ($p < 0.05$). EG patients could walk at least 100 meters on day 1.6 +/- 0.8 versus 2.0 +/- 0.9 in the SG ($p<0.05$). Day of discharge was 4.7 +/- 1.2 in the EG versus 6 +/- 1.6 days in the SG ($p<0.05$)[5]

Enhanced recovery in obstetrics may be possible and beneficial for women who undergo Cesarean section since the principle of enhanced recovery is to speed up a patient's recovery after surgery and to improve patient outcomes. In a randomized controlled trial published by Chion Tan et al, women discharged on day 1 compared to day 2 following elective cesarean section found no significant difference between the two groups looking at two primary outcomes: maternal satisfaction with discharge date and exclusive breastfeeding rates at six weeks. Maternal satisfaction for women discharged on day 1 was 87.1% compared with 85.5% for women discharged on day 2 (relative risk 1.1, 95% CI 0.6-2.1). A number of factors affect breastfeeding rates and it is well established that cesarean section (elective or emergency) has a negative impact, possibly as a result of the inability to breastfeed comfortably in the delivery room or in the immediate post- partum period. It has also been established that the long-term success of breastfeeding is largely dependent on factors outside the hospital. Therefore, it could be postulated that early discharge may lead to improved breastfeeding rates. However, this was not evident with exclusive breastfeeding rates at six weeks being comparable in both groups: day 1 discharge 44.7% compared with 44.9% on day 2 discharge (relative risk 1.0, 95% CI 0.7-1.5).[12]

There are already many aspects of current routine perioperative care of the patient undergoing a cesarean delivery that are consistent with components of ERAS. A survey of Obstetric anesthesiologists in the UK conducted in 2013 showed that majority of respondents supported the concept of ERAS for cesarean delivery and most were considering or were in the process of implementing ERAS protocol at their institutions.[1]

In a study done by I.J. Wrench entitled "Introduction of Enhanced Recovery for Elective Cesarean Section Enabling Next Day Discharge: A Tertiary Center Experience", they have introduced the ERAS protocol among Cesarean section mothers in Jessop Obstetric Unit, United Kingdom which is a tertiary referral center with approximately 7000 deliveries per annum. A multidisciplinary team was convened to introduce ERAS for elective CS to the unit which included anesthetists, obstetricians, hospital and community midwives, breastfeeding specialists, patient representative, senior neonatal nurse and pharmacist.[10]

Features for planned CS that were already consistent with fast-track surgery included minimal interruption of oral intake, clear fluids up to 2 hours before surgery.[10]

Scientific evidence has shown that intake of clear fluids until 2 hours before surgery does not increase gastric content, reduce gastric fluid pH, or increase complication rates. Hence, in patients without conditions associated with delayed gastric emptying the intake of clear fluids until 2 hours before the induction of anesthesia as well as a six-hours fast for solid food is now recommended. In order to reduce postoperative insulin resistance and associated risks for complications, carbohydrate loading before surgery has been advocated to achieve a metabolically fed state. In the last decade an increasing number of original studies, systematic reviews, and meta-analyses have shown that carbohydrate loading attenuates the increase in insulin resistance related to surgery and hence should be used routinely in major abdominal surgery.[7] The standard anesthetic technique utilized in the study of I.J. Wrench was a subarachnoid block with spinal diamorphine (94% of patients) and postoperative analgesia consisted of regular paracetamol and ibuprofen with liquid oral morphine for breakthrough pain. [10] In conclusion, this study resulted in a substantial rise in the proportion of patients leaving hospital the day after surgery. The proportion of women Discharged on day 1 increased from 1.6% in the first quarter of 2012 to 25.2% in the first quarter of 2014. There was no increase in the postoperative maternal

readmission rate after early discharge. The 30-day readmission rate was 4.4 % for those discharged on Day 1 and 5.6% for day 2. This readmission rate for those leaving after one night's stay was similar to those going home on Day 2, suggesting women were ready to be discharged at the earlier time. [10]

Based on the ERAS society recommendations on gynecologic surgery, the concept of achieving analgesia through the additive or synergistic effects of different types of analgesics is not new. Non-steroidal anti-inflammatory drugs (NSAIDS) have been extensively investigated, both as part of a multi-modal analgesic regime and are effective at reducing pain and opioid consumption and improving patient satisfaction and a combination of NSAID and acetaminophen is more effective than either drug alone.[8]

Management of postoperative nausea and vomiting was at the discretion of anesthetist, and patient mobilization and removal on the morning after surgery remained unchanged. [10] Dexamethasone appears to have analgesic effects, as well as preventing post-operative nausea and vomiting, so it may be useful as part of an enhanced recovery pathway. Intravenous lidocaine is gaining popularity as an analgesic adjunct in abdominal surgery.[8]

Preoperative counseling helps to line expectations about surgical and anesthetic procedures and can diminish fear, fatigue, pain and enhance recovery and early discharge. Education including verbal explanation, leaflets and multimedia information containing description of the procedure and cognitive interventions may improve control of pain, nausea and anxiety after surgery. [7]

In the intraoperative care which incorporates the prophylactic antibiotic, Cesarean delivery increases the danger infection 5 to 250-fold compared to vaginal delivery. There is however conclusive evidence that prophylactic antibiotics should be administered to all or any women undergoing cesarean delivery. Traditionally, prophylactic antibiotics are not being given until cord clamping due to concern of neonatal exposure to antibiotics. There is however conclusive evidence that prophylactic antibiotics be administered within 60 minutes before skin incision to diminish incidence of maternal postpartum infection. [1]

In case of a prolonged operation, severe blood loss and in obese patients the dose should be repeated. And if hair removal is mandatory then hair clipping is preferred rather than shaving. Chlorhexidine-alcohol is chosen than an aqueous povidone-iodine solution for skin cleansing.[7] The current recommendation may be a single dose of a broad spectrum antibiotic. [1]

The goal of intravenous fluid therapy is to sustain normovolemia and reduce flux across the extracellular space. Enhanced recovery protocols and modern surgical techniques decrease the necessity for both total volume and duration of intravenous fluid therapy. While salt and fluid overload within the postoperative period may be major explanation for morbidity, very restrictive fluid regimen also cause increased morbidity and mortality and thus should be avoided in favor of euvolemia.[7] The usefulness of goal-directed fluid therapy has not been investigated within the Cesarean delivery population.[1] However, within the ERAS society guidelines for intraoperative care in Cesarean delivery, the recommendations stated that maintaining adequate uterine perfusion does not only optimize fetal oxygenation but also can prevent acidosis as well as improve delivery of nutrients and eliminate waste products from the uterine myometrium. Perioperative and intraoperative euvolemia are important factors in patient perioperative care and can lead to improved maternal and neonatal outcomes after cesarean delivery.[11]

In an ERAS protocol, a total hourly volume of not greater than 1.2 ml/kg (including drugs, approximately 90 ml/hour for a 75 kg female) if an intravenous fluid must be maintained. Balanced crystalloid solutions are preferred to 0.9% normal saline since there is a cumulative risk of hyperchloremic acidosis. Oliguria as low as 20 cm^3/hour is a normal response to surgery, and the need for further intravenous fluid boluses should be assessed within clinical context. Intravenous fluids should be terminated within 24 hours after surgery. Balanced crystalloid solutions are preferred to 0.9% normal saline. [8]

During anesthesia and major operation there is a high risk of hypothermia due to exposure and impairment of the thermoregulatory response leading to accelerated heat loss. Hypothermia impairs drug metabolism, adversely affects coagulation and increase bleeding, cardiac morbidity and wound infection. Postoperative shivering also increases oxygen consumption at a critical time and may worsen pain. Warming should be continued into the postoperative period to make sure the patient leaves the post anesthetic care unit with a temperature >36 C.[7] A meta-analysis of 13 randomized trials by Sultan et. al reported that active warming in women undergoing elective cesarean delivery under spinal anesthesia reduced the utmost fall in temperature and decreased the incidence of hypothermia and shivering in comparison with controls not actively warmed. Maintaining normothermia can help facilitate early maternal bonding with the newborn.[1] ERAS guidelines of Cesarean delivery states that body temperature should be measured and maintained between 36.5 and 37.5 C after birth, through admission and stabilization.[11]

Pneumatic compression devices are recommended for all women undergoing Cesarean delivery and not already receiving pharmacologic thrombophophylaxis.[1] Pneumatic compression stockings reduce the speed of Venous thromboembolism when compared to observation. In gynecologic oncology patients, the risk reduction is equivalent in comparison to heparin and improved when combined with heparin. Graduated compression stockings decrease the percentage of DVT in hospitalized patients, especially when combined with another method. [8]

A variety of randomized trials on the topic of early feeding (defined as having oral intake of fluids or food within the first 24 hours after surgery) have been performed in gynecologic oncology. The benefits of early feeding include accelerated return of bowel activity, reduced length of stay, with no evidence of greater complication rates related to wound healing, anastomotic leaks or pulmonary complications. It is vital to note that early feeding is associated with a higher rate of nausea, but not vomiting, abdominal distension, or nasogastric tube use. Perioperative use of chewing gum had a positive effect on the incidence of postoperative ileus (36% vs 15%) and length of stay (1-day reduction) in a randomized trial of patients undergoing staging for gynecologic malignancies. [8]

The physiologic study of the digestive tract shows that the stomach and small bowel resume function within eight hours, large bowel activity returns within 48 hours and rectosigmoid function recovers within 72 hours postoperatively. Usually, clinicians withhold post-cesarean women from oral intake for 18-24 hours after surgery or until the presence of hunger, bowel sounds and/or the passing of flatus has been observed. Visceral irritation during Cesarean delivery causes dopamine and serotonin secretion, which stimulates the medullary vomiting center and causes postoperative nausea and/or vomiting.

The study of Nantasupha et. al.,investigated the effect of domperidone as a possible accelerator in gastrointestinal recovery. The main objective in the study was to compare the efficacy of early oral feeding (EOF) and early oral feeding plus domperidone with a standard diet schedule to look at tolerance to regular diet in women who had undergone a cesarean delivery (CD). Group A were given a conventional diet schedule: fasting for 18-24 hours after surgery, then sipping water, consuming a liquid diet, soft diet, and regular diet consecutively. Group B women received early oral feeding: started sipping water at 3-8 hours after surgery, followed by a soft and then a regular diet. Group C was the same as group B, plus three 10 mg doses of oral domperidone before the first three meals. The primary outcome was time to regular diet tolerance. Secondary outcomes indicated and as follows: time to first flatus; time to ambulation out of bed; duration of intravenous fluid infusion; duration of indwelling foley catheter; length of hospitalization; postoperative pain score; patient satisfaction score; breast milk expression and rate of postoperative complications. Outcomes of the study showed overall median time to regular diet tolerance and median length of hospitalization was 36.6 (27.2-51.8) hours and 65 (53.4-69.6) hours respectively. Most of the subjects in the two early oral feeding groups achieved regular diet tolerance within 24 hours postoperatively, especially in group B, while the subjects in the two EOF groups achieved regular diet tolerance within 24 hours postoperatively, especially in group B, while the

women with a conventional diet schedule achieved regular diet tolerance at 48 hours after CD.[9]

An early regular diet within eight hours after surgery has been shown to lead to a shorter time to bowel functions and a faster return to a solid diet. Shorter mean hospitalization stay has also been demonstrated. This study support EOF by showing that mean time to regular diet tolerance and mean time to flatus in both EOF groups were significantly shorter than those of the conventional diet schedule group, indicating an earlier return to normal bowel function. The resulting earlier ambulation and oral food intake led to a shorter urinary catheter indwelling period and intravenous infusion duration, which, in turn, lead to better ambulation. The patients had a faster return to normal daily activities and an accelerated ability to breastfeed. In other words, the EOF groups had better quality of life than the conventional group and recovered more quickly. Median length of hospital stay within the EOF groups was about 9-12 hours less than the conventional diet schedule group, resulting in reduced caregiver workload and reduced hospital costs. Compared to other major operation, during which visceral stimuli aggravate nausea and/or vomiting, visceral manipulation in CD is minimal. Based on our findings and our review, the resulting effects of CD could also be insignificant and EOF can be commenced with less undesired outcomes. [9]

In conclusion, there is no advantage of EOF with domperidone over EOF only. Visceral manipulation in CD may not be to the extent that any benefit would be perceivable from the anti-emetic mechanism of domperidone. Furthermore, multiple mechanisms may be relevant to recovery of postoperative gastrointestinal function, including the degree of autonomic nervous pathway disturbance, amount of inflammatory mediators and cytokines, anesthetic methods, pain control medicine and gut hormones. [9]

One more reason for the choice to use Domperidone was the expected lactation induction effect; however, breast milk expression wasn't statistically different among the study groups. We measured breast milk expression instead of breastfeeding time (as in previous studies), because breast milk expression can be assessed without affecting the well-being of the neonate. Domperidone didn't enhance the return of gastrointestinal function. To facilitate an accelerated return to normal activity and shorten the duration of clinical intervention in postoperative CD women, EOF should be used in routine practice. [9]

In a case control study done by Laronche et al, they concluded that application of Enhanced Recovery pathway (ERP) after cesarean delivery is associated with improved maternal satisfaction and more positive feelings toward the relationship with the newborn. The aim of this prospective, multicenter study was to compare one maternity unit where ERP was not used versus two maternity units where it had been used. ERP was defined as postoperative combination of the subsequent practice patterns: early mobilization within 6-8 hours after surgery (at least sitting in a chair), early drinking and feeding (within 6-8 hours after surgery and generally include drinking during the PACU stay), maintenance of Intravenous infusion for fewer than 24 hours, early urinary catheter withdrawal (withdrawal within the first 12 hours) and early use of oral analgesics (first oral analgesic pills given within the first 24 hours). The first mobilization takes place 12-24 hours after surgery. Drinking is advised during the stay in the PACU and the first light meal is provided 6 hours after surgery. In contrast to the conventional recovery (CR) program the urinary catheter is removed 24 hours after cesarean delivery or later with the venous cannula even later according to the time of return of the first flatus. This study showed that the ERP protocol applied in patients undergoing cesarean delivery is related to greater satisfaction towards the mother and baby relationship. This result is confirmed by the perceived better maternal-neonatal relationship and improved maternal experience of childbirth. The ERP group was more likely to report feeling close and/or to gain a secure contact with the newborn on Day 1 and 3. Also, within the ERP group, patients more often expressed to be "happy" and/or "reassured" on Day 1 and 3, compared to patients in the "conventional recovery" group. Positive or negative emotions expressed by the mothers in both groups are in relationship with the satisfaction that they feel towards the relationship with their babies. Differences between the ERP and CR groups were mainly observed on the first 24 hours after surgery, with results leading to the CR group becoming close to those of the ERP group on Day3. [13]

Postoperative enhanced recovery seems to improve mainly the maternal childbirth experience on the initial 24-48 hours postoperatively. The ERP seems to show that carrying and nursing of the baby was more frequent and less difficult. This difference is perhaps due to the fact that patients within the ERP group are rapidly mobilized and are less constrained by their intravenous infusion and urinary catheter but they also benefited by a faster recovery and oral intake.[13]

GENERAL OBJECTIVE

To determine the postoperative outcomes using ERAS versus standard protocol among post cesarean section deliveries at a tertiary hospital from September 2019 to September 2020

SPECIFIC OBJECTIVES

1. To present the demographic profile of pregnant patients who were admitted at OB Ward.
2. To determine whether there is a significant decrease in the length of hospital confinement between mothers randomized in the ERAS protocol compared to the standard operative procedure
3. To compare the cost of hospitalization between mothers randomized in the ERAS protocol versus the standard operative procedure
4. To compare the number of cases who developed post-operative infections (occurrence of fever, UTI, pneumonia) between mothers randomized in the ERAS protocol versus the standard operative procedure
5. To compare the length of time in hours from operation to breastfeeding initiation and continuation among mothers randomized in the ERAS protocol versus the standard operative procedure

DEFINITION OF TERMS

For the purposes of clarity and uniformity, for this study the following are the definition of each integral term used:

Hospital Expenses – the amount of money spent for expenses solely on Hospitalization will not include miscellaneous expenses such as Diapers, formula milk if used, etc.

Early Resumption of Diet – considered early if diet (which includes even clear liquids and water) was resumed within 30 minutes post-Cesarean section

Early Ambulation – whether the ambulation was initiated within 12 hours post-Cesarean section

Breastfeeding Initiation – first feeding of breastmilk within the first hour of delivery as recommended in the Essential Intrapartum and Newborn Care. However in this study, we will consider breastfeeding initiation from the length of time from transfer to the OB Ward or Room of choice post-cesarean section (not counting the hours of stay in the recovery room) to the first feeding of breastmilk to infant.

Serious and Complex Illness – severe illness which can be life threatening, with a significant degree of impairment or disability which also increases the need for comprehensive care and management (e.g Pulmonary hypertension, cancer, stroke)

Multimodal Intervention – holistic treatment that strives to combine a broad interactive set of systematic strategies and offer particular assessment tactics that enhance diagnosis, and improve treatment outcomes

Normothermia - core temperature between 36.5 and 37.5 degrees Celsius

Multimodal IV therapy – administration of 2 or more drugs that act by different mechanisms for providing analgesia

Aspiration – entry of materials such as food, pharyngeal secretions or stomach contents from the oropharynx or gastrointestinal tract into the larynx, lower respiratory tract, trachea or lungs
Hypertension in pregnancy – Elevated systolic blood pressure =/> 140 and diastolic blood pressure >/= 90 occurring after 20 weeks age of gestation on two occasions at least 4 hours apart

Gestational hypertension – clinical diagnosis defined by the new onset of hypertension (defined as systolic blood pressure ≥140

mmHg and/or diastolic blood pressure ≥90 mmHg) at ≥20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction The blood pressure readings should be documented on at least two occasions at least four hours apart.

Proteinuria - greater than or equal to 300 mg/24 hours urine collection; Protein/creatinine ration>/= 0.3, Dipstick reading of +1 in urinalysis

Preeclampsia - new onset of hypertension and proteinuria or hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman

Preeclampsia with severe features – diagnosed after 20 weeks age of gestation in previously normotensive women who develop: Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg and proteinuria (with or without signs and symptoms of significant end-organ dysfunction) or Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (with or without proteinuria) and one or more of the following signs and symptoms of significant end-organ dysfunction: (New-onset cerebral or visual disturbance, severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnosis or serum transaminase concentration ≥2 times upper limit of normal for a specific laboratory, or both, <100,000 platelets/microL, Progressive renal insufficiency (serum creatinine >1.1 mg/dL [97.3 micromol/L]; some guidelines also include doubling of serum creatinine concentration in the absence of other renal disease), and pulmonary edema

Chronic Hypertension – hypertension of any cause that predates pregnancy. BP >/= 140/90 before pregnancy or before 20 weeks age of gestation or both

Superimposed Preeclampsia - worsening baseline hypertension accompanied by new-onset proteinuria or other findings supportive of preeclampsia in a chronic hypertensive patient

Eclampsia – women diagnosed with preeclampsia and have convulsions that cannot be attributed to another cause.

HELLP syndrome - (Hemolysis, Elevated liver enzymes, Low platelets) probably represents a subtype of preeclampsia with severe features in which hemolysis, elevated liver enzymes, and thrombocytopenia are the predominant features, rather than hypertension or central nervous system or renal dysfunction, although the latter do occur.

Hyperthyroidism – Low Thyroid stimulating hormone (TSH) values based on trimester specific ranges: (0.1 mIU/L –first trimester, 0.2 miU/L- second trimester, and 0.3 miU/L – third trimester), and FT3, FT4 are above normal

Hypothyroidism – Increased TSH values based on trimester specific ranges: (2.5 mIU/L –first trimester, 3.0 miU/L- in the second and third trimester), and FT3, FT4 are below normal

Thyroid Storm – Hypermetabolic complication of hyperthyroidism characterized by Hyperpyrexia (temperature of >41 degrees Celsius), cardiovascular compromise (tachycardia out of proportion to the fever, dysrhythmia, cardiac failure), gastrointestinal upset (diarrhea), central nervous system changes (restlessness, nervousness, changed mental states, confusion), and seizures.

