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Welcome to the first issue of The PCMC Journal for 2023!

This issue reflects our gradual recovery from the emergency phase of the COVID-19 pandemic, as it has articles on the pandemic and its aftermath, with a focus on resilience of healthcare workers, surely a part of our clinical practice that's here to stay.

We also have articles that are potentially high impact as they address the top causes of morbidity, with a pediatric malnutrition screening tool and a study on prescribing patterns for pediatric community-acquired pneumonia.

Finally, we have articles that highlight our strength as a tertiary referral center, with a meta-analysis on the use of lidocaine for emergence agitation in children under sevoflurane anesthesia, and our center experience on children and adolescents with intrathoracic masses.

All in all, an apt snapshot of our work as the premier pediatric hospital in the country. See you next issue!

The *Philippine Children's Medical Center Journal (PCMC Journal)* is a peer-reviewed journal that is published bi-annually and publishes original scientific papers in basic and clinical pediatrics. It uses a single-blind peer review process, with papers from identified authors being reviewed by unidentified reviewers. The articles it accepts for publication may be in the form of collective and current reviews, original papers, case reports, lectures, essays, editorials, abstracts, or letters to the editor. All authors, reviewers, and members of the editorial board are required to submit a declaration of Conflict of Interest (COI) form of their financial and non-financial relationships and activities in relation to the journal.

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ARTICLE

Determination of the ideal timing of delivery among growth- restricted fetuses at less than 32 weeks age of gestation using a stage-based doppler protocol for admitted patients at the Philippine Children's Medical Center

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OBJECTIVES: Early onset fetal growth restriction substantially contributes to neonatal morbidities and mortalities. The main dilemma lies on the timing of delivery, especially for pre- and peri-viable fetuses, due to the challenge in creating an ideal balance of minimized in-utero hypoxia-induced fetal injury or death versus the risks of iatrogenic preterm delivery. We wished to determine the ideal timing of delivery among growth-restricted fetuses <32 weeks gestation using a stage-based doppler protocol.

MATERIALS AND METHODS: A retrospective-cohort study of 67 singleton-pregnant women with growth restriction at <32 weeks gestation and hospitalized from January 2010 to September 2021 was conducted. Medical records were reviewed, and the outcomes were extracted. The primary outcomes were arterial pH at birth and mortality, while secondary outcomes included neonatal morbidities.

RESULTS: Fetal growth restriction progressed by an average of 3 stages (41.79%) within a 2- to 3.5-week period. More than half had arterial pH <7.20, which was lowest at Stage II FGR (50.00%). The prevalence of neonatal
mortality was 16.42% and was lowest at Stage I (8.70%) and Stage II FGR (18.75%).

CONCLUSION: Doppler studies may be conducted weekly for Stage I, biweekly for Stage II, every 1-2 days for Stage III and every 12 hours for Stage IV. Delivery is ideal at **Stage II** as this resulted in the least number of acidosis and neonatal mortalities.

KEYWORDS: *Early Onset Fetal Growth Restriction; Doppler Staging; Ideal Timing of Delivery; Uteroplacental
Insufficiency*

INTRODUCTION

Fetal Growth Restriction (FGR), considered by the American College of Obstetricians and Gynecologists as the "most common and complex problem in modern obstetrics", is defined as the pathologic inhibition of intrauterine fetal growth and the failure of the fetus to achieve its growth potential. [1)] World over, fetal growth restriction (FGR) is observed in about 24% of newborns and approximately 30 million infants suffer from fetal growth restriction every year.

[(2)] To this date, it has proven to be a public health concern, especially in under-resourced countries such as the Philippines, where FGR has a general incidence of 8.77% as of 2019. [(3)] The Perinatology section of Philippine Children's Medical Center has a total of 130 fetal growth-restricted deliveries, accounting for 2.3% of the 4,557 deliveries from 2010 to 2021, with hypertension as its leading cause (72%). [(4)] Much dilemma is seen on the timing of delivery, as concerns of delivering an extremely premature baby versus subjecting these fetuses to further hypoxia in utero remains to be a daily

challenge for the obstetrician. International recommendations on the timing of delivery are available, but local recommendations are still lacking. An extensive search has shown that to date, this is the first local retrospective study that showed the use of this stage-based doppler protocol for early onset growth restricted fetuses and created an evidence-based recommendation on the most ideal doppler stage of delivery to optimize neonatal outcomes and prevent neonatal mortalities.