Gestational Diabetes Mellitus - if the fasting blood sugar >/= 92 mg/dL or the 2nd hour 75 g post prandial blood glucose >/= 140 mg/dL

Overt Diabetes – if any of the following values are elevated: fasting blood sugar >/= 126 mg/dL, glycosylated hemoglobin (HbA1C >/= 6.5%), random plasma glucose >/= 200 mg/dL or 2nd hour 75 g post prandial glucose >/= 140 mg/dL

Controlled Blood Sugar –capillary blood glucose monitoring maintained at normal levels (fasting glucose level of 95 mg/dL or less, pre-meal values of 100 mg/dL and 2 hour post-prandial of 120 mg/dL or less) During the night, glucose levels should not decrease to less than 60 mg/dL. Mean capillary glucose levels should be maintained at an average of 100 mg/dL with a glycosylated hemoglobin A1C (HbA1C) concentration no higher than 6%.

Pathologic Tracing – baseline fetal heartrate is not < 100 beats per minute, reduced or increased

variability, sinusoidal pattern. No repetitive late or prolonged decelerations for > 30 minutes (or > 20 minute if reduced variability). Decelerations for > 5 minutes.

COVID-19 – Infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a new strain of virus first detected in Wuhan, China in 2019. It is known to target a person's respiratory system. Infected patients may exhibit symptoms such as fever, cough, shortness of breath and in some cases muscle pain and sore throat. Some patients may also be asymptomatic. On March 11, 2020, the World Health Organization (WHO) characterized COVID-19 as a pandemic due to the exponential increase of the number of cases in more than 100 countries.

Level 4 Personal Protective Equipment (PPE) - this includes Coveralls, Surgical cap, N-95 mask, Scrubsuits, Goggles/Face Shield, Double gloves, Dedicated shoes, Shoe covers

Level 3 Personal Protective Equipment (PPE) - this includes cap and goggles or face shield, N-95 mask, gloves, Gown or coveralls

METHODOLOGY

Study Design

This study was a Randomized controlled trial which aimed to determine if Cesarean delivery mothers randomized to ERAS protocol had better postoperative outcomes versus patients randomized to Standard postoperative procedure. This Research protocol was mostly based from the guidelines that ERAS society published for Antenatal and Pre-operative care in Cesarean Delivery Recommendations. Others were patterned from previous ERAS protocols designed for colorectal, gynecologic and other fields of surgical specialty. This research proposal was presented to the Consultant staff of the OB-Gyne and Anesthesia Department of MCU-Hospital to help with the improvement of this paper and made consensus as to the standard dose of Anesthetic (Intrathecal morphine 0.1-0.2 mg/dose) to be used in the ERAS protocol of this research paper.

Setting of the study

The subjects were recruited among patients admitted at MCU Hospital Obstetrics-Gynecology Labor Room and Ward.

Study Population

This study was composed of 72 parturients, irregardless of parity who were admitted under the Department of OB-Gyn, MCU- FDTMF Hospital who underwent either an Elective or Emergency Cesarean Section.

- **Inclusion Criteria**
  - Filipino women, ages 18 to 40 years old
  - Live, singleton/multiple pregnancy, at 37-42 weeks age of gestation
  - Pregnant women complicated by:
    - Hypertension with no evidence of eclampsia, or HELLP syndrome
    - Overt/Gestational Diabetes Mellitus with controlled blood sugar
    - Thyroid disorder in euthyroid state
- **Exclusion Criteria**
  - Patients who are in eclampsia, HELLP syndrome or in thyroid storm
  - Patients with uncontrolled Diabetes mellitus
  - Patients with serious and complex illness such as pulmonary hypertension, chronic renal disease, cancer, history of stroke, heart failure., etc.
  - Cesarean delivery resulting to complications such as post-partum hemorrhage, bladder injury and uterine atony
  - Cesarean delivery under general anesthesia
  - Difficulty in administration of Spinal or epidural anesthesia (more than 2 attempts)
  - Hypersensitivity to NSAIDS
  - Mothers who developed headache, migraine, vertigo, post-cesarean section

- COVID positive patients
- Patients with symptoms of cough, dyspnea, fever, loose bowel movement
- Patients with travel history especially from Wuhan, China for the last 14 days

Withdrawal or Drop-out Criteria

Mothers who changed their minds and decided to refuse to participate at any time of the study

Sample Size

The number of samples collected was computed using a 95% confidence level and 80% power of the study. A sample of at least 72 was computed. A 20% allowance was added to account for drop-outs or withdrawal. 86 subjects (43 each group) were needed to detect a 0.4 days in the length of stay of patients between the ERAS and control group, with an estimated Standard deviation of 0.5 and 1.2 days respectively. The estimated SD was based from the study of Tiouririne (ERAS for Cesarean Delivery: A Propensity Matched Scoring Analysis - 2015)

Where:

$Z\alpha$ = 95% confidence level = 1.96

$Z\beta$ = power of the study = 80% power of the study = 0.84

SD = Standard Deviation $\frac{(1.2 + 0.5)}{2} = 0.85$

E = Measure of effect = difference in the length of stay between ERAS and Control group = 2.9 – 2.5 = 0.4

$$n = \frac{(1.96 + 0.84)^2 (0.85)^2}{(0.4)^2}$$

$$= \frac{5.6644}{0.16}$$

n = 36 (+ 20% drop out rate)

n= 43 each group

COVID protocol [14]

Patients allowed for admission at the Labor Room/Delivery room complex are the following:

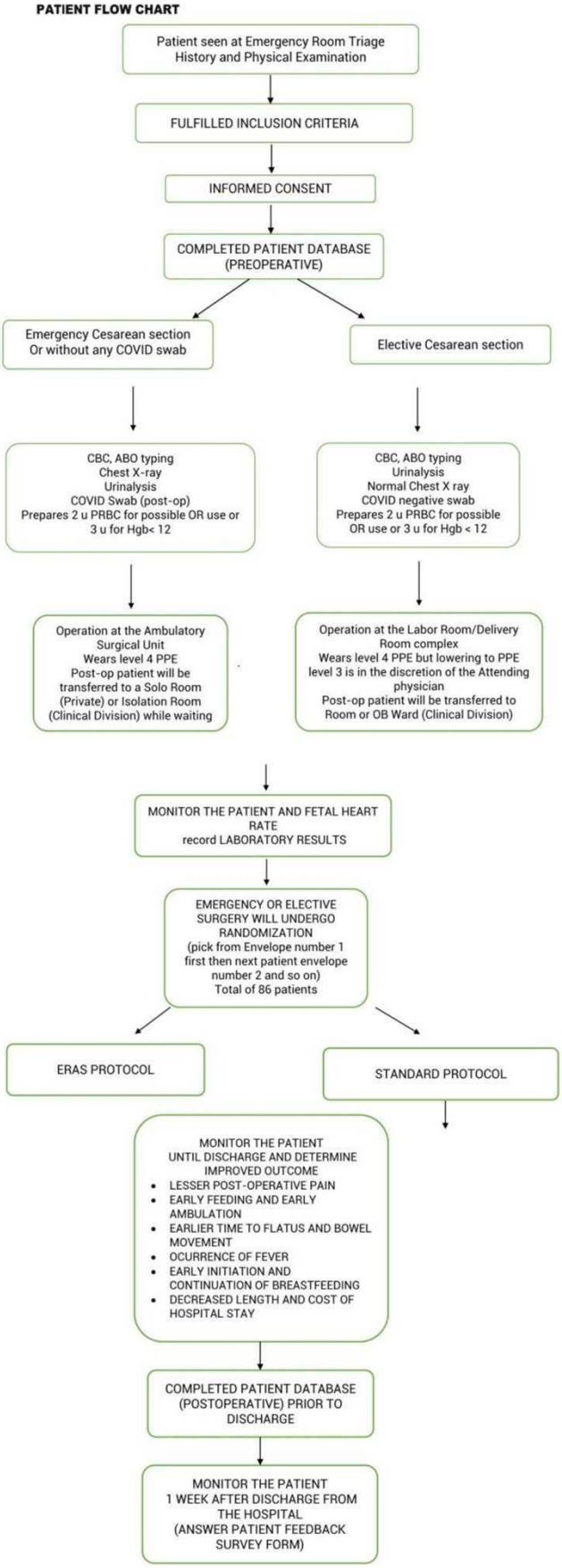
1. Has normal CBC & Urinalysis (Urinalysis can be performed as early as 35 weeks in symptomatic patients to give enough time for treatment prior to term. Otherwise, it can be requested in our hospital as early as 37 weeks) done at our Laboratory Department.
2. Has recent Chest X-ray, PA view with normal official results & performed at our Radiology Department, in COVID (suspect, probable, confirmed) patients.
3. Negative PCR result from DOH accredited laboratory or hospital facility for COVID (previously swabbed due to exposure or with symptoms).
4. Does not fall under the current classification of probable & confirmed COVID cases.
5. Provides 2 units of Packed Red Blood Cell for Hemoglobin level of ≥10 or ≥3 units for levels below 10.
6. Wearing of level 4 PPE despite negative (-) COVID swab result, but lowering the level to PPE 3 is in the discretion of the attending physician.

Septic Deliveries (PPROM/PROM or Probably COVID)

1. Performed at the Ambulatory Surgical unit with the Emergency room OB-Resident physician trainee on duty to assist. These cases will be brought to the Isolation room post partum

Elective Cesarean section or Primary cesarean section will be performed at the Labor Room/Delivery Room complex provided that:

1. Official CBC result is 1 day before the scheduled surgery
2. Official Chest X-ray result 48 hours before the scheduled surgery for patients with symptoms or co-morbidities. This procedure is NOT recommended for patients with RT-PCR COVID negative results, asymptomatic and low risk.
3. Negative COVID swab fourteen (14) days before the scheduled surgery and Strict self-quarantine following the swab test was observed.



The patient's demographic profile was recorded such as: maternal age, status, gestational age, gravidity and parity, BMI, educational attainment, occupation, normal baseline blood pressure in a form of a patient database. Complete history and physical examination were done to the patient at the time of admission to Ambulatory surgical unit (Emergency cases without COVID swab) or Labor room/Delivery Room complex (Elective cases with COVID negative swab). Complete blood count with quantitative platelet count and Urinalysis were sent to the Laboratory. COVID swab for Emergency cases was done post-operatively. The informed consent was well-explained and handed to the patient prior to the Cesarean section.

Sampling Technique: Table Of Random Numbers

The allocation of ERAS or Standard protocol for patients was completely random meaning, in no way was the attribution of whether the patient was to be placed in the study or the control was affected by the patient's profile. Allocation concealment of the treatment groups was done using sequentially numbered, opaque, sealed envelopes. There was a total of 4 envelopes, a third person placed the numbers 1-86 in the 4 different envelopes (Envelopes 1 and 2 contain 21 numbers and Envelopes 3 and 4 contain 22 numbers and each of these numbers either represented ERAS or Standard protocol based on the table of random numbers) in which the researcher had no knowledge of where the numbers were placed in the 4 envelopes. The patient or a representative then picked a number from the four envelopes opened sequentially from 1 to 4. The number picked was the assignment in the treatment groups (ERAS or Standard) based on the table of random numbers using Microsoft excel. Each patient from 1 to 86 was assigned a random number and ranked from lowest to highest.

Patient number	Random Number	A-ERAS B-STD
Patient 85	0.007365604	A
Patient 64	0.020828545	B
Patient 46	0.050396523	A
Patient 7	0.081431375	B
Patient 51	0.100916778	A
Patient 18	0.107874428	B
Patient 70	0.123884924	A

Based on the table of random numbers, Forty three samples with lowest random number assigned was randomized to ERAS then the Forty three samples with highest random number assigned was randomized to Standard protocol.

The researcher had no control on the allocation and pre-determined by a method of using random numbers. However, after the allocation of the patients to facilitate proper interventions, both the patient and the researcher was made aware as to whether they are going to follow the ERAS or the Standard protocol as to ensure compliance from both parties concerned.

20% Drop out rate/withdrawal was allowed for each sample arm (total of 36 patients each arm). This may be attributed to patients who decided to back out anytime from the study due to personal choice or reasons.

Upon discharge the patients were given the contact number of the researcher so that they may report any complications and they were followed up after one week. The patients were given Survey forms in which they completed on the day of follow up.

The duration of participation was from the time of admission to the Labor Room/ASU until one week after Cesarean delivery which was their schedule of follow up. On that day, patient was given or emailed a patient feedback form by the researcher which she answered and submitted back to the researcher either in person or through email. The purpose of the feedback form was to let the researcher know the current state and well-being of the patient.

ERAS PROTOCOL – Enhanced Recovery After Surgery Protocol

This is a single program incorporating multimodal interventions in the peri-operative period to expedite recovery.

Preoperative Period

- Diet: Clear liquids which includes black tea, black coffee, pulp free juice. Milk and soda were not allowed 2 hours prior to Anesthesia. Patient may have 2 slices of white bread 6-8 hours prior to anesthesia
- No Bowel Preparation
- No preoperative sedation
- CBC with QPC and Urinalysis were requested

Intraoperative Period

- Nausea and vomiting prophylaxis: Ondansetron 8 mg/IV 5 minutes prior to induction of anesthesia and Ranitidine 50 mg/IV
- Prophylactic antibiotic: Cefazolin 2 g/IV one hour prior to Cesarean section after negative skin test
- Delayed cord clamping: 1 minute for term, 30 seconds for preterm
- Oxytocin – Given carboprost 1 ampule post delivery, then prophylactic low dose oxytocin infusion (15-18 u/hour) to prevent postpartum hemorrhage
- Venous thromboembolism prophylaxis: Anti-embolic stockings

  Analgesia: Intrathecal morphine 0.1-0.2 mg/dose after negative skin test

Postoperative Period

- Chewed gum to reduce ileus at the Recovery room
- Normothermia- Drop light or Warmer; IV fluids warmed by placing part of the IV in a warm water during infusion; No drop of temperature from baseline (first obtained temperature upon doing physical examination) by a mean of 1.3 degrees Celsius
- Pain: Multimodal IV therapy – (Choice of pain medications upon the discretion of the Anesthesiologist from the following: Morphine, Paracetamol, Ketorolac, Tramadol)
- Early feeding: 30 minutes after procedure may have clear liquids in which they may choose from the following: either black tea,

black coffee or pulp-free juice; if tolerated, may have full diet

- May remove and change dressing 12 hours post-operatively
- Remove foley catheter 12 hours post-operatively
- May mobilize 12 hours after surgery
- Initiate breastfeeding as early as 12 hours
- Given Bisacodyl 1 tablet per orem if still without bowel movement prior to discharge
- Discharge after 24 hours from the time of surgery if without complaints and if with stable vital signs (no BP elevation of >160/110, non-tachycardic > 90 beats per minute, non-tachypneic Respiratory rate >20 counts per minute, afebrile with temperature not =/> 38 C) provided that patient has access to reliable means of communication with Attending physician (private patients) and the researcher to contact them if with concerns.

STANDARD OPERATIVE PROTOCOL (CLINICAL PRACTICE GUIDELINES ON CESAREAN DELIVERY 2012)

Preoperative

- Uncomplicated patient who will undergo elective cesarean delivery may have modest amounts of clear liquids (approx. 1 cup calibrated glass – 210 cc) up to 2 hours before induction of anesthesia.
- Solid foods were avoided in laboring patients. The patient who underwent elective surgery (e.g. scheduled cesarean delivery or postpartum tubal ligation) were fasted for a period of 6-8 hours.
- CBC with QPC and Urinalysis were requested
- An indwelling catheter was inserted prior to doing the Cesarean section

Intraoperative Period

- Aspiration prophylaxis: Before surgical procedures, practitioners considered the timely administration of non-particulate antacids, H2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis
- Regional or Spinal anesthesia was done: the dose and drug was dependent upon the discretion of the anesthesiologist
- Prophylactic antimicrobial agent was given to women undergoing Cesarean section: Either Penicillins or Cephalosporins were the recommended agents. Patient may be given either Cefuroxime 1.5 g/IV or Cefazolin 2 g/IV after negative skin test.

Postoperative Period

- Foley catheter may be removed less than 24 hours after CS.
- Feeding: It was customarily practiced by obstetricians that patients who underwent CS were not allowed to eat or drink until bowel function has returned, as substantiated by the presence of normoactive bowel sounds or passage of flatus. Some argue that there was a high risk of complications from giving oral fluids or food after surgery. Sellers, et al recommended 12-24 hours prior to introduction of fluids. When fluids were well tolerated, bowel sounds were heard and flatus had been passed, should regular diet be commenced. In this research, patients were allowed to drink water after 12 hours or if already with normoactive bowel sounds or passage of flatus. If tolerated, patient were given general liquids (ex. Juice or tea). Then were progressed to soft diet if with flatus then regular diet once with bowel movement.
- IV pain medications and Oral medications was according to the discretion of the anesthesiologist
- Changed the dressing prior to discharge.
- There was no evidence of adverse outcomes associated with early postnatal discharge (three to four days). In this study, patient may be discharged after 48-72 hours or longer.
- Post cesarean delivery mothers were evaluated in terms of lesser degree of the following from the time of Cesarean section:

occurence of fever, post-operative site dehiscence, vomiting, bloatedness, Infections such as UTI, Surgical site infection and pneumonia, lesser degree of post-operative pain and occurence of ileus (time to flatus/bowel movement), faster initiation and continuation of breastfeeding and ultimately shorter and lower cost of hospital stay.

Data Analysis

Data was encoded and tallied in SPSS version 10 for Windows. For numerical data, mean and standard deviation were computed. For nominal data, frequency and percentage were operated.

Data was analyzed using the following test statistics:

T- test (or Mann Whitney U test as needed) was used to compare two groups with numerical data (e.g age of patient, age of gestation, BMI, length of hospital stay, time to initiation of breastfeeding, hospital cost)

Chi-square (or Fisher Exact test as needed for 2x2 table) was used to compare or associate nominal data (e.g. civil status, educational attainment, occupation, post-operative infection

Scope and Limitations

The research paper was conducted primarily to determine if Cesarean delivery patients randomized to ERAS protocol will have better postoperative outcomes versus Standard operative protocol.

As different surgeons employed different skills and techniques and had varying speeds and accuracies, the duration of the procedure and the post-operative outcomes may be affected. This study was not designed to take the underlying effects into consideration.

This research study may not have generalized the benefit of ERAS protocol in all Cesarean deliveries since the population was only limited to low risk patients.

GANTT CHART

A. Preliminary report

	DECEMBER 2019	JANUARY 2020	FEBRUARY 2020	MARCH 2020	APRIL 2020
Data Collection					
Review of Data collected					
Review of paper					
Finalizing paper					

B. Final report

	MAY 2020	JUNE 2020	JULY 2020	AUGUST 2020	SEPTEMBER 2020
Data Collection					
Review of Data collected					
Review of paper					
Finalizing paper					

RESULTS

A total of 72 subjects were included in the study. Thirty two (44.4%) were randomized to the ERAS protocol while 40 (55.6%) patients were randomized to Standard postoperative procedure. Two subjects were not included due to conversion to General anesthesia.

Table 1 shows the comparison of the different demographic characteristics between the two groups. There were no significant differences noted as proven by all p values >0.05. This means that both groups were comparable in terms of the different characteristics indicating that the randomization was properly done.

Table 1. Comparison of the Demographic Characteristics Between the Two Groups

	Groups		p-value*
	ERAS Protocol (n=32)	Standard Protocol (n=40)	
Age (in years)			
Mean ± SD	32.16 ± 5.53	31.25 ± 6.05	0.51 (NS)†
Pay/CD			
CD	12 (37.5%)	11 (27.5%)	0.37 (NS)‡
Pay	20 (62.5%)	29 (72.5%)	
Emergency/Elective			
Elective	6 (18.8%)	2 (5.0%)	0.13 (NS)§
Emergency	26 (81.3%)	38 (95.0%)	
Status			
Married	15 (46.9%)	19 (47.5%)	0.96 (NS)‡
Single	17 (53.1%)	21 (52.5%)	
Educational Attainment			
High School Undergraduate	0	1 (2.5%)	
High School Graduate	7 (21.9%)	6 (15.0%)	
College undergraduate	2 (6.3%)	4 (10.0%)	
College Graduate	22 (68.8%)	27 (67.5%)	0.62 (NS)‡
Doctor	0	1 (2.5%)	
Masters	0	1 (2.5%)	
Vocational	1 (3.1%)	0	
Occupation			
Employed	20 (62.5%)	30 (75.0%)	
Self-employed	8 (25.0%)	10 (25.0%)	0.07 (NS)‡
Housewife	4 (12.5%)	0	

** p>0.05- Not significant; p ≤0.05-Significant*
†T-test; ‡Chi-square test; §Fisher Exact test

Table 1. Comparison of the Demographic Characteristics Between the Two Groups

	Groups		p-value*
	ERAS Protocol (n=32)	Standard Protocol (n=40)	
Monthly Salary (in Pesos)			
<10,000	3 (9.4%)	3 (7.5%)	
10,000 – 20,000	10 (31.3%)	20 (50.0%)	0.40 (NS)‡
20,001 – 50,000	16 (50.0%)	13 (32.5%)	
50,001 – 100,00-	3 (9.4%)	4 (10.0%)	
BMI			
Underweight	0	1 (2.5%)	
Normal	4 (12.5%)	5 (12.5%)	0.68 (NS)‡
Overweight	17 (53.2%)	17 (42.5%)	
Obese	11 (34.4%)	17 (42.5%)	
Gravidity			
Primigravida	10 (31.3%)	18 (45.0%)	
Secundigravida	10 (31.3%)	11 (27.5%)	0.47 (NS)‡
Multigravida	12 (37.5%)	11 (27.5%)	
Parity			
Primipara	12 (37.5%)	19 (47.5%)	0.39 (NS)‡
Multipara	20 (62.5%)	21 (52.5%)	
Age of Gestation (in weeks)			
Mean ± SD (Median)	38.71 ± 0.88 (38.57)	38.41 ± 2.31 (38.86)	0.77 (NS)‖
Comorbidities			
Yes	21 (65.6%)	28 (70.0%)	0.69 (NS)‡
No	11 (34.4%)	12 (30.0%)	
Apgar Score at 1 minute			
Mean ± SD (Median)	8.63 ± 0.66 (9)	8.39 ± 1.18 (9)	0.67 (NS)‖
Apgar Score at 5 minutes			
Mean ± SD (Median)	8.90 ± 0.29 (9)	8.82 ± 0.51 (9)	0.61 (NS)‖
Birthweight (grams)			
Mean ± SD (Median)	3210.94 ± 325.46 (3250)	3123.75 ± 602.66 (3250)	0.91 (NS)‖
Ballard Score (weeks)			
Mean ± SD (Median)	38.47 ± 0.76 (38)	38.58 ± 2.29 (39)	0.12 (NS)‖

Table 2 shows the comparison of the length of hospital confinement from admission to discharge between mothers randomized in the ERAS protocol compared to the standard operative procedure. There was a significant difference noted as proven by the p value of <0.0001. Mothers randomized to the ERAS protocol had significantly shorter length of stay compared to mothers in the standard operative procedure with a mean of 53.01 hours (2.21 days) and 78.86 hours (3.29 days) respectively.

Table 2. Comparison of the Length of Hospital Stay Between the Two Groups

	Groups		p-value*
	ERAS Protocol (n=32)	Standard Protocol (n=40)	
Length of Stay from Admission to Discharge (in hours)			
Mean ± SD	53.01 ± 14.54	78.86 ± 32.30	<0.0001 (S) ‖
Median	48.40	72.52	

** p>0.05- Not significant; p ≤0.05-Significant*
‖Mann Whitney U test

Table 3 shows the comparison of the cost of hospitalization between mothers randomized in the ERAS protocol compared to the standard operative procedure. There was a significant difference noted as proven by the p value of <0.0001. Mothers randomized to the ERAS protocol spent significantly lower hospitalization cost compared to mothers in the standard operative procedure with a mean of 36,902.22 pesos and 60,685.48 pesos respectively showing that the cost of hospitalization of mothers in the standard operative procedure was almost twice higher than the cost of hospitalization of mothers in the ERAS protocol group.

Table 3. Comparison of Cost of Hospitalization Between the Two Groups

	Groups		p-value*
	ERAS Protocol (n=32)	Standard Protocol (n=40)	
Cost of Hospitalization (in pesos)			
Mean ± SD	36,902.22 ± 11,441.77	60,685.48 ± 20,738.01	<0.0001 (S)‖
Median	38,703.50	58,740.00	

** p>0.05- Not significant; p ≤0.05-Significant*
‖Mann Whitney U test

Table 4 shows the comparison of the post-operative infections between mothers randomized in the ERAS protocol compared to the standard operative procedure. There was no significant difference noted in the proportion of mothers with fever between the two groups (p=0.25). However, there

was a significant difference noted in the post-operative pain as proven by the p values 0.001. Mothers randomized to the ERAS protocol had significantly lower post-operative pain compared to mothers in the standard operative procedure with a mean of 3.96 and 5.63 respectively for the post-operative pain.

Table 4. Comparison of the Post-operative Infections Between the Two Groups

	Groups		p-value*
	ERAS Protocol (n=32)	Standard Protocol (n=40)	
Fever			
(+)	0	3 (7.5%)	0.25 (NS)§
(-)	32 (100%)	37 (92.5%)	
Post-operative Pain			
Mean ± SD	3.96 ± 1.98	5.63 ± 2.20	0.001 (S)†

** p>0.05- Not significant; p ≤0.05-Significant*
†T-test; §Fisher Exact test

Table 5 shows the comparison of the length of time in hours from operation to breastfeeding initiation between mothers randomized in the ERAS protocol compared to the standard operative procedure. There were significant differences noted in the length of times as proven by all p values <0.05. Mothers randomized to the ERAS protocol had significantly shorter times compared to mothers in the standard operative procedure with a mean of 4.55 hours and 11.61 hours respectively for the time from NPO to start of the OR. The duration of OR was significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure with a mean of 1.64 hours and 1.88 hours respectively. The time from OR until general liquids was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure with a mean of 4.99 hours and 9.33 hours respectively. Similarly, the time from OR to flatus was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure with a mean of 12.17 hours and 17.47 hours respectively. Also, the time from OR to bowel movement was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure with a mean of 22.86 hours and 35.56 hours respectively. The time from OR to removal of foley catheter was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure with a mean of 11.52 hours and 21.29 hours respectively and the time from removal of catheter to voiding with a mean of 2.20 hours and 5.28 hours respectively. Finally, there was a significant difference noted in the length of time from OR to breastfeeding as proven by all p value of 0.02. Mothers randomized to the ERAS protocol had significantly shorter times compared to mothers in the standard operative procedure with a mean of 30.67 hours and 43.09 hours respectively.

Table 5. Comparison of the Length of Time in Hours from Operation to Breastfeeding Initiation and Continuation Among Mothers in the ERAS protocol Versus the Standard Operative Procedure

	Groups		p-value*
	ERAS Protocol (n=32)	Standard Protocol (n=40)	
Time from NPO to Start of OR (in hours)			
Mean ± SD	4.55 ± 1.75	11.61 ± 4.88	<0.0001 (S)‖
Median	4.33	10.31	
Duration of OR (in hours)			
Mean ± SD	1.64 ± 0.42	1.88 ± 0.50	0.03 (S)†
Time from OR until general liquids			
Mean ± SD	4.99 ± 1.64	9.33 ± 2.59	<0.0001 (S)‖
Median	4.52	8.66	
Time from OR to flatus (in hours)			
Mean ± SD	12.17 ± 5.35	17.47 ± 9.49	0.03 (S)‖
Median	11.83	15.38	
Time from OR to Bowel Movement			
Mean ± SD	22.86 ± 8.81	35.56 ± 12.08	<0.0001 (S)†
Time from OR to removal of foley catheter (in hours)			
Mean ± SD	11.52 ± 2.76	21.29 ± 8.62	<0.0001 (S)‖
Median	11.28	21.75	
Time from removal of catheter to voiding (in hours)			
Mean ± SD	2.20 ± 1.51	5.28 ± 5.06	0.03 (S)‖
Median	1.69	3.00	
Time from OR to breastfeeding (in hours)			
Mean ± SD	30.67 ± 13.85	43.09 ± 21.97	0.02 (S)‖
Median	31.46	37.00	

** p>0.05- Not significant; p ≤0.05-Significant*
†T-test; ‖Mann Whitney U test

Table 6 shows the comparison of the post-operative variables (One week post discharge) between mothers randomized in the ERAS protocol compared to the standard operative procedure. There was a significant difference noted in the pain scale between the two groups (p=0.008). The pain scale of mothers in the ERAS group was significantly lower than mothers in the standard protocol group. However, length of stay and hospital charge were significantly higher among mothers in ERAS group as proven by the p values <0.001.

Mothers randomized to the ERAS protocol had significantly higher number of breastfeeding done on their baby (p=0.001) compared to mothers in the standard operative procedure.

Table 6. Comparison of the Post-operative Variables Between the Two Groups

	Groups		p-value*
	ERAS Protocol (n=32)	Standard Protocol (n=40)	
Pain Scale			
Mean ± SD	2.29 ± 1.71	3.57 ± 2.05	0.008 (S)†
Length of Stay			
Mean	4.19 ± 0.65	3.51 ± 0.85	<0.001 (S)†
Hospital Charge			
Mean ± SD	3.74 ± 0.51	2.91 ± 0.98	<0.001 (S)‖
Median	4.0	3.0	
Breastfeed Baby			
1x – 3x	2 (6.3%)	11 (27.5%)	
4x – 7x	10 (31.3%)	19 (47.5%)	0.003 (S)‡
>7x	20 (62.5%)	10 (25.0%)	

** p>0.05- Not significant; p ≤0.05-Significant*
†T-test; ‖Mann Whitney U test; ‡chi-square test

DISCUSSION

Cesarean section is one of the most significant procedures done and perfected by an OB-gynecologist specialist. There is a rising trend of Cesarean delivery rates which is currently at 22.7% in the Philippines and 21% worldwide which is high compared to the established rate of only 10-15% by the World Health Organization. It is therefore vital to consider the effect of this rising trend with regards to the pre-operative preparations, post-operative pain, breastfeeding, especially the length of stay and the costs to the Filipino mothers who will undergo Cesarean delivery.

Enhanced recovery after surgery is a concept initially developed for patients undergoing colorectal surgery but has been adopted by other surgical specialties with similar positive outcomes. The adoption of the ERAS protocol in obstetric population is gaining popularity especially in the US, Canada and the UK.

There has been no local studies published yet on the ERAS protocol application among Cesarean delivery mothers hence, the researcher adopted the ERAS protocols that were utilized by the UK and US and applied it to the local setting and in this case, the MCU-FDTMF Hospital which is a tertiary center in the Philippines.

This COVID pandemic also contributed to the added burden of the Filipino mothers in terms of the difficulty in having prenatal check-ups leading to unaddressed comorbidities (e.g. uncontrolled hypertension, diabetes mellitus and preterm delivery) due to the lockdown and has resulted into economic instability which brought unemployment and decreased income. This research will also help improve the length of exposure of patients in the hospital and decrease the cost hospital bills if they could be discharged earlier than the usual standard.

In this research, a total of 72 subjects were included 32 (44.4%) and 40 (55.65%) were randomized to ERAS and Standard protocols respectively. Two subjects were not included since they were converted to General anesthesia. There was no significant difference noted in the demographic profile of patients in terms of the following: Age, Pay/CD, Emergency/Elective, Marital status, Educational attainment, Occupation, Monthly salary, BMI, Gravidity, Parity, Age of gestation, birthweight, APGAR SCORE, Ballard score opon delivery and finally Comorbidities between the two groups as seen in Table 1, indicating that the randomization was done and properly achieved.

ERAS protocol spans the multimodal approach in the pre-operative, intraoperative and post-oparative clinical pathway of Cesarean delivery. In the pre-operative pathway, ERAS protocol diet consists of clear liquids (black tea, black coffee, pulp free juice) and a minimum of 2 hours NPO, 2 slices of white bread 6-8 hours prior to anesthesia maybe initiated however, most of the cases were Emergency Cesarean section hence the 2 hours were not strictly followed but with a mean of only 4.55 hours in the ERAS protocol but was significantly shorter as compared to 11.61 hours in the standard protocol. This implies that if we could safely shorten the time of NPO in ERAS and not develop complications such as aspiration, vomiting, and abdominal discomfort as shown in the ERAS study subjects, it would therefore be very much favorable for the patient since it will reduce their thirst and hunger which contributes more to the pain of labor and Cesarean delivery.

For the intra-operative period, the modes of anesthesia were either Spinal or Epidural and mostly the prophylactic antibiotics used were Cefazolin, Cefuroxime and Ampicillin. Factors that would affect the duration of Cesarean section could possibly be the skill of the surgeon and the complexity of the procedure. Surprisingly, the duration of OR was also significantly shorter among mothers randomized to the ERAS protocol compared to mothers in the standard operative procedure with a mean of 1.64 and 1.88 hours respectively.

Post operatively, there were 3 mothers who developed fever with (Tmax of 38.9 degrees Celsius) under the standard protocol, 2 of them received blood transfusion with 2 units PRBC properly typed and crossmatched. None developed fever under the ERAS protocol however no significant difference in between the 2 groups.

The husband or relatives of the patients under ERAS arm were instructed prior to the OR to have the gum and water available post-operative so that they could readily chew the gum and may sip water at the Recovery room as soon as they wake up from anesthesia. None of them vomited nor developed abdominal pain or discomfort. The time to general liquids were also significantly shorter with a mean of 4.99 and 9.33 hours respectively. Early feeding is defined variably as feeding regular diet as early as 30 minutes and up to 8 hours after cesarean delivery contrary to progressive feeding wherein it is started when there is already normoactive bowel sounds and passage of flatus. This research demonstrated a reduction in thirst and hunger and improved maternal satisfaction and ambulation with no evidence of development of complications related to wound healing or infection. Early refeeding is also beneficial since the mother is expected to increase nutrient and caloric intake since she is expected to be breastfeeding her baby.

Similarly the time from OR to flatus and bowel movement were also significantly shorter among mothers randomized to ERAS protocol compared to standard operative procedure with a mean of 12.17 hours vs. 17.47 (flatus) and 22.86 and 35.56 hours (bowel movement) respectively.

In the ERAS arm, the catheter was removed at 12 hours or earlier with a mean of 11.52 hours as compared to the standard operative protocol of 21.29 hours where it was only removed when the patient achieved an adequate urine output >30 cc/hour. However, this study showed significant time from removal of catheter to voiding with a mean of 2.20 hours and 5.28 hours respectively. In a non-randomized clinical trial with 344 patients, Senanayake demonstrated that there was low incidence of postoperative urinary retention after cesarean delivery in patients without an indwelling urinary catheter.[15] Even the prospective study of Nasr in 420 patients randomly assigned to a non-catheterized versus 12 hours removal showed that the mean time to patient ambulation, first postoperative voiding, oral rehydration, bowel movement, and length of hospital stay were significantly less in than noncatheterized group. [15] This may conclude that in women who do not need ongoing strict assessment of urine output, the urinary catheter should be removed immediately after cesarean delivery if placed. This could also shorten the time to ambulation probably leading to earlier bowel movement and breastfeeding.

Based on the Visual Acuity Scoring (VAS), there was significantly lower pain under the ERAS protocol with a mean of 3.96 versus 5.63 over 10 under Standard operative protocol. There was a significant difference noted in the length of time from OR to breastfeeding randomized to the ERAS protocol which was 30.67 versus 43.09 hours respectively. The babies were all delivered term with a mean of 38 weeks and even though some mothers had UTI antenatally wherein their baby was admitted longer in the NICU for antibiotic therapy, this probably did not affect the time to breastfeeding since they could easily breastfeed their babies in the NICU.

Notably, the length of stay was significantly shorter in the ERAS arm which was 53 +/- 14 hours versus 78.86 +/- 32 hours in the standard arm.

Lastly, the cost of hospital stay from the time of admission to discharge was obtained from the Billing section. Professional fees of Private patients and Philhealth deductions were not included in both study arms hence the costs were most likely comparable in between the PAY and CD

patients. However, this study has shown that the costs were significantly different wherein the patients under the standard protocol paid twice as much with a mean of Php 60,685 +/- 20,738.01 compared to only Php 36,902.22 +/- 11,441.77 in the ERAS protocol.

One week after hospital discharge, the patients were given a Satisfaction survey form which they answered either during follow-up at the OPD or through email and messenger. It has four questions namely the pain scale, length of stay, hospital bills and the number of times she was able to breastfeed the baby per day. The satisfaction survey also favored the ERAS protocol than the standard operative protocol wherein all of the 4 parameters showed significant difference as shown in Table 6 of the results.

CONCLUSION AND RECOMMENDATIONS

Enhanced Recovery After Surgery protocol in Cesarean delivery allowed the mother to experience decrease in physiological stress, thirst and hunger thus enabled them to recover more quickly, pass flatus, defecate, ambulate and breastfeed earlier. It decreased significantly the length of stay and resume routine activities more quickly than with standard surgical care. It also simultaneously improved patient satisfaction and their quality of life. More importantly during this COVID pandemic, not only did it shorten hospital exposure but decreased the cost of hospital bills twice as much as the Standard operative protocol.

The pre-operative, intraoperative and post-operative elements of ERAS pathways will continue to evolve as new evidence emerges. There is wide variability in the strength of evidences in the components of the previously published ERAS protocols for Cesarean delivery. Future studies on developing and evaluating the impact of various components are needed.

Further research may be done with regards to not placing a urinary catheter in patients undergoing Cesarean delivery who have normal kidney function and where urine output measurement is not necessary.

Since the researcher only considered post-operative monitoring after one week, further studies might include possible number of post-operative readmissions due to complications in ERAS versus Standard operative protocol.

This research consisted only of Cesarean delivery mothers with controlled Hypertension, Diabetes and thyroid disease as the population hence, another study is suggested to be done on patients who have uncontrolled co-morbidities to formulate and improve the ERAS protocol

This pioneer study yielded good and significant results hence, more study subjects are recommended and may serve as a benchmark for further investigative studies to address existing knowledge gaps and can be replicated in other tertiary institutions most especially in the Government hospitals who cater to deprived and underprivileged patients.

Successful implementation of an ERAS program requires a multidisciplinary team effort as well as the active participation of the Obstetrician, Anesthesiologist and the patient. As Clinicians and Researchers, we are required to be periodically updated and very adaptive to the changing times. We must all be receptive to transformation, paradigm shifts and be knowledgeable as to how to impact our patients to deeply understand each new concept, accept, and adhere to modern modifications necessary to a better superior practice of Obstetrics and in this case formulate new ways to improve on the ERAS protocol in Cesarean delivery.

Initiation of an ERAS Clinical pathway in a timely, cost-effective manner can be logistically challenging hence the practice of the elements of the ERAS protocol can take years to occur but it is the hope of the Researcher that the ERAS protocol will already be considered the new standard in Cesarean delivery practice in the Philippines in the near future and even be applicable worldwide.

ETHICAL CONSIDERATIONS

The researcher adhered to the Ethical principles of Autonomy, Non-maleficence and Beneficence. All the Elective or Emergency Cesarean sections to be performed were with medical

indications and deemed necessary. The Clinical Practice Guidelines on Cesarean Section published by the Philippine Obstetrical and Gynecological Society last November 2012 was the basis for the Standard Operative Protocol while the ERAS protocol was patterned from several previous researches done mentioned in the review of related literature which has also been approved by Ethical review board.

I. Conflict of Interest

The researcher declared no conflict of interest as she conducted this investigation.

II. Privacy and Confidentiality

In order to protect the integrity of the subjects, the researcher did not disclose any personal information (names, home addresses, etc.). When not in use, the written questionnaires, survey forms were kept in a locked file cabinet to be accessed only by the researcher. The confidentiality was strictly kept by the researcher and data was de-identified by substituting the participant's name to participant's number instead.

The researcher stated in the informed consent that the use of private data collected were necessary to conduct the study and was used solely for the purpose of research.

Data encoding was done with the use of a password-protected laptop owned by the researcher in which she solely had access to. At the end of the study, all the Data sheets and survey questionnaires were disposed by the researcher herself through paper shredding.