Early adaptation in fetal hypoxia includes preferential shunting and distribution of blood flow to the fetal brain, heart, and adrenal glands at the expense of the splanchnic and peripheral circulation referred to as "brain sparing". This is associated with increased fetoplacental vascular resistance leading to a progressive decrease in the diastolic flow, apparent when 30% of the placenta is affected and progresses to absent (AEDF) or reversed end- diastolic flow (REDF) in the umbilical artery when the damage extends to 60-70% [(5)] With more marked placental disease, decreasing middle cerebral artery impedance follows. Over time, brain autoregulation may become abnormal. The cerebroplacental ratio (CPR) becomes less than 1, and eventually, normalization of the CPR occurs when cerebral edema is present. [(6)] Subsequent venous shunting across the ductus venosus (DV) occurs, suggestive of central cardiac failure, reflected as a decrease, absence, and ultimate reversal of blood flow in the atrial systolic component of the DV waveform. [(6)] Umbilical venous pulsations are seen with tricuspid insufficiency resulting from severe cardiac dilatation. With ineffective downstream delivery of the cardiac output, breathing, movement and tone may be lost. Variable decelerations are likely when there is oligohydramnios while late decelerations are due to a drop in oxygen tension or due to depressed cardiac contractility. [(6)] Spontaneous late deceleration is a preterminal event and an ominous sign. If the fetus remains undelivered, stillbirth is likely. This presumed sequence and the anticipation of fetal deterioration form the basis for Doppler surveillance in fetal growth restriction. [(6)] Fetuses subjected to chronic hypoxia in utero are at an increased risk of pulmonary hypertension, necrotizing enterocolitis, polycythemia, and an increased likelihood of developing infections in the neonatal life. Mortality rate is at 5-18% with absent or reversed umbilical artery end diastolic flow, with the rates doubling once ductus venous abnormalities are seen. [(7)]

Gratacos et al in 2014 proposed a stage - based doppler classification, monitoring and delivery. This is the current international guideline, which is based on a different setup and different neonatal intensive care unit setting, differing largely from the current local setting.

The general objective of this study was to determine the ideal timing of delivery among growth -restricted fetuses at less than 32 weeks age of gestation using a stage-based doppler protocol among admitted patients at the Philippine Children's Medical Center. Specifically, this study aimed to 1) identify the distribution of the four stages of growth-restricted fetuses at less than 32 weeks using a stage-based doppler protocol, 2) determine the following neonatal outcomes seen in each stage: primary outcomes of arterial pH at birth and neonatal mortalities, and secondary outcomes of birth weight, APGAR score, length of stay in the neonatal intensive care unit, surfactant use, respiratory compromise (need for ventilatory support), and neonatal

complications (necrotizing enterocolitis, infections, polycythemia, persistent pulmonary hypertension and renal tubular injury and 3) determine the doppler stage during the time of delivery which resulted to the least number of neonatal morbidities and mortalities centering on the primary outcomes of arterial pH at birth and birth and neonatal mortalities.

Early Onset Fetal Growth Restriction (FGR) refers to a fetus with an estimated fetal weight less than the 10th percentile seen on an ultrasound scan at less than 32 weeks age of gestation that, because of a pathologic process, has failed to reach the potential growth. The most common cause is **Uteroplacental Vascular Insufficiency**, defined as abnormalities of the placental formation or blood supply, leading to fetal hypoxia. Doppler ultrasound investigates the fetal hemodynamic state. The vessels used include the **Uterine Artery** (UtA), the main vessels supplying blood to the uterus; **Umbilical Artery** (UA), which carries deoxygenated blood from the fetal circulation to the placenta, the **Middle Cerebral Artery** (MCA), which supplies the majority of the lateral surface of the hemisphere, the **Ductus Venosus** (DV) , which carries oxygenated blood from the umbilical vein to the inferior vena cava and, ultimately, the left heart for systemic circulation and the **Umbilical Vein** (UV) , which carries oxygenated, nutrient-rich blood from the placenta to the fetus. Measurement of the vascular resistance in the vessels evaluates the quality of placental blood flow exchange which is assessed by the **Resistance index (RI),** calculated by getting the difference of the systolic and diastolic velocity divided by the systolic velocity and the **Pulsatility index (PI),** calculated by getting the difference of the systolic and diastolic velocity divided by the mean velocity.

Materials and Methodology

This is a retrospective cohort study of women with growth-restricted fetuses at less than 32 weeks age of gestation which is a single center, institutional study within an eleven-year period at the Section of Perinatology of Philippine Children's Medical Center from January 1, 2010, to September 30, 2021.

Conceptual Framework

Early onset Fetal Growth Restriction Stage -based doppler protocol	
Stage I	EFW <3rd percentile CPR <p5 UA PI >p95 MCA PI <p5 UtA PI >p95
Stage II	UA AEDV
Stage III	UA REDV DV PI >p95
Stage IV	DV reversed a flow FHR decelerations

→

Primary outcomes:	1)Arterial pH at birth (pH <7.2) 2)Neonatal mortalities
Secondary outcomes:	Birth weight, APGAR score, length of stay in the neonatal intensive care unit, surfactant use, respiratory compromise, and neonatal complications (necrotizing enterocolitis, infections, polycythemia, persistent pulmonary hypertension and renal tubular injury

Figure 1. *Conceptual Framework of the study.*
The stages of fetal growth restriction based on the stage-based doppler protocol are the independent variable while the primary and secondary neonatal outcomes derived from the doppler stage at birth are the research's dependent variables. Through the empirical evidence and statistical analysis presented in this study, a direct relationship between these variables is established.