III. Informed Consent and Recruitment Process

The informed consent contained the nature and purpose of the study in which they were randomized either to ERAS or Standard protocol in Cesarean section and determined the difference in post-operative outcomes in terms of: length of hospital stay, hospital expenses, occurrence of fever etc. The content of the informed consent were thoroughly explained by the researcher. If it was an elective procedure, the informed consent was given at the OPD during her prenatal check-up at least a week prior to the Cesarean section. If it was an emergency procedure, the informed consent was explained verbally at least an hour prior to the procedure. The patient's participation in the trial was voluntary and she may refuse to participate or withdraw from the trial at any time, without penalty. The patients were given the contact number of the researcher and attending physician for which answers to any questions about the research may be addressed and informed if the patient experienced any complications post-operatively.

Lastly, it is important to note that all the Consent forms of the participants; data privacy and the study protocol have passed the technical review and the review of the Institutional Review Board (IRB).

IV. Risk and Benefits

The patients were well-explained that they will undergo Cesarean section which is a major operation which might have risks like surgical site infection, postpartum hemorrhage, adverse reaction to the anesthesia, antibiotics and the pain medications, scar or keloid formation after the surgery.

Measures were done to mitigate these risks by doing a thorough and accurate history taking and physical examination. The intravenous Cefazolin, Cefuroxime, Tramadol, Paracetamol and Ketorolac were only administered to the patient when the skin test was negative. Post-operatively the patient's vital signs were closely monitored for BP elevations, tachycardia, tachypnea, or fever. The patients were given the researcher's contact number to call in cases of complications post-operatively and they were instructed to follow up after 1 week from discharge.

Directly the patient benefited from the study since the Cesarean section was clinically an indicated procedure. Once the data is generated and analyzed and would prove that the ERAS protocol is superior than the standard operative procedure, this will possibly promote the implementation of ERAS protocol in all cesarean deliveries and improve the standard of care among patients undergoing Cesarean deliveries in the future. The patient will be able to ambulate and breastfeed earlier and be

discharged a day after the operation. She will have the privilege to be able to rest and be given the full support of the family including other relatives at the comforts of her own home instead of being visited in the hospital after a major operation.

V. Vulnerability

Vulnerable subjects which include members of a group with hierarchical structure (e.g armed forces personnel, staff and students of medical, nursing and pharmacy academic institution), patients with incurable diseases, refugees were not included in the study. Unemployed and impoverished patients with low educational background were included in the study provided that the researcher made sure that simple language and the Filipino version of the informed consent was thoroughly explained to the subjects who are educationally deprived.

VI. Assent

Minors (below 19 years old) had either parent to give their consent and were made to understand the nature, risks and purpose of the study. Once the minor and either parent fully comprehend the study, they were asked to sign the consent form before the Cesarean delivery.

VII. Compensation and Incentives

The researcher did not give any monetary benefits nor financial assistance to subjects who participated in this research. The researcher did not solicit any financial assistance from companies nor pharmaceutical and/or medical organizations deemed to benefit from the results of the study.

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The Mask of Furrow: A Case of a 28-year-old Filipino Male with Pachydermoperiostosis*

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ABSTRACT

Pachydermoperiostosis (PDP) or primary hypertrophic osteoarthropathy (PHO) is a rare genetic disorder that affects mainly skin and bones. Its main clinical features are pachyderma (thickening of the skin), periostosis (excessive bone formation) and clubbing of fingernails. The disease is more common among males with a 7:1 ratio, starts during adolescence and stabilize and cease progression after 5 – 20 years.

OBJECTIVE

To discuss the summary of the case, new management options, and outcomes of the management options.

CASE SUMMARY (Methods)

A 28-year-old male presents with a 9-year history of wrinkling of his facial skin. Other associated symptoms were seborrhea, acne, clubbed fingers, and occasional minimal knee joint pain. Histopathology results showed thickened dermis, fibrosis of the papillary dermis and around the folliculosebaceous units, hyalinized collagen bundles involving the fibrous trabeculae of the subcutis, and prominence of sebaceous and eccrine glands. The patient was given oral isotretinoin at 0.5 mg/kg/day, underwent fractional CO2 laser for rhytides and large pores, and given botulinum toxin A injection (total of 16 U) on 5 sites at the glabellar region. The patient was referred to plastic surgery for frontal rhytidectomy, and orthopedic surgery for management of joint pains.

RESULTS

The patient noted 80% improvement from baseline.

CONCLUSION

Treatment of pachydermoperiostosis is mainly symptomatic and requires a multi-specialty approach. Because of its rarity, treatment options for pachydermoperiostosis have yet to be standardized. In this particular case, all available options in the institution were utilized which led to satisfaction of the patient of the outcome.

Keywords: pachydermoperiostosis, primary hypertrophic osteoarthropathy

INTRODUCTION

Pachydermoperiostosis or primary hypertropic osteoarthropathy is a rare hereditary disorder that was first described in 1868. It is characterized by digital clubbing, pachydermia (thickening of the facial skin and/or scalp), and periostosis (swelling of periarticular tissue and subperiosteal new bone formation. It is associated with pain, polyarthritis, cutis verticis gyrata, seborrhea, eyelid ptosis, and hyperhidrosis. Touraine et al described 3 forms of pachydermoperiostosis or primary hypertropic osteoarthropathy: (1) a complete form with pachydermia and periostitis, (2) an incomplete form with evidence of bone abnormalities but lacking pachydermia, and (3) a forme fruste with prominent pachydermia and minimal-to-absent skeletal changes. [1,2]

*1st Place, 2021 Philippine Medical Association Case Report Presentation, June 21, 2021

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The male to female ratio is 7:1, and the disease usually starts during adolescence, progressing up to 5-20 years and later on stabilizes. There is no known treatment for this disease, however, symptomatic therapies have been tried mostly with favorable results. The aim of this case report is to discuss the summary of the case, new management options, and outcomes of the management options. [1,2]

CASE REPORT

We are presented with 28-year-old male, Filipino, electrician helper, from Quezon City. His chief complaints were furrows on the face, plaques on the scalp and face, and digital clubbing. Nine years prior to consult when the patient noted few fine wrinkles on his forehead with a sudden increase in oiliness of his face. There were no other associated symptoms at that time. In the interim, the patient noted an asymptomatic clubbing of all his fingers as well as occasional minimal bilateral knee joints pain. The patient denies any dyspnea, cyanosis, or chest tightness. There was also no change in appetite or weight loss. Three years prior to consult the patient noted pruritic plaques with scales on both mandibular areas and frontal areas. The patient applied fruit peelings from "calamansi" and astringent which would cause an intense stinging sensation. This led the patient to discontinue using the fruit peelings and astringent. The patient also noticed increased wrinkling on his face, for which he was teased as "laging galit. He was advised 2D echo which was subsequently done and revealed normal results – hence he was referred to the dermatology department.

His review of systems was generally unremarkable except for bilateral knee joint pains. He was not known to have any co-morbidities. His family history revealed allergies to chicken meat, hypertension, and diabetes mellitus. The family genogram is demonstrated in the figure below. He is a non-smoker and an occasional alcoholic beverage drinker.

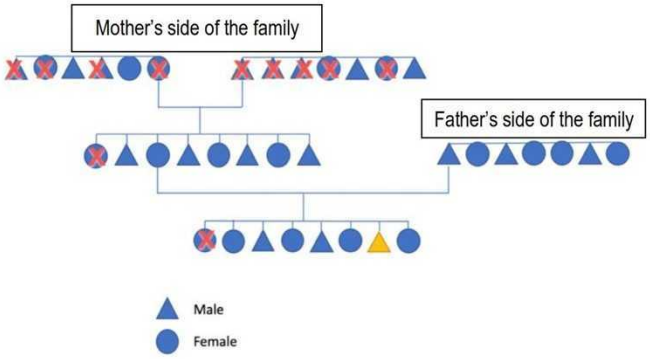

Figure 1. Family Genogram of the Patient

Physical examination was generally unremarkable except for bilateral swelling of knee joints. His cutaneous examination revealed thickened and greasy facial skin with deep frontal, glabellar, and perioral rhytides, erythematous plaques with greasy scales on bilateral mandibular areas, frontal scalp, and bilateral eyebrows, skin colored to yellowish papule on the nose and mentum, erythematous papules on the face, large pores and digital clubbing.

Figure 2. Picture of the patient's face showing deep wrinkles, seborrhea, acne, and seborrheic dermatitis

Figure 3. Picture of the patient's trunk and extremities with noted swelling of both knees

Figure 4. Picture of the patient's fingers and toes showing digital clubbing

Skin punch biopsy was done which showed somewhat thickened dermis, fibrosis of the papillary dermis and around the folliculosebaceous units, slightly thickened collagen bundles in the reticular dermis, focal area of mild edema and mucin deposition in the mid-reticular dermis, focal area of markedly thickened, hyalinized collagen bundles involving the fibrous trabeculae of the subcutis, prominence of sebaceous and eccrine glands and a mild lymphocytic infiltrate around the superficial plexus and folliculosebaceous units. The epidermis shows slight acanthosis. The findings were compatible with Pachydermoperiostosis.

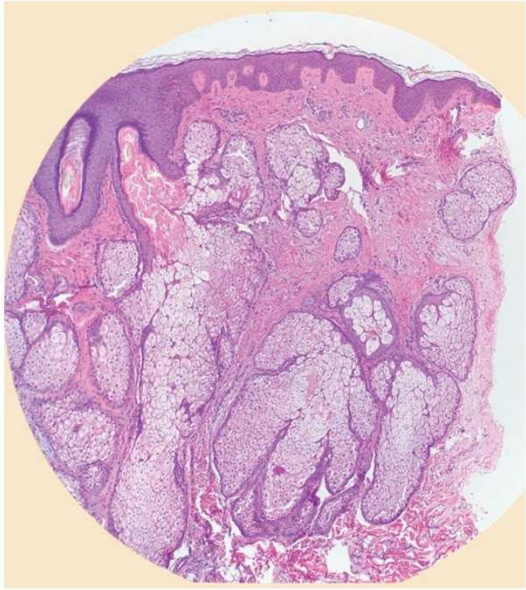

Figure 5. Histopathology (H & E stain) of the patient's skin showing prominence of sebaceous and eccrine glands.

Other ancillary tests such as CBC, Thyroid Panel, Serum growth hormone, Lipid profile, Liver and Kidney function tests were normal. Bones series showed periosteal reaction, no fractures, and infiltrates on the chest were seen.

Figure 6. Roentgenogram of patient's extremities showing periosteal reaction.

The patient was started on oral isotretinoin at 20 mg/ day, topical antifungals and hydrocortisone for the Seborrheic dermatitis, and Celecoxib 100 mg/ day as needed for joint pains. The patient was referred to Orthopedics and Plastics Surgery. Frontal rhytidectomy was done improving the patient's deep wrinkles on the forehead. Fractional CO2 laser for deep rhytides setting and Botulinum toxin injection (total of 16 Units on 4 sites on the forehead) were performed.

The patient noted an 80% improvement overall with noted decrease in oiliness, acne eruption, and seborrheic dermatitis flares. The deep wrinkles on his face have also become more superficial. The patient was scheduled to have monthly sessions of fractional CO2 laser and every

3 to 6 months repeat injections of Botolinum toxin however he was lost to follow-up. The patient was last seen on his 8th consult (7 weeks post-frontal rhytidectomy, 2 weeks post-fractional CO2 laser, and 4 days post-Botulinum toxin type A injection).

DISCUSSION

Pachydermoperisotosis (PDP, Touraine–Solente– Gole syndrome or Primary Hypertrophic Osteoarthropathy) is a rare disorder characterized by digital clubbing, pachydermia (thickening of the facial skin and/or scalp), and periostosis (swelling of periarticular tissue and subperiosteal new bone formation. It is associated with pain, polyarthritis, cutis verticis gyrata, seborrhea, eyelid ptosis, and hyperhidrosis. Touraine et al described 3 forms of pachydermoperiostosis or primary hypertropic osteoarthropathy: (1) a complete form with pachydermia and periostitis, (2) an incomplete form with evidence of bone abnormalities but lacking pachydermia, and (3) a forme fruste with prominent pachydermia and minimal-to-absent skeletal changes. The male to female ratio is 7:1, and the disease usually starts during adolescence, progressing up to 5-20 years and later on stabilizes. (Joshi, et al). According to the Philippine Dermatological Society, there were only 8 cases reported from 2011 to 2018. Worldwide prevalence rate was reported to be at an estimated 0.16% [1,2,3]

The diagnosis of PDP can be made clinically and radiologically, however, due to rarity of this disorder it is often overlooked.[1] Dermatologists help establish the diagnosis by doing clinical and histopathological correlation.

The diagnostic criteria for PDP include major criteria consisting of pachyderma, periostosis, and finger clubbing, as well as minor criteria including hyperhidrosis, arthralgia, gastric ulcer, cutis verticis gyrate, blepharoptosis, joint effusion, column-like legs, edema, seborrhea, acne, and flushing. On the basis of the physical examination, radiologic, and histopathologic findings, the final diagnosis is that of a complete form of PDP. [1,2]

The differentials for PDP include the following:

Leprosy (Hansen's Disease) is a chronic infectious disease which is acquired through the droplet route from chronic exposure to affected individuals. It primarily involves the cutaneous system and peripheral nerves. The etiologic agent is an acid-fast bacilli Mycobacterium leprae. Hansen's disease is classified according to clinical manifestations and number of bacilli, from the tuberculoid type (TT) to the lepromatous type (LL). Lepromatous leprosy, the form with the least cellular immunity and most number of bacilli, initially manifests as erythematous macules, papules, nodules, and plaques. Some patients also manifest with ocular problems, widening of the nasal root, enlargement of ear lobes, thickening of the forehead skin and folding hence the "leonine facies". Other signs and symptoms include hypoesthesia or anesthesia in a stocking or glove pattern, enlarged peripheral nerves, madarosis, saddle nose deformity. The most commonly involved areas are the face and buttocks, mostly on cool areas. [4] The patient presented with **thickened forehead skin** and **furrows resembling the leonine facies,** however he does not have exposure to patients with Leprosy, he denies hypoesthesia or anesthesia, he does not have enlarged peripheral nerves, other cutaneous findings such as macules, papules, nodules, or plaques, nor madarosis. Hence, Hansen's disease is not a likely diagnosis.

Thyroid acropachy is rare manifestation of an autoimmune thyroid disorder and usually presents first with **ophthalmopathy** (ptosis, exophthalmos, upper eye lid retraction, and conjunctivitis), followed by **dermopathy** (erythematous and edematous lower extremities especially the tibial regions), and finally **acropachy** (soft-tissue swelling of the hands and feet and digital clubbing). [1] The patient denies any history suggestive of thyroid problems such as palpitations, heat or cold intolerance, appetite changes, weight changes. The patient does not have ophthalmopathy and dermopathy, although he has acropachy. The thyroid function tests of the patient also turned out normal.

Acromegaly. Gigantism refers to abnormally high linear growth due to excessive action of insulinlike growth factor I (IGF-I) while the epiphyseal growth plates are open during childhood. Acromegaly is the same disorder of IGF-I excess but occurs after the growth plate cartilage fuses in adulthood. The average time of diagnosis of acromegaly is between 40-45 years old. Acromegaly can be an insidious disease. The symptoms are either due to the excessive Growth Hormone/IGF-1 or intracranial tumor. Patients with acromegaly may present with soft tissue swelling and enlargement of extremities, increase in ring or shoe size, hyperhidrosis, coarsening of facial features, large pores, wide spacing of teeth, deepening of the creases on the forehead and nasolabial folds, cutis verticis gyrate, skin tags, oily skin, acanthosis nigricans,hypertrichosis, prognathism, macroglossia, arthritis, and increased incidences of DM, electrolyte disturbances, and CHF. [1,2] Although the patient has **coarse facial features**, **arthritis, oily skin, and large pores**, he does not have other acromegalic features as mentioned. The patient's GH is normal, hence we can rule this out.

Phymatous rosacea is a subtype of rosacea characterized by centrofacial flushing, centrofacial erythema and telangiectasia seen in other forms of rosacea. This disease shows marked skin thickening and irregular surface nodularities of the nose, chin, forehead, one or both ears and/or the eyelids and patulous follicular orifices. [5] However, in our patient while there is thickening over the facial area, the other characteristics of rosacea are absent. Furthermore, there are no joint or bone abnormalities seen in rosacea.

Treatment options vary for PDP, in general. One case report noted that colchicine improved the articular symptoms, folliculitis, and pachyderma. Another report showed joint symptoms were responsive to IV pamidronate. Oral isotretinoin helped with skin manifestations (pachyderma and cutis verticis gyrate). Variants of PDP include RosenfeldKloepfer syndrome (characterized by enlargement of the jaws, especially mandible, and of the hands and feet, nose, lips, tongue, and forehead, along with cutis vertices gyrata and corneal leukoma); Currarino idiopathic osteoarthropathy (an incomplete form of PDP seen in children and adolescents and characterized by the presence of eczema and sutural diastases); and a localized form with only radiographic features of PDP in the lower extremities. [2]

This patient was given oral isotretinoin to help with increased sebum production which predisposes him to acne and recurrent seborrheic dermatitis. Isotretinoin is usually given at 0.5 mg/kg/day with a maximum of 2.0 mg/kg/day. Park et al reported giving oral isotretinoin to a patient with PDP with a favorable result and patient satisfaction in terms of facial seborrhea. [6]

He was then referred to orthopedics and plastic surgery for evaluation. Orthopedics disposition included close observation and agreed with giving of pain medication for the knee joint pains. Plastics surgery performed frontal rhytidectomy.

Figure 7. Frontal rhytidectomy done on the patient.

In 2019, Salah et al reported a case of a 19-year-old male with PDP who underwent frontal rhytidecotomy which significantly improved the deep wrinkles on the patient's face. This was the basis in doing the same procedure to our patient. Similar results were also achieved with the said procedure. [7]

In two separate journals, Salah et al and Chen et al reported the use of Botulinum toxin type A for deep rhytides and seborrhea. The doses given were between 1 to 4 Units per site in 4 to 5 sites of the face. The patients were followed-up every 6 months and re-injection of Botulinum toxin type A were done on follow-up with noted treatment satisfaction from the patients. Botulinum toxin type A temporarily helps in pachyderma and seborrhea by blocking the release of acetylcholine which is the principal neurotransmitter of the neuromuscular junction. [7,8] In our patient, a total of 16 Units was given (4 units per site for 4 sites) on the frontal areas. The patient was lost to follow-up hence the effect of Botulinum toxin type A could not be assessed.

In published journals, the use of Fractional CO2 laser for the treatment of deep wrinkles seen in PDP has not been documented yet. To the author's knowledge, this is the first case in the Philippines that the said laser technique was used for this specific case. This modality was chosen due to its safety profile, efficiency, and precision. [9] The wavelength of CO2 is 10,600 nm which targets water (dermis contains a very high water percentage). This makes the CO2 fractional laser ideal for deep wrinkle whose main pathology lies on the dermis. [9]

The pathophysiology of PDP has been linked to a range of processes which include malignancy, autoimmune diseases such as Crohn disease, and myelofibrosis. (2) Patients with PDP harbor defects in either the HPGD (15-hydroxyprostaglandin dehydrogenase) gene or the SLCO2A1 (solute carrier organic anion transporter family member 2A1) gene, resulting in elevated prostaglandin E2 levels. Thus, it is postulated to play roles in pleiotropic actions in different tissues. [7]

As a consequence of increased soft tissue bulk and hyperostosis, complications of PDP to watch out for include ptosis, compression of the nerve endings, hearing problems, kyphosis, arthrosis, osteonecrosis of the femoral head, and carpal tunnel syndrome. [2]

Figure 8. Comparison photos of the patient from baseline to his eighth consult.

CONCLUSION

The diagnosis of PDP can be done clinically however the help of histopathology increases the accuracy of the diagnosis given that this condition is rare and requires expertise and experience from clinicians to be able to diagnose the disease. It is also useful to differentiate primary from the more insidious secondary type of hypertrophic osteoarthropathies.

Treatment of pachydermoperiostosis is mainly symptomatic and requires a multi-specialty approach. Because of its rarity, treatment options for pachydermoperiostosis have yet to be standardized. In this patient, we note that he benefited significantly through a holistic approach such as plastic surgery, laser surgery, and botulinum toxin injection as well as oral and topical therapies for his secondary problems such as acne and seborrheic dermatitis. In this particular case, all available options in the institution were utilized which led to patient satisfaction of the outcome.

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Subcutaneous Panniculitis-like T-Cell Lymphoma with Hemophagocytic Syndrome: A Case Report*

Ranillo V. Gamutan, MD[1]

ABSTRACT

Introduction: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare disease, accounting for less than 1% of non-Hodgkin's lymphomas that is characterized by infiltration of T-cells in the subcutaneous adipose tissue.

Case presentation: A 21-year-old Filipino female presented with intermittent fever which eventually was associated with multiple eruption of cutaneous lesions. The serum antinuclear antibody (ANA) titer and pattern revealed negative results. Further clinical investigation prompted a skin lesion punch biopsy revealing atypical lymphoid infiltrates with lobular panniculitis consistent with SPTCL. Immunohistochemical studies stained strongly positive for CD3, CD8, granzyme B and negative for CD20, CD4, and CD56. The case was also compounded with the existence of hemophagocytic syndrome having fulfilled five of the eight criteria. She was given prednisone (1 mg/kg/day) with gradual resolution of cutaneous lesions leaving marked hyperpigmentation and lipoatrophy.

Discussion: SPTCL presents with a myriad of systemic symptoms but will always present with skin lesions. The biopsy for histopathological interpretation is commonly performed as a first diagnostic step followed by immunohistochemical staining. Clinical presentation, histo-pathological findings, and immunohistochemical results together clinched the diagnosis of SPTCL.

Conclusion: Patients with history of intermittent fever associated with cutaneous lesions and systemic clinical findings, SPTCL should be a differential diagnosis. However, lupus erythematosus panniculitis (LEP) must be ruled out first as its closest mimicker. This case report along with other large case series provides further evidence that monotherapy with oral prednisone can be an initial choice of therapy.

Keywords: *Subcutaneous panniculitis-like T-cell lymphoma, lupus erythematosus panniculitis*

INTRODUCTION

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare disease, accounting for less than 1% of non-Hodgkin's lymphomas. It is characterized by infiltration of T-cells in the subcutaneous adipose tissue.[1] The annual incidence of cutaneous lymphoma is estimated to be from 0.5 to 1 per 1,000,000 persons per year.[2] There is only one published case of SPTCL in the Philippines.[18]

Diagnosing SPTCL is a challenge. It presents with a myriad of symptoms that are mostly constitutional, hence, a high index of suspicion is needed for early diagnosis. A comprehensive history and physical examination complemented with proper diagnostic evaluation including biopsy and immunohistochemical are essential for the diagnosis. Currently, no standard therapeutic approach exists.

This case report aims to describe a rare case of SPTCL in a 21-year old female and the clinical challenges of arriving at a diagnosis including the diagnostic dilemmas, and differential diagnoses. Also, this report aims to supplement to the small amount of data there is as to the treatment and management of SPTCL.

CASE PROTOCOL

A 21-year-old female, single, from Samal presented with fever and multiple cutaneous lesions.

*2nd Place, 2021 Philippine Medical Association Case Report Presentation, June 21, 2021

[1]From Southern Philippines Medical Center, Davao del Sur

Five months prior, the patient complained of intermittent fever with appearance of warm, erythematous, petechial, and nodular skin lesions on both lower extremities. This was associated with swelling of both lower extremities and body malaise. Consult was done and unrecalled antibiotics were given with gradual resolution of fever and skin lesions. The swelling of both legs persisted, however the skin lesions gradually resolved into hypopigmented patches.

Four months prior, cutaneous lesions recurred and progressed into pruritic skin lesions that were nodular. They were gradually enlarging in size associated with intermittent fever and body malaise. Scratching of the affected areas led to skin thickening and ulcerations. She opted application of herbal liniment. Lesions progressed in size and diameter with persistence of intermittent fever and bipedal edema.

Two weeks prior, multiple non-tender erythematous and pruritic patches appeared on her upper extremities that evolved into ulcers with serous discharges admixed with pus. Redness and swelling were noticed around the right eye. Cough productive of yellowish non-blood-streaked sputum developed. Several consultations were done where she was given unrecalled medications without resolution of her symptoms. The persistence of symptoms prompted consultation in a tertiary hospital where she was admitted.

She has no co-morbid medical conditions or prior surgeries. There were no known allergies to food and drugs. There was no history of pulmonary tuberculosis (PTB) exposure. Her family history was unremarkable. She is a non-smoker, non-alcoholic beverage drinker with no illicit drug use. She has one sexual partner with two offspring. There was no recent history of travel for the past five years. She has no exposure to chemical and industrial substances.

The patient came in awake, oriented, with generalized edema, jaundiced, and lying flat in bed. She was tachycardic at 110 bpm, tachypneic at 28 cpm,

and hypotensive at 70/50 mmHg in all extremities. There was swelling of the right eye with violaceous pigmentation on the upper and lower eyelid (Figure 1A) and icteric sclerae with pale palpebral conjunctivae.

Figure 1. Patient's Skin Lesions. A. Unilateral swelling of the right eye with bipalpebral violaceous pigmentation **B.** Crusted and hyperpigmented plaques with irregular borders surrounding an ulcerated erythematous base with areas of scaling and weeping on the left forearm measuring 10 x 9 cm **C**. Upper extremity lesions **D.** Lower extremity lesions

Chest and lung examination revealed fine crackles on both basal lung fields. The abdominal girth measured 62 cm with no caput medusae and spider angiomata. She had normoactive bowel sounds. Shifting dullness with a positive fluid wave test was elicited. The abdomen was soft and non-tender. The liver span measured 16 cm and 10 cm along the midclavicular and midsternal lines, respectively. The Castell's sign – a physical exam for splenomegaly was not present. Multiple poorly circumscribed erythematous plaques topped with scales and hemorrhagic crust with areas of ulceration were seen in both upper extremities. Multiple well-circumscribed hypopigmented patches with scaly borders were found in the lower extremities. The trunk was spared. There was bipedal edema up to the level of the thighs (Figure 1D). Neurological examination was essentially normal.

She was admitted with a working impression of septic shock secondary to

community acquired pneumonia-high risk (hypotension) and infected skin lesions. Systemic lupus erythematosus and malignancy were considered.

Hematology report revealed normocytic hypochromic anemia at 76 g/L, thrombocytopenia of 97 x10^3, and normal WBC count at 9.04 x10^3. The chest x-ray revealed pulmonary congestion with bilateral pneumonia.

A liver pathology was considered due to icterisia, jaundice, anasarca, and hepatomegaly. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were both elevated at 2.8x and 8.5x from upper limit of normal (ULN), respectively. The total bilirubin was also markedly elevated at 177.31 umol/L including the direct bilirubin 90.47 umol/L and indirect bilirubin 58 umol/L. Activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR) were all elevated. Severe hypoalbuminemia of 8.13 g/L was also present. Further work-up revealed markedly elevated lactate dehydrogenase (LDH) at 1,403 U/L and a peripheral blood smear with normocytic hypochromic red cells without immature leukocytes. The hepatitis profile and human immunodeficiency virus (HIV) screening were negative. Other laboratory results were unremarkable (Appendix A).

The ANA titer and pattern revealed a negative result, which made systemic lupus erythematosus less likely.

The ultrasound of the whole abdomen revealed an enlarged liver and spleen, ascites, and gallbladder wall edema. Malignancy was also entertained, hence, computed tomography (CT) scan of the whole abdomen and chest revealed bilateral pleural effusion with passive atelectasis of both lower lobes, hepatomegaly with steatosis, splenomegaly, moderate ascites, and subcutaneous edema. The blood, sputum and wound culture results were all negative.

A skin lesion punch biopsy revealed atypical lymphoid infiltrates with lobular panniculitis on Hematoxylin-Eosin (H&E) staining (Figure 2) consistent with SPTCL. On immunohistochemical staining, it revealed strongly positive for CD3, CD8, granzyme B and negative for CD20, CD4, and CD56 (Appendix C).

A distinctive associated clinical feature of SPTCL is hemophagocytic syndrome (HPS). This and the other associated clinical findings of liver injury and anemia of the patient fulfilled five of the eight criteria cytopenias (anemia, thrombocytopenia), hypertriglyceridemia (449.6 mg/dL), elevated ferritin (943 ng/mL; Normal range 13-400), fever and splenomegaly for SPTCL.

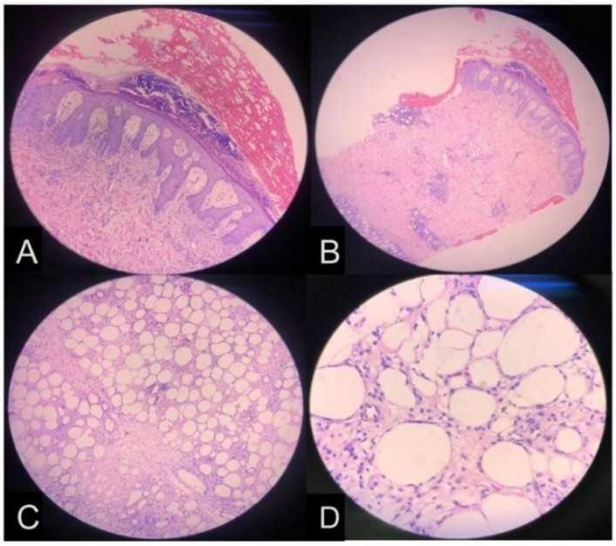

Figure 2. Final Histopathology Report: Skin punch biopsy showed **A.** epidermal necrosis overlying a mildly acanthotic and spongiotic epidermis. (x40) **B.** The dermis revealed scattered macrophages, erythrocyte extravasation, and focally dense perivascular infiltrates (mononuclear cells, neutrophils, and eosinophils) (x10). **C.** Adipocytes rimmed by lymphocytes (40x) **D.** Adipocytes rimmed by lymphocytes, disruption of adipocyte membranes, and foci of histiocytes containing cellular debris highly suggestive of subcutaneous panniculitis-like T-cell lymphoma (x100)

Cefepime and azithromycin were completed. She was clinically out of infection. Other supportive measures included albumin infusion for the severe hypoalbuminemia. Tetanus toxoid and immunoglobulin were also given for tetanus prophylaxis. Fusidic acid cream and miconazole cream were applied on the skin lesions. Essentiale, a hepatoprotectant was also started. Prednisone was started at 1 mg/kg/day with gradual resolution of ulcers, non-appearance of new skin lesions, and lysis of fever. There was marked lipoatrophy and hyperpigmentation (Figure 38) with areas of cutaneous depression.

Figure 3. Patient's cutaneous lesions during steroid therapy.
A. There is a significant resolution of lesions with reduced swelling of the right eye (yellow arrow) with disappearance of violaceous pigmentation and **B.** Resolution of the plaque in the upper extremity (red arrows) leaving marked hyperpigmentation and

The patient was discharge improved with oral prednisone. She was advised close follow-up in our outpatient department. Final diagnosis was subcutaneous panniculitis, T-cell-like lymphoma with hemophagocytic syndrome.

DISCUSSION

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone marrow, spleen, liver, and GI tract. According to 2015 Philippine cancer Facts and Estimates3, the estimated age-standardized national incidence rates of NHLs are 3.1 per 100,000 in both sexes, 3.6 among males, and 2.7 among females. The classification of non-Hodgkin lymphoma is complex and ever-evolving, with more than 50 different subtypes listed in the latest World Health Organization classification[4].

Cutaneous T-cell lymphoma (cTcLs), cancers of the T lymphocytes, is a rare group of NHLs that arise primarily in the skin. They account for four percent of all cases of NHL.[5] It has various signs and symptoms, outcomes, and treatment options.[5] Mycosis fungoides (MF) and Sezary syndrome (SS) are the two most common subtype of cTcLs, which are still considered rare disorders.

SPTcL is classified under cTcLs with indolent clinical behavior.[10] It is also one of the rarer subtypes of cTcLs, comprising less than 1% of the entire NHL.[1] It is a cytotoxic T-cell lymphoma that preferentially infiltrates the subcutaneous adipose tissue. The exact prevalence and incidence of this disease is unknown globally. The largest case series from eight European cutaneous lymphoma centers reported 83 cases. Another 10-year retrospective study from different centers listed less than 20 cases. [8,12]

We are presented with a 21-year-old female with a history of intermittent fever associated with waxing and waning of skin indurations. It mostly occurs in females with a median age of 29 years old based on four Asian case series on SPTcL.[12,19,20,21] There has been no published data for any racial predilection.

The associated clinical sign and symptoms in SPTcL are nonspecific. Sixty percent of patients with SPTcL may have systemic symptoms such as fever, chills, night sweats, and weight loss.[1,2,9] Other clinical findings include hepatomegaly and/or splenomegaly, abdominal abnormalities (tenderness, distension), and serosal effusions.[1,7] Facial swelling has also been reported in some cases.[10] All of these systemic findings are seen in our patient. These non-specific signs and symptoms of SPTcL more often presents as a diagnostic dilemma to clinicians.

Despite the myriad of systemic symptoms of SPTcL, skin lesions will always be present.[10,12,17,18,19] They are classically indurated, poorly circumscribed, cutaneous nodules and plaques, often multifocal, and mostly involving the limbs.[6,7] Most patients presented with generalized skin lesions involving the legs (45 cases), the arms (39 cases), and/or the trunk (35 cases), and less commonly the face (16 cases). Fourteen patients presented with solitary or localized skin lesions.[10] They remain discrete or coalesce to form large indurated plaques up to 20 cm in diameter and with varying skin color.[7,8,10] Ulcerations can occur but are significantly uncommon.[9,10] Facial involvement is rare [10] and orbital involvement is even lesser.[10,24] It is interesting to note that this patient initially

had fever followed by the appearance of skin lesions after two weeks. However, it only included the lower extremities, and eventually resolved leaving hypopigmented patches. It then re-appeared in the upper extremities with more prominent indurations including a right eye swelling.

Approximately 14-17% of SPTcL have hemophagoyctic syndrome.[25] This is a rare feature in certain cases of SPTcL. However, cases are sporadic and less dueto its rarity. These patients have cytopenias and elevated liver enzymes.[9] These laboratory findings, along with hypertriglyceridemia, elevated ferritin, presence of fever, hepatomegaly, and/or splenomegaly support the diagnosis of HPS (Appendix8). All patients with HPS show hepatosplenomegaly, high serum ferritin, and high LDH level. The presence of HPS harbors a poorer prognosis. However in the case series by Willhemze, this statement was contradicting.[10] Patients with HPS were not associated with mortality. Interesting to note that upper extremity involvement portends a poorer prognosis.[10]

The biopsy for histopathological interpretation is commonly the first step for diagnosis.[10] All cases show a predominantly subcutaneous atypical lymphoid infiltrate resembling lobular panniculitis. It exhibits adipotropism where individual fat cells are rimmed by lymphocytes. This is very characteristic of SPTcL.[1,9,10,12] However, the H&E staining is not enough to support the diagnosis of SPTcL. Lupus erythematous panniculitis (LEP) is a mimicker of SPTcL and its closest differential. Clinically distinguishing the two can be very difficult. In a large case series, some of the patients had co-existent LEP and SPTcL. Some cases were initially classified as LEP but turned out to be SPTcL. LEP and SPTcL can have overlapping features both clinically and histologically hence some describe both as a spectrum.[22]

LEP always presents with nodular lesions that could also indurate. Biopsy of LEP shows epidermal involvement, mucin depositions, presence of reactive germinal centers, clusters of 8 cells, or considerable numbers of admixed plasma cells.[23] All of which are absent for this case.

Differentials for LEP/SPTcL include squamous cell carcinoma of the skin. Polyarteritis nodosa and erythema induratum (EI) were considered based on constitutional symptoms and skin lesions. However, history and biopsy findings ruled them out. Furthermore, El shows marked septal and lobular granulomatous panniculitis which is not found in our patient. Immunohistochemical staining is warranted to differentiate these entities.

All cases of SPTcL are positive for cD3, cD8, granzyme B and negative for cD20, and cD56 in a large case series.[10,12] One patient had positive cD4 stain but was still considered as SPTcL. Our patient demonstrated strong positivity for cD3, cD8, granzyme B and negativity for cD20, cD4, and cD56. cD8+ staining is useful in identifying neoplastic cells rimming adipocytes.[17] The diagnosis of SPcTL is based on the patient's clinicopathologic and immunohistochemical findings.

There is no standard of treatment approach in these patients due to the rarity of this condition. The patients are treated with systemic immunosuppressive alone or in combination with chemotherapy such as in cHOP regimen (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone) in one case series.[10] Initial treatment with cHOP regimen resulted in a sustained complete remission in 16 (64%) of 25 patients. However, treatment with only prednisone or other immunosuppressive agents gave similar results.[16] This observation raises the question whether such patients should be routinely treated with cHOP (-like) therapy or even more aggressive regimens. In our patient, prednisone (1 mg/kg/day) was given alone to our patient with gradual clearing of the skin lesions with no recurrence since. Other treatment modalities include radiotherapy, stem cell transplantation, and phototherapy. However, therapies are variegated and standardized treatments have yet to be established.

The tropism of SPTcL for adipocytes answers the lipoatrophy consistent with response to steroid therapy. General reduction of fat tissue contributes to the cutaneous depression and lipoatrophy of patients after resolution of these neoplastic lymphocytes around adipocytes. Resolution of lesions result in lipoatrophy followed

by localized cutaneous depression and hyperpigmentation.[7,9,10] Our patient had significant resolution of cutaneous lesions which left lipoatrophy and marked hyperpigmentation.

SPTcL has a favorable prognosis with a 5-year survival rate of 80%.[10] However, the presence of hemophagocytic syndrome harbors a poorer prognosis, hence a close follow-up for these patients must be instilled.[10,19] Although in some large retrospective studies with systemic involvement and HPS, these were not associated with increased mortality.[12]

SUMMARY

Subcutaneous panniculitis-like T-cell lymphoma is a rare disorder. An associated hemophagocytic syndrome makes this case an even rarer one.

This is a 21-year old Filipino female who sought consultation due to intermittent fever associated with multiple eruptions of cutaneous lesions. Further clinical investigation prompted a skin lesion punch biopsy revealing atypical lymphoid infiltrates with lobular panniculitis consistent with SPTcL. Immunohistochemical studies stained strongly positive for cD3, cD8, granzyme 8 and negative for cD20, cD4, and cD56. She was given prednisone (1mg/kg/day) with gradual resolution of cutaneous lesions leaving a marked hyperpigmentation and lipoatrophy.

A step-wise approach of history and physical examination, biopsy, and immunohistochemical staining is essential to the proper diagnosis of these cases. No existing standard therapeutic approach for SPTcL exists. Patients may receive a variety of treatments. She was given prednisone at 1mg/kg/day with gradual resolution of ulcers, non-appearance of new skin lesions, and lysis of fever. Our experience will contribute to the pool of knowledge in these types of patients.

CONCLUSION

Malignancy particularly lymphoma should be a differential diagnosis in patients with recurrent intermittent fever and constitutional symptoms. SPTcL should be considered when malignancy is associated with recurrent cutaneous lesions. A step-wise approach involving thorough history and physical examination followed by skin biopsy and immunohistochemical staining is essential in diagnosing these patients. Additional laboratory work up may disclose possible associations leading to diagnosis of syndromes such as hemophagocytic syndrome in our case. No standard therapeutic regimen exists. cHOP and cHOP-like regimens are successful in treating the disease. However, monotherapy with oral prednisone has been shown to work as well and was seen in our case.

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Appendix A
Laboratory Results

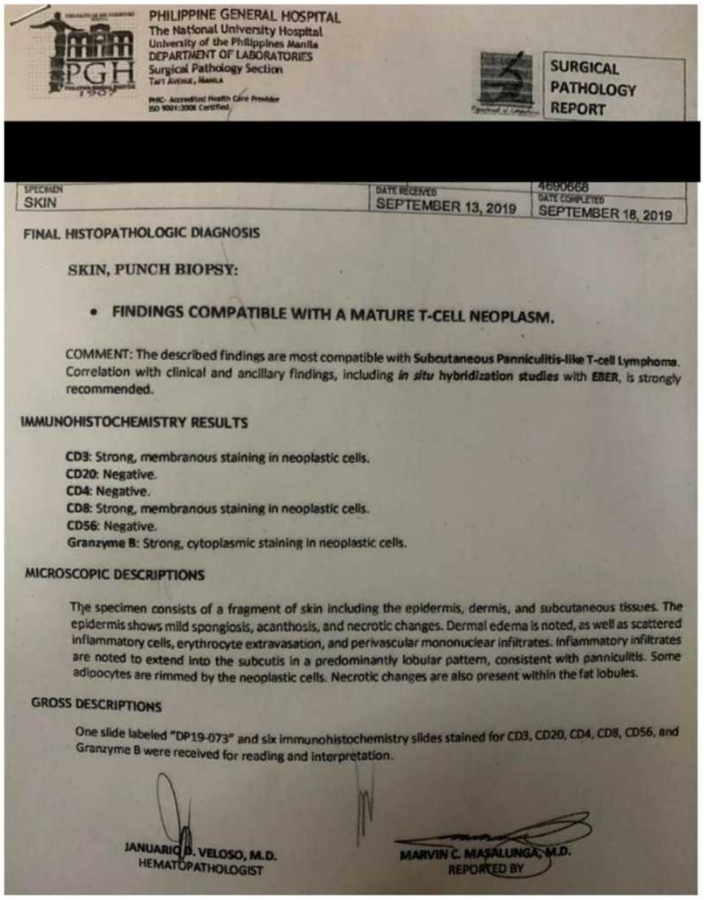
	Result	Normal range
Creatinine	48.24 umol/L	39-91 umol/L
Potassium	3.7 mmol/L	3.6-5.1 mmol/L
Sodium	138 mmol/L	136-144 mmol/L
Reticulocyte count	1.9%	0.5-1.5%
Anti HcV	Non-reactive	
HbSAg	Non-reactive	
calcium	1.81 mmol/L	2.23-2.58 mmol/L
Magnesium	0.75 mmol/L	0.74-1.03 mmol/L
cRP	1.320	cut off: 1
Anti streptolysin 0	Negative	<200
Ferritin	943 ng/mL	13-400 ng/mL
Triglycerides	449.6 mg/dL	
Anti-dsDNA	negative	

Appendix B
Diagnostic Criteria of Hematophagocytic Syndrome

Clinical features	Laboratory features
Fever* Hepatomegaly and/ or Splenomegaly*	Cytopenias of at least two lineages in the peripheral blood* Hemoglobin* <90 g/L Platelets <100 x 10^9/L Neutrophils <1.0 x 10^9/L Hypertriglyceridemia* and/or hypofibrinogenemia Fasting triglycerides ≥265 mg/dl * Fibrinogen ≤1.5 g/l Hemophagocytosis in bone marrow, spleen, or lymph nodes Low/absent natural killer-cell activity Hyperferritinemia (>500 mg/L)* High soluble interleukin 2 receptor (scD25) (>2,400 U/mL)

[a]Adapted from Jordan et al. [11]Five of eight features are required for the diagnosis
*present in the patient

Appendix C
Skin Punch Biopsy Results



PHILIPPINE GENERAL HOSPITAL
The National University Hospital
University of the Philippines Manila
DEPARTMENT OF LABORATORIES
Surgical Pathology Section
Taft Avenue, Manila

SURGICAL PATHOLOGY REPORT

[redacted]

SPECIMEN	DATE RECEIVED	DATE COMPLETED
SKIN	SEPTEMBER 13, 2019	SEPTEMBER 18, 2019

FINAL HISTOPATHOLOGIC DIAGNOSIS

SKIN, PUNCH BIOPSY:

- FINDINGS COMPATIBLE WITH A MATURE T-CELL NEOPLASM.

COMMENT: The described findings are most compatible with **Subcutaneous Panniculitis-like T-cell Lymphoma**. Correlation with clinical and ancillary findings, including ***in situ* hybridization studies** with **EBER**, is strongly recommended.

IMMUNOHISTOCHEMISTRY RESULTS

CD3: Strong, membranous staining in neoplastic cells.
CD20: Negative.
CD4: Negative.
CD8: Strong, membranous staining in neoplastic cells.
CD56: Negative.
Granzyme B: Strong, cytoplasmic staining in neoplastic cells.

MICROSCOPIC DESCRIPTIONS

The specimen consists of a fragment of skin including the epidermis, dermis, and subcutaneous tissues. The epidermis shows mild spongiosis, acanthosis, and necrotic changes. Dermal edema is noted, as well as scattered inflammatory cells, erythrocyte extravasation, and perivascular mononuclear infiltrates. Inflammatory infiltrates are noted to extend into the subcutis in a predominantly lobular pattern, consistent with panniculitis. Some adipocytes are rimmed by the neoplastic cells. Necrotic changes are also present within the fat lobules.

GROSS DESCRIPTIONS

One slide labeled "DP19-073" and six immunohistochemistry slides stained for CD3, CD20, CD4, CD8, CD56, and Granzyme B were received for reading and interpretation.

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HEMATOPATHOLOGIST

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REPORTED BY

A Rare Case of *Coniochaetta Hoffmannii* Fungus Ball in an Immunocompetent Host*

Nabila Tasnim L. Angkaya, MD[1]

ABSTRACT

Introduction: Fungal balls are commonly associated with the *Aspergillus* species. The hyaline hyphae is not diagnostic of a fungus ball's causative organism hence the need for fungal culture. Systemic fungal infections are rarely seen in immunocompetent persons.

Case: A 45-year-old male presented with a nine month history of nonproductive cough progressing to hemoptysis. His chest tomography with contrast revealed a mass measuring 6.5cm x 5.5cm x 6.9cm located in the left upper lobe, with a smooth lining and air crescent sign consistent with aspergilloma. Serum galactomannan assay was positive. Patient was treated medically for *Aspergillus sp* infection with voriconazole and itraconazole for six months with no response. A left upper lobectomy was done. Lung tissue biopsy and histopathologic examination showed hyphal elements with branching short lateral necks. Culture studies revealed a rare microorganism namely *Coniochaetta hoffmannii*. Post-operatively, our patient improved and was eventually discharged.

Discussion: *Coniochaetta hoffmannii* is a rare human pathogen and is only implicated in those immunocompromised. Thorough clinical investigation led to the identification of this organism. Literature review reveals scant inconclusive treatment approaches. Surgical intervention proved therapeutic for our patient.

Conclusion: Not all fungal balls are caused by *Aspergillus sp*. Culture studies remains the gold standard in identifying specific organism causing fungus balls. Rare micro-organisms such as *Coniochaeta hoffmanii*. can be isolated. Invasive fungal infection can occur in an immunocompetent host. The outcome of this study will contribute to the limited pool of information on the diagnosis and management of similar cases.

Keywords: *aspergilloma, fungus ball, coniochaeta*

INTRODUCTION

Over 300 million people are afflicted with a serious fungal infection globally and 25 million are at risk of dying.[1] *Aspergillus spp* (specifically, *A fumigatus*) is by far the most common etiologic agent and aspergilloma as its best recognized form.[2] A non-aspergillus species as a primary cause is rarely documented. It is even rarer to isolate a known non-pathogenic fungus in an immunocompetent host.

Currently, there is paucity in clinical data about *C. hoffmanii* and there are no existing standardized medical guidelines on diagnosis and treatment. This paper presents a rare case of a pulmonary fungal ball formed by a rare mold, *Coniochaeta hoffmanii* in an immunocompetent 45-year old male. The aim of this case report is to highlight the importance of a complete and cost-effective diagnostic and treatment approach to fungal balls. The use of culture studies to identify other possible causative agents of fungal balls is pivotal to provide targeted therapy.

CASE PROTOCOL

A 45-year old male, married, Filipino, from Davao del Norte, was admitted due to persistent hemoptysis.

*3rd Place, 2021 Philippine Medical Association Case Report Presentation, June 21, 2021
[1]From Southern Philippines Medical Center, Davao del Sur

Seven months prior, his cough increased in frequency with dyspnea on exertion. Consultation was done and chest radiograph revealed a confluent density in the left upper lobe.

Figure 1. A chest radiograph taken at posterior-anterior view with a subtle crescentic lucency (in yellow arrows) around a confluent density in the left upper lobe (in blue arrows).

Chest computed tomography (CT) scan with contrast confirmed a huge regular oval mass measuring 6.5cm x 5.5cm x 6.9cm in the left upper lobe with a smooth lining. Dilated airways communicated with the contents of the mass. Fibrotic and bronchiectatic changes were present in the rest of the left upper lobe. Findings were consistent with aspergilloma and pulmonary bronchiectasis.

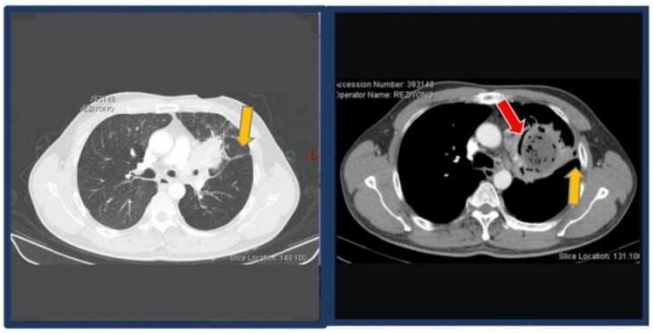

Figure 2. A sagittal chest computed tomography scan showed a 6.5cm x 5.5cm x 6.9cm mass located in the left upper lobe surrounded by air crescent sign (in red arrow). Note the presence of septation between the mass and the cavity wall (in yellow arrow).

Pulmonary malignancy was considered. However, features of the mass revealed a soft tissue attenuation and a characteristic septated separation of the mass from the cavity wall, the 'air crescent sign', hence malignancy was ruled out. Pulmonary tuberculosis was also considered however, the sputum acid fast bacilli and GeneXpert tests revealed negative results. A serum galactomannan antigen test was done to confirm chest CT scan finding of an aspergilloma and it tested positive (Appendix B).

Left upper lobectomy was advised but he opted for a trial of medical management. He was started on voriconazole 200mg tablet once a day for four months with good compliance. However, the cough persisted this time associated with weight loss.

Three months prior, voriconazole was shifted to itraconazole 130mg tablet once a day for two months. His cough increased in frequency and severity associated with episodes of blood-streaked sputum despite good compliance with medications.

He was tested for human immunodeficiency virus which turned out negative. The fasting blood glucose was normal and other inflammatory markers were also negative (See appendix).

Two weeks prior, hemoptysis increased in frequency prompting surgical referral for lung resection hence this admission.

He had pulmonary tuberculosis infection 20 years ago with six months therapy. He had no reported heredofamilial disease. He plants trees and trades lumber for 10 years. He is a 12 pack year smoker and occasional drinker.

On admission, vital signs were normal except for tachypnea of 22 breaths per minute. Pertinent physical examination findings centered on the lungs. Chest examination revealed decreased breath sounds on the left upper lung field with increased vocal and tactile fremitus.

Laboratory tests showed only a slight elevation of WBC 10.75 (normal value 5.0-10). Other laboratory tests were within normal limits. (Please see Appendix B).

He underwent intra-operative bronchoscopy and open posterolateral thoracotomy with left lung

lobectomy. The fungus ball was successfully removed encased within a capsule along with its draining lymph nodes. Histopathologic findings were consistent with aspergilloma.

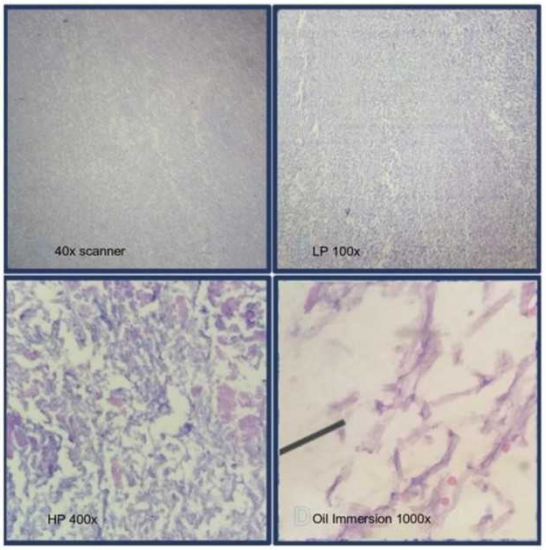

Figure 3. Histopathologic appearance of sample biopsy on hematoxylin-eosin stain showed fungus with septated hyphae (A) at scanner objective 40x, (B) at low power objective 100x, (C) at high power objective 400x, (D) and noted hypha on oil immersion 1000x (black pointer).

Post operatively, the patient developed fever and was started on cefepime 1 gram every 8 hours for secondary bacterial infection. He showed improvement and his hemoptysis disappeared.

Standard pleural fluid gram stain and culture were negative. Culture with Saboraud dextrose agar showed narrow hyaline hyphae with conidia. Small collarettes formed directly laterally on the hyphae. Identification of the organism showed *Conochaeta hoffmanii* previously known as *Lecythophora hoffmanii*.

Figure 4. Frontal chest radiograph of the patient (A) Pre-surgical chest radiograph taken in antero-posterior view showing an inhomogenous opacity (in red circle) with air bronchograms see in the left upper lung field; (B): Post-surgery taken at postero-anterior view showing recent area of lucency devoid of pulmonary vascular markings with an approximate volume of 35% (in yellow line). Staple wires are seen in the left chest. Surgical clips are likewise seen in the left hilar region (in blue arrows).

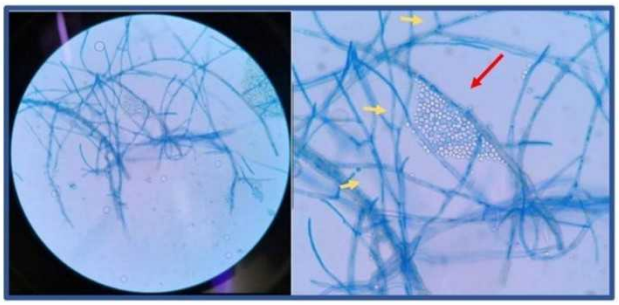

Figure 5. *Coniochaeta hoffmanii*'s conidia (in red arrow). Note presence of branching, septated, hyphae (in yellow arrow).

A normal CD4+ count, positive Tetanus Toxoid, and positive Mantoux skin test (Appendix C) indicate an intact cellular immunity and inflammatory response.

The patient gradually improved and was subsequently discharged. Cough and dyspnea resolved after one week. A repeat chest CT scan done 2 months post-operatively revealed bullae formation in the post-operative area.

DISCUSSION

The global burden of fungal infections is increasing.[3] Fungal lung disease leads to over a million deaths annually. It is the third most common fungal disease and the most serious.[4]

The diagnosis of fungal pneumonias is difficult to prove and is often made on a presumptive basis. It relies on a combination of clinical, radiologic, and microbiological factors.[5] Some fungal diseases are only recently recognized.[6] Emerging fungi previously thought to be nonpathogenic are now recognized as playing a significant role in the increased incidence of fungal diseases.[8]

A fungal ball or mycetoma consists of a rounded conglomerate of hyphae, mucus, and

debris which is contained within a thick fibrotic wall. It usually forms in approximately 15 – 25% of patients within a preexisting cavitating lung disease resulting from tuberculosis, sarcoidosis, bullous emphysema, bronchiectasis, or other conditions.[8,9] The sequelae of structural deformities impairs the clearance of the infection and allows this chronic condition to take hold.[11]

Clinical presentations of fungus ball are characteristic. Most patients are often asymptomatic. Some may present with chronic cough, malaise, and weight loss. Hemoptysis occurs in 50–80% of cases and may be massive and life-threatening.[11] One retrospective study noted a male predominance with half of the patients in their fourth decade.[12] These findings are similar with our patient who came in with cough, malaise and weight loss, he was at his 4th decade, male and with a history of pulmonary tuberculosis.

The radiological signs may be variable. Classically, mycetoma is surrounded by a crescent of air in the cavity – "ball-in-a-hole". However, this radiological appearance is non-specific and differential diagnoses includes lung abscesses, cavitary carcinomas, and ruptured hydatid cysts.[22] In chest computed tomography (CT), fungus ball is characterized by a mass with soft-tissue attenuation within a lung cavity. The mass is typically separated from the cavity wall by an airspace – the "air crescent" sign and is often associated with thickening of the wall and adjacent pleura.[24] These radiologic findings were seen in our patient.

Differential diagnoses include pulmonary malignancy, tuberculosis, lung abscess, infectious consolidations, or pulmonary hemorrhage. However, thorough clinical history, characteristic imaging findings, along with supportive serological exam (galactomannan), and a history of exposure to endemic mycotic areas, a diagnosis of mycetoma is likely. The histopathologic report supports our diagnosis but isolation and microscopic determination in cultures identify the specific causative organism.

Mycetomas are most commonly caused by *A. fumigatus hence the popular term aspergilloma*. However, it can also be caused by other molds such as *Zygomycetes* and *Fusarium*.[14] All hyphate fungi can produce fungus balls in the lungs.[18]

One diagnostic tool for detecting fungal infection is histopathological examination of affected tissues.[15] However, errors in identification of fungal pathogens often occur.[19] The histopathologic appearance of the aspergilli in tissue is similar to that observed with other hyaline molds and differentiation among genera and species usually is not possible.[16]

A positive serum galactomannan assay test may be supportive of aspergilloma. However, galactomannan is found in varying amounts in other fungi including *Penicillium, Fusarium, Altenaria* and *Histoplasma.* Hence, a positive result on galactomannan test is not specific to *Aspergillus*.

The gold standard for the diagnosis of the causative agent is culture and isolation of the fungi.[25] Histologic misidentification of fungal forms may occur. Four out 10 cases misclassified on histologic examination were interpreted as *Aspergillus*. However thru cultures, these 4 cases grew *Rhizopus*, *Fusarium*, and *Scedosporium apiospermum*.

Our fungal cultures grew *Coniochaeta hoffmanii* (formerly *Lecythophora),* a mold and a plant pathogen. It is locally known as the "soft rot fungus".[26] *C. hoffmanii* is characterized by its hyaline hyphae and intercalary phialides with very short lateral necks, periclinal wall thickening, and flaring collarettes.[28] Penetration of fine hyphae through wood cell walls initiates the process of colonization and subsequent decay.[27] Most pulmonary fungal infections occur after inhalation of fungi when their natural habitat is disturbed.[33] Once in the lung alveoli, the fungus is engulfed by macrophages and other cells involved in the primary immune response. Our patient works in the timber and lumber industry. Prolonged exposure may be a risk factor for *C. hoffmanii* infection.

An ubiquitous organism usually becomes pathogenic to humans with immunodeficient system or state. Commonly, infections are severe, complicated, in multiple sites, resistant to treatments, with unusual organism, and clustering

of cases. *C. hoffmannii* has been isolated as the cause of a prosthetic valve endocarditis in a diabetic patient.[29] Other clinical presentations of *C. hoffmanii* include a case report of septic shock in an 18 year old patient on chronic mechanical ventilator due to mitochondrial encephalopathy, chronic sinusitis in a patient diagnosed with AIDS, and a fungal peritonitis in a patient on continuous peritoneal dialysis.[30,31,32] Our patient did not have any primary or secondary immunodeficient state based on work ups done. There were no similar cases in the family precluding the diagnosis of familial immunodeficiency. Further studies regarding this microorganism's interplay with human pathogenesis remains to be determined.

Treatment options for a fungal ball include surgical or medical approach. Voriconazole is now considered the drug of choice as triazoles are preferred agents for treatment and prevention of invasive aspergillosis.[39,40] *C. hoffmanii* has been proven to be resistant to multiple antifungal agents. A study reported that it was resistant to all antifungal agents tested with no zone recorded for amphotericin B, ketoconazole, itraconazole, fluconazole, or flucytosine. This could explain the failure of medical management in our case despite use of two anti-fungal medications.

A local study reports that surgical resection of aspergilloma is effective in preventing hemoptysis and is recommended in symptomatic patients.[35] The Centers for Disease Control and Prevention strongly recommends resection for patients with symptoms, especially with significant hemoptysis and with a single aspergilloma if there are no contraindications. Peri-/postoperative antifungal therapy is not routinely required. However, if the risk of surgical spillage of the aspergilloma is moderate (related to location and morphology of the cavity), antifungal therapy with voriconazole (or another mold-active azole) or an echinocandin is suggested.[36] Despite the risks, surgery offers three potential benefits: control of symptoms, prevention of hemoptysis, and prolongation of life.[38] A study reported an in-hospital mortality of 4.1%. Postoperative complications occurred in 63.3% of patients. These were prolonged air leak (26.3%), arrhythmias (20.4%), residual pneumothorax (16.3%), respiratory failure (14.3%), atelectasis (12.3%), and bleeding (12.3%). Surgical treatment of pulmonary aspergilloma should be restricted to symptomatic patients in whom lobectomy can be performed due to the increased risk of complications.[37]

Patients who underwent surgical intervention have good long term prognosis. One case reported successful nonrecurrence and improvement sixteen months post operation.[41] Patients treated by pulmonary resection lived longer than patients treated medically in a ten year survival study.[42] Our patient subsequently had a lobectomy after failure of initial anti-fungal therapy.

SUMMARY

A 45-year-old male presented with a nine-month history of nonproductive cough progressing to hemoptysis. He was diagnosed with aspergilloma based on chest tomography with contrast which revealed a mass measuring 6.5cm x 5.5cm x 6.9cm located in the left upper lobe, with a smooth lining and an air crescent sign. Serum galactomannan assay was positive and he was treated medically for *Aspergillus spp* infection with voriconazole and itraconazole for six months. However, lack of clinical response warranted further investigation. His worsening condition prompted referral to a surgeon and lung lobectomy with removal of the aspergilloma was done. Lung tissue biopsy and histopathologic examination findings of hyphae with branching on short lateral necks was seen indicating a growth of a mold which was still consistent with initial impression of *Apergilloma*. However, culture studies which is the gold standard for fungal diagnosis, revealed a rare mold namely *Coniochaeta hoffmanii* as the specific causative organism. Post-operatively, his condition gradually improved and was eventually discharged.

No epidemiological data are available to date, although sporadic cases have been reported however treatment outcomes have been inconclusive.

On follow up, there were no recurrence of complaints although close monitoring is still advised as no treatment guidelines and prognostic data have yet been published.

CONCLUSION

This study shows that not all fungus balls are caused by Aspergillosis. This case demonstrates the importance of culture studies to identify other possible causes of fungal balls.

In this case report we were able to isolate *Coniochaeta hoffmanii* which is an extremely rare microorganism, with limited data on its pathogenesis and clinical manifestations as a human pathogen. The prognosis of this condition is yet to be known since this is the first ever documented case of *C. hoffmannii* fungal ball in an immunocompetent individual. Treatment is still surgical with possible pre-/post anti-fungal treatment. Close monitoring and surveillance is highly recommended.

The diagnosis, management, and outcomes of this study will contribute to the evolving knowledge of this disease. It will help to establish proper protocols in handling similar cases.

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APPENDIX A
Complete Blood Count

Values	1st Hospital Stay	7th Hospital Stay	10th Hospital Stay	12th Hospital Stay	16th Hospital Stay
Hgb (g/L) *135-175*	131	88	116	92	115
Hct *0.40-0.52*	0.36	0.25	0.34	0.28	0.34
WBC (x 10^3/uL) *5.0-10.0*	10.7 H	10.6 H	20 H	10.45 H	12.11 H
Neutrophil (%) *55-75*	70	79 H	96 H	82 H	83 H
Lymphocytes (%) *20-35*	23	15	2	13 L	11 L
Monocytes (%) *2-10*	5	4	2	3	4
Eosinophil (%) *1-8*	2	2	0	2	2
Basophil (%)	0	0	0	0	0
Platelet Count (x 10^3/uL) *150-400*	435 H	357	409	305	390

Blood Chemistry

Sodium (mmol/L) *136-144*	138		136		
Potassium (mmol/L) *3.6-5.1*	3.7		4.10		
Creatinine (umol/L) *57-113*	77.2		75.39		

Surgical Pathology Report

Specimen	Result
Lymph Node, Aspergilloma, left lobe with capsule	Pulmonary Aspergillosis with lung abscess, anthracosis, lymphoid hyperplasia

APPENDIX B
Complete Blood Count & Electrolytes

	Smear Microscopy		Xpert MTB/RIF
Specimen	1	2	
Visual Appearance			Mucosalivary
Reading			MTB not detected
Lab Diagnosis			

Microbiology
Serum Galactomannan

Specimen No: **********	
Specimen	Serum
Serum Galactomannan	POSITIVE
Remarks	Patent Index = 2.26 Reference Index: POSITIVE = greater than or equal to 0.50 NEGATIVE = less than 0.50

HIV Rapid

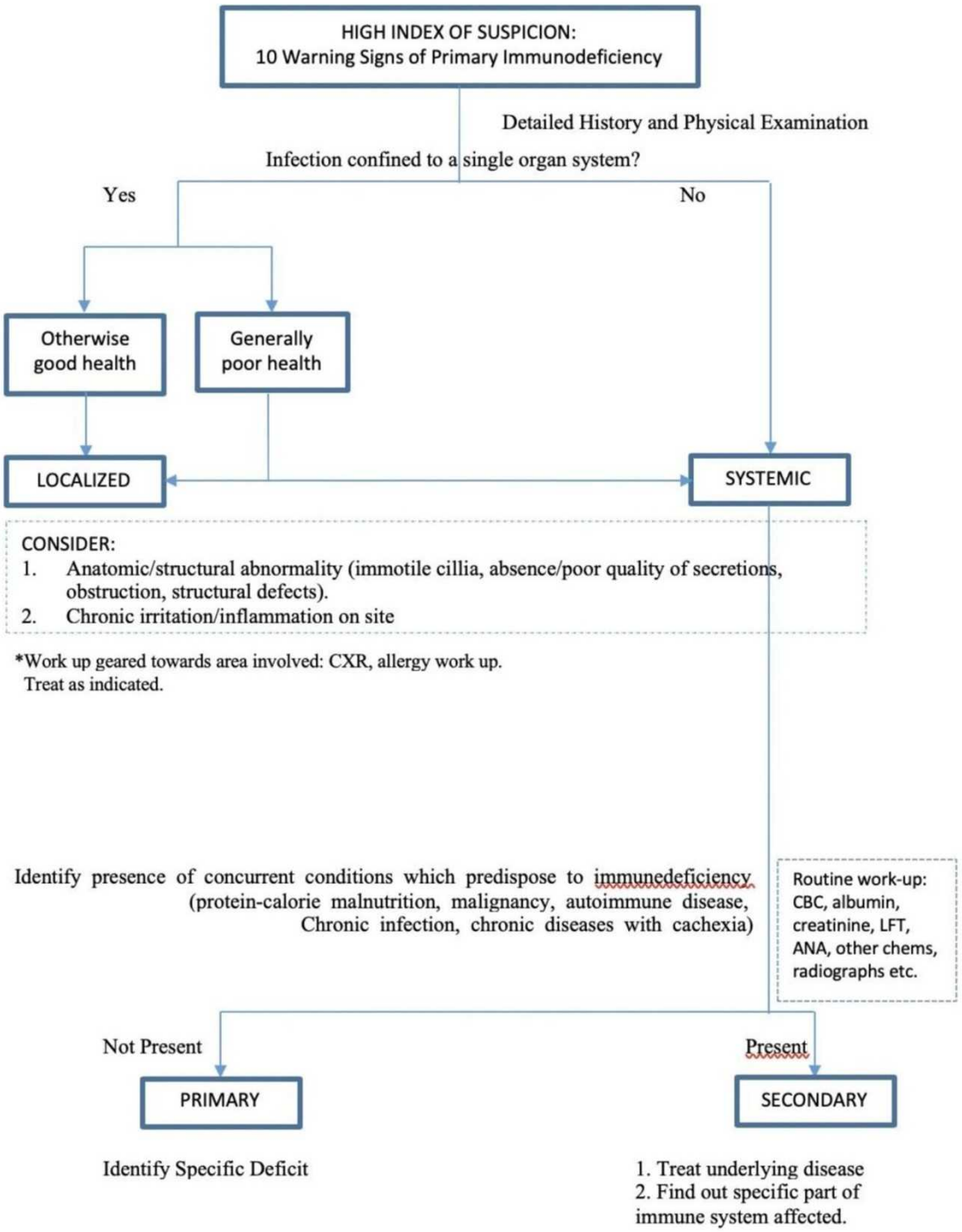
Specimen	Result
Blood	NONREACTIVE

APPENDIX C

CD4 Count

Analysis: Immune Panel CD4 Percentage and Absolute CD4 Count	
Results:	
CD4+ (cells/ul)	881
CD4%	44.92
Hemoglobin (g/dl)	14.40

APPENDIX D


HIGH INDEX OF SUSPICION:
10 Warning Signs of Primary Immunodeficiency
Detailed History and Physical Examination
Infection confined to a single organ system?
Yes
No
Otherwise good health
Generally poor health
LOCALIZED
SYSTEMIC
CONSIDER:
1. Anatomic/structural abnormality (immotile cillia, absence/poor quality of secretions, obstruction, structural defects).
2. Chronic irritation/inflammation on site
*Work up geared towards area involved: CXR, allergy work up.
Treat as indicated.
Identify presence of concurrent conditions which predispose to immunedeficiency (protein-calorie malnutrition, malignancy, autoimmune disease, Chronic infection, chronic diseases with cachexia)
Routine work-up: CBC, albumin, creatinine, LFT, ANA, other chems, radiographs etc.
Not Present
Present
PRIMARY
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Identify Specific Deficit
1. Treat underlying disease
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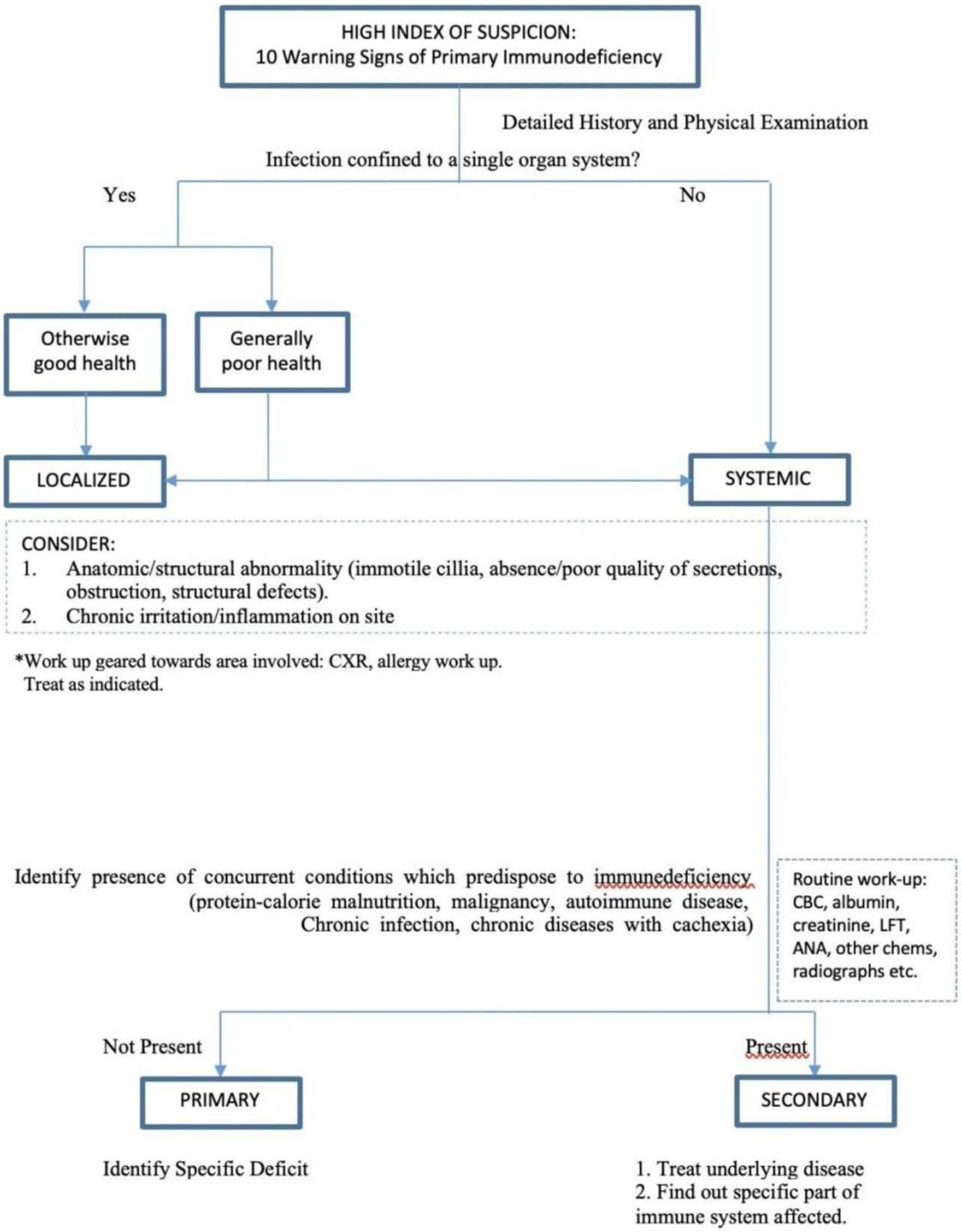
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Routine work-up: CBC, albumin, creatinine, LFT, ANA, other chems, radiographs etc.
Not Present
Present
PRIMARY
SECONDARY
Identify Specific Deficit
1. Treat underlying disease
2. Find out specific part of immune system affected.

A Case Report on Alopecia Areata Incognita in a 19 Year Old Filipino Female*

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Katrina Carmela M. Belen, MD, FPDS[2]
Maria Jasmin J. Jamora MD, FPDS[2]

ABSTRACT

Introduction: Alopecia areata incognita is a rare form of alopecia areata which was first reported in 1987. The prevalence of this disease is unknown but it is more common in women. The usual presentation of alopecia areata incognita is acute, diffuse hair thinning. In most cases, it lacks the typical alopetic patches seen in alopecia areata. It may resemble telogen effluvium and androgenetic alopecia. The prognosis of this disease is favorable and recovery is rapid and spontaneous. **Case:** A 19-year-old Filipino female presents with a two-month history of alopecia areata incognita. She initially had a solitary round patch of hair loss on the scalp with proximally tapered hair, rapidly evolving into diffuse hair thinning. CBC, TFTS, FBS, HBA1c, ANA and VDRL were unremarkable. Histopathology demonstrated dense peribulbar lymphocytic infiltrate, miniaturized hair and increased catagen hair consistent with alopecia areata. There was gradual hair growth after treatment with minoxidil 5% lotion and topical betamethasone dipropionate 0.05% lotion.

Keywords: alopecia areata incognita

INTRODUCTION

Alopecia areata incognita (AAI) is a rare type of non-scarring alopecia. The prevalence is unknown and studies show a female predominance. It is more common in patients aged 20 to 40. In AAI, there is abrupt hair loss presenting as rapid hair thinning within weeks to months.[1] In most cases, it lacks the classic presentation of alopecia areata which appears as round to oval bald smooth patches on the scalp. It may be clinically mistaken for telogen effluvium or androgenetic alopecia (Table 1). Since the different diagnoses have different courses and prognosis, it important to confirm the diagnosis thru a scalp biopsy. AAI subtype of alopecia areata has a shorter clinical course followed by rapid recovery. It has a more favorable prognosis than alopecia totalis, universalis and ophiasis, telogen effluvium and androgenetic alopecia.[2]

Table 1. Differential diagnosis of non-scarring alopecia

Non-scarring alopecia	
Diffuse loss	**Patchy loss**
Telogen effluvium	Alopecia, localized type
Alopecia areata incognita	Tinea capitis
Androgenetic alopecia	Trichotillomania
Systemic disease (Thyroid, Iron deficiency, SLE, Dermatomyositis)	Syphilis

CASE REPORT

A 19-year-old female presented with a two month history of diffuse hair loss. History started two months prior to consultation when she noticed a circular patch of hair loss on the vertex of the scalp. A week later, irregular diffuse hair loss was noted on the vertex and parietal areas of the scalp which prompted consult. On physical examination, there was diffuse hair thinning on the scalp with some ill-defined circular patches with proximally tapered hairs at the periphery (Figure 1). The skin mucosa and nails were normal. The hair pull test was positive. The patient had a good general health and she had no history of psychological stress,

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sudden weight loss, pregnancy or intake of any medication.

Histopathology of the scalp biopsy showed decreased follicular density with increased catagen hair and miniaturized hair. There was increased peribulbar infiltrate of lymphocytes and histiocytes (Figure 2a, 2b, 3). The microscopic diagnosis was consistent with a non-scarring alopecia areata. Laboratory examinations were as follows: CBC was normal; thyroid stimulating hormone was slightly decreased (4.69%) with normal thyroid function (FT3 and FT4) for which no medical intervention was given; FBS was normal; HBA1c was slightly elevated at 6.21%, for which patient was advised diet modification; ANA and VDRL were negative. The laboratory examination results were unremarkable. She was treated with minoxidil 5% lotion and betamethasone dipropionate 0.05% lotion. After 2 months, there was a significant response to therapy with remarkable hair growth (Figure 4).

Figure 1. Diffuse hair loss on the scalp with some ill-defined circular patches with proximally tapered hair or "exclamation mark hairs" at the periphery

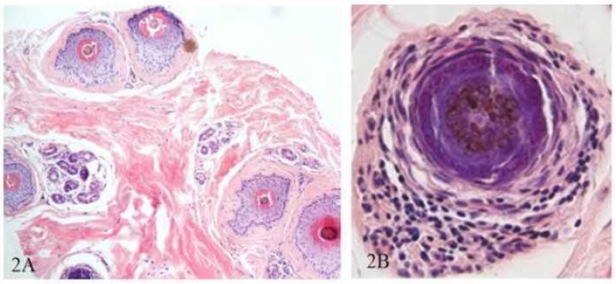

Figure 2. Scalp biopsy specimen from the patient demonstrating (A) non-scarring alopecia with decreased follicular units and increased catagen and miniaturized hairs and (B) heavy lymphocytic infiltrates surrounding the hair bulb.

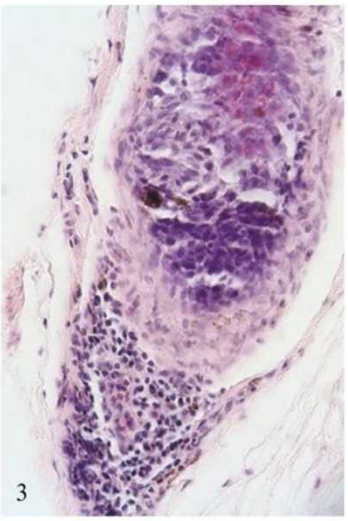

Figure 3. Classic peribulbar "swarm of bees" inflammation in alopecia areata

Figure 4. Hair growth after 2-month use of minoxidil 5% lotion and betamethasone dipropionate 0.05% lotion.

DISCUSSION

From 1987 until 2011, there have only been 112 reported cases of AAI. Molina et al reported a strong female predominance comprising 86.6% of the 112 cases.[3] AAI is characterized by an abrupt, diffuse and severe hair thinning. It differs from the classic alopecia areata because in AAI the borders are indistinct and the alopetic patches tend to merge.[1,4,5]

The pathophysiology of AAI is controversial. Rebora et al theorized that AAI occurs when alopecia areata affects patients with a high percentage of telogen hair in the scalp. Early anagen hair is scarce and its high mitotic rate makes it

vulnerable to noxious events resulting in diffuse hair loss rather than patches.[4]

Inui at el examined patients with acute, diffuse and total alopecia and they noted that exclamation mark hairs and broken hairs are specific diagnostic markers for alopecia areata. Sudden follicular miniaturization causes the short broken off hairs and decrease in hair shaft diameter proximally. [6]

Histopathologic findings are similar to the classical forms of alopecia areata despite different clinical presentation. The most consistent finding in AAI biopsy is an inflammatory infiltrate around the terminal hair bulb.[3] A reversal in the anagen-telogen and telogen-vellus ratio is observed.[5]

Treatment includes topical and intralesional corticosteroids, minoxidil, topical immunotherapy, and topical retinoid.[7] In a study by Iorizzo on 50 patients with AAI, treatment with clobetasol propionate 0.05% cream every night for 6 months and intramuscular triamcinolone acetonide 40 mg once a month for two months showed complete hair regrowth in all patients after six months with regrowth maintained after steroid withdrawal.[8] Other treatment options include anthralin, PUVA turban[8], bexarotene[9], topical immunotherapy with diphenylcyclopropenone and squaric acid dibutylester[10]. A properly treated case of AAI has a good prognosis.

In our patient, she initially had an alopetic patch which rapidly progressed to diffuse hair thinning. Despite having a high index of suspicion that it is a case of AAI, it is imperative that other diagnoses which present like AAI are ruled out. Telogen effluvium and androgenetic alopecia also present with diffuse hair thinning like AAI, however the former have different prognosis and management. With inspection of the hair characteristics and skin biopsy, we were able to make an accurate diagnosis. Our patient had proximally tapered hairs which is consistent with alopecia areata. In addition, histopathology of the scalp biopsy showed increased peribulbar infiltrate of lymphocytes and histiocytes, which strengthens our diagnosis. Her response to treatment with topical steroid and minoxidil solution was very good.

CONCLUSION

AAI, a rare type of alopecia areata, clinically resembles other alopetic conditions. In cases with acute and diffuse hair loss, histopathology is helpful in establishing the correct diagnosis. Treatment includes topical and intralesional steroids and minoxidil. Prognosis of AAI is good compared to other types of alopecia, such as alopecia totalis, universalis and ophiasis.

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A Pilot Study on the Safety and Efficacy of Abelmoschus Esculentus (Okra) 5% Extract in the Treatment of Non-Bullous Impetigo among Paediatric Patients at Jose R. Reyes Memorial Medical Center, Department of Dermatology*

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INTRODUCTION

Impetigo is a common, contagious, superficial skin infection most commonly presenting as erythematous crusting papules and pustules on the face and or extremities. The pathogens usually implicated in this skin disease are gram- positive organisms including Staphylococcus aureus, and less frequently, group A β-hemolytic Streptococcus pyogenes. In JRRMMC, Department of Dermatology, this disease always ranks in the top 10 most common skin diseases annually. Treatment options for this disease include topical and oral antibiotics depending on the condition's severity. Mupirocin and Fusidic acid are considered as gold standard in the treatment of impetigo.[1]

Abelmoschus esculentus or more commonly known as Okra is readily available in the Philippines and is assumed to have medicinal properties like antioxidant antispasmodic, demulcent, diaphoretic, diuretic, emollient, and stimulant. An in- vitro study has proven its broad anti-bacterial property[2] and that maybe due to its palmitic and stearic acid component[3]. Development of an alternative topical treatment option that may be more accessible to the majority of the population due to its cheaper price could create a positive impact in the cure and prevention of common cutaneous bacterial infections. This has led to the idea of challenging the hypothesis if Okra 5% extract can be effectively used in-vivo for superficial bacterial skin infection like impetigo.

OBJECTIVES

General: To determine the safety and efficacy of Abelmoschus esculentus (Okra) 10% extract for the treatment of non-bullous cases of impetigo.

Specific:

1. To determine the efficacy of Okra 5% extract in the treatment of non- bullous impetigo.
2. To determine the safety of Okra 5% extract when treating cases on non-bullous impetigo.

Review of Related Literature

Impetigo frequently occurs in children. Worldwide it represents the most common bacterial skin infection in this group. It is extremely contagious, spreading rapidly via direct person-to-person contact or through fomites. Factors including a warm ambient temperature, high humidity, poor hygiene, an atopic diathesis, skin trauma, and participation in contact sports predispose a patient into developing this skin condition.

Several treatment options may be employed in the management of this disease. In few superficial lesions with no systemic manifestations, the recommendation is giving of either Mupirocin 2% ointment or Retapamulin 1% ointment in combination with daily local wound care. The extent of involvement, co-morbid conditions, patient's immune status and local drug-resistance patterns should be taken into account when deciding whether topical, oral or intravenous therapy is most appropriate.

High and low level resistance against Mupirocin has been elucidated and has been attributed mainly due to the unrestricted over-the-counter usage of this medication.[4] Resistance is a major concern for our part as medical practitioners

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as this would mean less efficacy of our more commonly used topical anti-bacterials.

Several scientific studies have already proven its anti-oxidative effect[5], anti-diabetic[6] anti-cancer[7] and broad anti-microbial properties.[2,8]

The lipid fraction of the okra gum, namely palmitic and stearic acid were found to be the compounds responsible for the antibacterial properties[3]. Usage has been diversified into its usage as a moisturizing component of a hand-sanitizing gel in one study as well[9]

The in-vitro studies have already established its efficacy on both gram-positive and gram-negative pathogenic organisms.[2,7] Although this is a significant breakthrough, no studies have been made yet to apply this new discovery in vivo.

As Okra is readily available in markets and can easily be cultivated even in our own backyard, this study aims to seek a possible alternative topical medication for superficial bacterial skin infections like impetigo.

METHODOLOGY

Study Design:

The study design was an Experimental, Prospective Study

Sampling Design:

Patients considered in the study were those of primary, non-bullous cases of Impetigo in the 2-17 years of age seen at the JRRMMC Department of Dermatology, OPD.

Sample Size:

The researcher had 30 subjects for the study.

Primary Outcome Measure: The proportion of subjects with *Clinical success* or *improvement* and / or bacteriologic cure from baseline.

Secondary Outcome Measure: The proportion of subjects with side - effects noted like erythema, burning/stinging sensation or pruritus.

Operational Definition

1. Clinical success is defined by sufficient resolution of signs and symptoms of infection of the target lesion such that no additional antimicrobial therapy is required to treat the impetigo, as evidenced by the Skin Infection Rating scale (SIRS) score of 0 each for exudate/pus, crusting and pain and 0 or 1 each for erythema/inflammation and itching.[10]
2. Bacteriologic cure - defined as elimination of Staphylococcus aureus and Streptococcus pyogenes or response was such that no culture material would be available and therefore evidence of pathogen eradication at the end of treatment visit.
3. Clinical Improvement – is determined by a SIRS score of 0 for exudate/ pus, which does not meet all the criteria for clinical success. [10]
4. Clinical failure is determined by a SIRS score of 1 or greater for exudate/pus.[10]
5. Unevaluable was recorded when a valid clinical assessment could not be made.

Inclusion Criteria

The study included 30 patients clinically diagnosed as cases of Primary, Non-bullous Impetigo with a score of at least 4 and a maximum of 15 in the SIRS and without systemic manifestations like fever, lymphadenopathy, or abscess formation. Lesions had a maximum of 5 per patient on only one area of the body.

Exclusion Criteria

The study did not include patients with extensive lesions (bullous form, extension to delicate areas of eyes, cellulitis), with fever of at least 24 hours duration, lymphadenopathy, with other co-morbid conditions like scabies and lesions that were already treated previously with topical and oral antibiotics.

Stopping Guidelines:

Any patient that reported worsening of lesions, systemic symptoms like fever or

lymphadenopathy that would develop during the course of the treatment were asked to discontinue the tested extract and were given the appropriate oral medication upon assessment.

Materials:

Okra used in the study was the Native White variety that is very accessible to most people in the markets of Manila. This variety is described to be yellow-white fruit color with a more long and slender fruit pod and a slightly bended tip. The okra was placed in white-capped round "latitas" and stored at room temperature. (25^0C)

Study Intervention:

1. Upon consent, base line photos and microbiologic samples were taken from the lesions to be applied with the test ointment.
2. General instruction included application of the tested medication on the lesions twice a day for 2 weeks in combination with local wound care – daily cleaning with mild soap and water and saline compression twice a day and with open dressing. All participants were advised not to self- medicate with any other topical or oral medication during the interim of the study.

Clinical Assessment:

1. Index grading for the impetigo lesions were based on the SIRS scale and was done by an independent assessor at baseline, day 7 and day 14.
2. Lesions were graded according to pre-determined parameters of the SIRS including Blistering, Exudate, Crusting, Erythema and Pruritus/Pain. Grade would range from 0 – absent, 1-mild, 2-moderate and 3-severe. Total score can start at 4 up to 15 depending on severity.
3. Patients were asked to follow-up at day 7 and 14 with re-evaluation of the SIRS grade and update on patient's photos.
4. The same independent assessor took note of the primary and secondary outcome measures at day 7 and 14.

Bacteriologic Sampling and Culture:

Samples were taken from cleaned, unroofed crusts and placed in Trypticase Soy Broth tubes and incubated for at least 24 hours. The broth was then evaluated for growth and compared to McFarland standard. If seen comparable to the standard, the broth is swabbed onto 5% Sheep's Blood Agar Plate and incubated for another 24 hours.

Culture plates with growth was gram stained and checked for presence of cocci in clusters (Staphylococcus sp.) and/ or cocci in chains (Streptococcus sp.).

Statistical Analysis

Data analysis were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean ± SD was generated. Analysis of the different variables was done using the following test statistics:

Repeated Measures ANOVA was used to compare more than two groups with numerical data that were dependent.

Paired T-test – was used to compare two groups with numerical data that are dependent.

Friedman Test - a non-parametric equivalent of the Repeated Measures ANOVA.

Wilcoxon Signed Rank-test – pairwise comparison after Friedman test (non- parametric test.

LIMITATIONS OF THE STUDY

The patients included in the study were the ones seeking consult at the Jose R. Reyes Memorial Medical Center, Department of Dermatology for non-bullous type of impetigo. Bacteriologic identification was limited to culture in Blood Agar plate and gram stains only.

RESULTS AND DISCUSSION

Table 1: Baseline Characteristics of patients included in the Study

A total of 30 subjects were included in the study. Table 1 shows the distribution of subjects according to demographic characteristics. Their age ranged from 0 to 10 years with majority (93.3%) at the 0-5 years old category. An almost equal distribution of males and females was noted. More than 75% of the subjects impetigo lesions were located on the head.

Table 1. ***Demographic Characteristics of Subjects***

	Frequency (n=30)	Percentage
Age (in years)		
0 – 5	28	93.3
6 – 10	2	6.7
11 – 15	0	0
16 – 17	0	0
Gender		
Male	16	53.3
Female	14	46.7
Localization		
Head	23	76.7
Trunk	5	16.7
Limbs	2	6.7

Table 2: Skin Infection Rating Scale (SIRS) comparison for Baseline, Day 7 & 14

Table 2.1 ***Comparison of Blistering Grade from Baseline Until Day 14***

	Baseline (n=30)	Day 7 (n=30)	Day 14 (n=30)
Swelling			
3 – Severe	0	0	0
2 – Moderate	0	0	0
1 – Mild	1 (3.3%)	0	0
0 - None	29 (96.7%)	30 (100%)	30 (100%)
Mean ± SD (Median)	1.03 ± 0.18 (1)	1 ± 0 (1)	1 ± 0 (1)
*p value		0.36	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*
Friedman Test

Table 2.1 shows the comparison of blistering grade from baseline until day 14. The result showed that there was no significant difference noted as proven by the p value of 0.36. At baseline, only 1 (3.3%) had mild blistering was noted. None of the subjects had blister development at day 7 and 14.

Table 2.2 ***Comparison of Exudate from Baseline Until Day 14***

	Baseline (n=30)	Day 7 (n=30)	Day 14 (n=30)
Size of Lesion			
3 – Severe	17 (56.7%)	9 (30.1%)	4 (13.3%)
2 – Moderate	12 (40.0%)	7 (23.3%)	4 (13.3%)
1 – Mild	1 (3.3%)	13 (43.3%)	10 (33.3%)
0 – None	0	1 (3.3%)	12 (40.0%)
Mean ± SD (Median)	3.72 ± 0.68 (4)	2.96 ± 1.18 (3)	2.10 ± 1.26 (1)
***p value**		<0.0001	

** p-values >0.05- Not significant; p-values ≤ 0.05-Significant*

Table 2.2 shows the comparison of the exudate of lesion from baseline until day 14. The result showed that there was a significant difference noted as proven by the p value of <0.0001. The exudate significantly decreased until day 14.

Table 2.3 ***Comparison of Crust Grade from Baseline Until Day14***

	Baseline (n=30)	Day 7 (n=30)	Day 14 (n=30)
Crust			
3 – Severe	21 (70.0%)	2 (6.7%)	0
2 – Moderate	8 (26.7%)	8 (26.7%)	4 (13.3%)
1 – Mild	1 (3.3%)	16 (53.3%)	2 (6.7%)
0 – None	0	4 (13.3%)	24 (80.0%)
Mean ± SD (Median)	4.16 ± 0.95 (4.5)	2.26 ± 0.79 (2)	1.33 ± 0.71 (1)
***p value**		<0.0001	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*
Friedman Test

Table 2.3 shows the comparison of crust grade from baseline until day 14. The result showed that there was a significant difference noted as proven by the p value of <0.0001. The median crust grade significantly decreased until day 14.

Table 2.4 ***Comparison of Erythema Grade from Baseline Until Day14***

	Baseline (n=30)	Day 7 (n=30)	Day 14 (n=30)
Erythema			
3 – Severe	30 (100.0%)	7 (23.3%)	4 (13.4%)
2 – Moderate	0	15 (50.0%)	1 (3.3%)
1 – Mild	0	8 (26.7%)	13 (43.3%)
0 – None	0	0	12 (40.0%)
Mean ± SD (Median)	4.60 ± 0.50 (5)	3.06 ± 0.90 (3)	96. 1.16 (2)
***p value**		<0.0001	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*
Friedman Test

Table 2.4 shows the comparison of erythema grade from baseline until day 14. The result showed that there was a significant difference noted as proven by the p value of <0.0001. The median erythema significantly decreased until day 14.

Table 2.5 ***Comparison of Pain/Itch Grade from Baseline Until Day14***

	Baseline (n=30)	Day 7 (n=30)	Day 14 (n=30)
Number of Lesion			
3 – Severe	0	0	0
2 – Moderate	4 (13.3%)	1 (3.3%)	0
1 – Mild	26 (86.7%)	24 (80.0%)	11 (36.7%)
0 – None	0	5 (16.7%)	19 (63.3%)
Mean ± SD (Median)	2.13 ± 0.34 (2)	1.86 ± 0.43 (2)	1.36 ± 0.49 (1)
***p value**		<0.0001	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*

Table 2.5 shows the comparison of the pain/itch from baseline until day 14. The result showed that there was a significant difference noted as proven by the p value of <0.0001. The pain/itch significantly decreased until day 14.

Table 2.6 ***Comparison of TOTAL Score from Baseline Until 14***

	Baseline (n=30)	Day 7 (n=30)	Day 14 (n=30)
Total Score			
Mean ± SD	10.67 ± 2.04	7.17 ± 2.78	0.77 ± 3.34
(Min - Max)	11 – 13	7 – 9	0 – 3
***p value**		<0.0001	

** p-values >0.05- Not significant; p-values ≤0.05-Significant*
Repeated Measures ANOVA

Table 2.6 shows the comparison of the total score from baseline until day 14. The result showed that there was a significant difference noted as proven by the p value of <0.0001. The mean total score significantly decreased until day 14.

Table 2.7 ***Comparison of Erythema Grade from Baseline Until Day14***

	Blistering	*Exudate*	*Erythema*	*Crust*	*Pain/Itch*
Baseline vs Day 7	0.32	<0.0001	<0.0001	<0.0001	<0.01
Baseline vs Day 14	0.32	<0.0001	<0.0001	<0.0001	<0.0001
Day 7 vs Day 14	1.00	<0.0001	<0.0001	<0.0001	<0.0001

** p-values >0.05- Not significant; p-values ≤0.05-Significant*
Wilcoxon Signed Rank Test

Table 2.7 shows the pairwise comparison of erythema grade, crust grade, swelling grade, size of lesion and number of lesion from baseline until day 14. Supporting the results in tables 2.1 to 2.5, there were significant decreases noted at day 7 when compared to baseline (p<0.0001) and even until day 14 (p<0.0001) except for blistering (p>0.05).

Table 3 shows the distribution of subjects according side effects. There were 8 (26.7%) with erythema and 6 (20.0%) with pruritus, none had burning sense

Table 3 ***Distribution of Subjects According to Side Effects***

	Frequency (n=30)	Percentage
Erythema	8	26.7
Pruritus	6	20.0
Burning Sensation	0	0

Table 4 shows the distribution of subjects according to the growth assessed from the samples taken from their lesions at baseline. There were 10 (33.33%) with growth of *Staphylococcus epidermidis*, 8 (26.67%) with *Staphylococcus aureus* and 12 (40%) of lesions sampled had *Streptococccus pyogenes*.

Table 4 ***Distribution of Subjects According to Bacteria Isolated***

	Frequency (n=30)	Percentage
Staphylococcus epidermidis	10	33.33
Staphyloccocus aureus	8	26.67
Streptococcus pyogenes	12	40

Table 2.1 showed a non-significant difference in the blistering of the lesions from baseline to day 14. The reason for that being the sample population gave priority in choosing non-bullous impetigo and that 1 patient was included with an isolated mild blistering grade because the patient had other lesions counted for the study. The average of the total scores obtained by the study patients using the SIRS showed significant reduction from baseline to day 7 and day 14.

During the course of the treatment, some of the patients complained of erythema and pruritus however all of the said symptoms eventually subsided after completion of the 14-day period.

CONCLUSION

This pilot study has showed that an ointment-based 5% extract of Abelmoschus esculentes (Okra) is effective in the treatment of Non-bullous impetigo. All parameters showed significant improvement even only after 7 days. Mild side- effects noted like erythema and pruritus were observed in some of the patients however, these symptoms dissipated upon completion of the 14-day treatment.

RECOMMENDATION

The author recommends that a more accurate microbiologic documentation be done before, during and after the treatment period to specifically identify the organisms in the patient's lesions. The appearance of new lesions was not monitored after the 14-day treatment. Follow up after 1 month of treatment may be employed for this reassessment. A clinical trial with a bigger sample size should be done to further test its efficacy in a wider range of superficial skin infections. A comparison with a positive control and I or a placebo should be done to further solidify its effectivity.

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APPENDIX

Figure 1. Philippine Lady Finger (Native Variety)

Sign/ symptom	Score	Definition
Blistering	0=Absent	No evidence of blisters
	1=Mild	Few raised vesicles present on close evaluation
	2=Moderate	Fluid filled vesicles are obvious and are bothersome to the patient
	3=Severe	Extensive area covered with many vesicles which may include large bullous vesicles
Exudate/pus	0=Absent	No evidence of exudate or pus
	1=Mild	Small amounts of fluid/pus coming from the lesions
	2=Moderate	Exudate/pus infected area is moderate
	3=Severe	Extensive areas infected and there is draining exudate
Crusting	0=Absent	No evidence of crusting
	1=Mild	A few areas have some evidence of crusting lesions
	2=Moderate	Crusting is present throughout the infected area
	3=Severe	Thick crusting appears over the entire impetiginous area
Erythema/ inflammation	0=Absent	Skin tone and color are normal; no signs of erythema or inflammation
	1=Mild	Skin is pink with minimal signs of inflammation
	2=Moderate	Skin is red with definite signs of inflammation
	3=Severe	Skin is red and severe inflammation is present
Itching/pain	0=Absent	No signs of itching or indication of pain
	1=Mild	Some evidence of scratching or rubbing the area is evident and patient reports minor discomfort
	2=Moderate	Evidence of scratching and patient reports bothersome, painful lesions
	3=Severe	Evidence of extensive scratching and patient reports pain that interferes with daily activities or sleep.

Figure 3. Patient 1

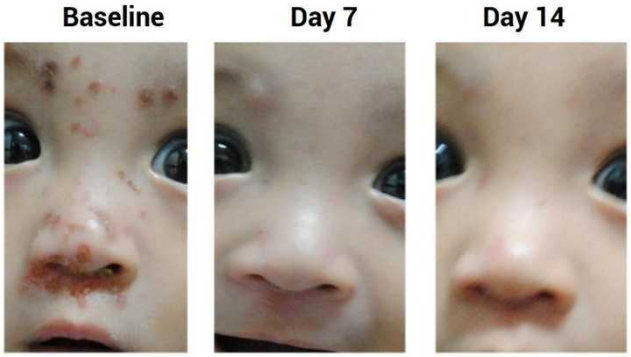

Figure 4. Patient 2

Figure 5. Patient 3

Figure 6. Patient 4