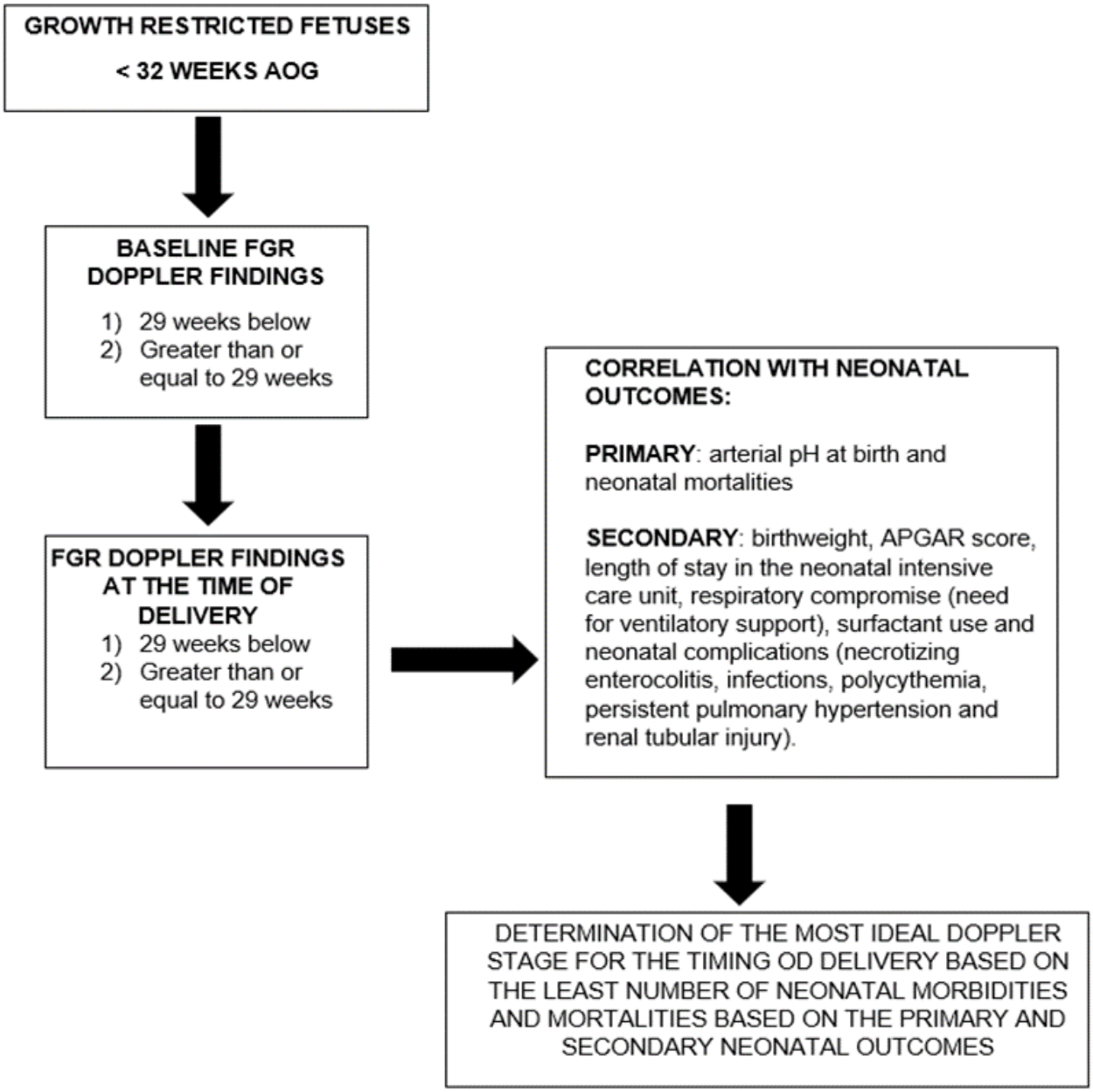

Figure 2. *Stage – based doppler classification at the time of diagnosis and at the time of delivery correlated with neonatal outcomes*

The inclusion criteria included singleton pregnancies with growth-restricted fetuses at less than 32 weeks of gestation with an estimated fetal weight below their respective 10th percentile, with abnormal Doppler findings, irrespective of parity and socioeconomic status.

Fetuses with structural malformations, aneuploidy, evidence of genetic syndromes or congenital viral infection, prelabor and premature ruptured membranes, multiple pregnancies, pregnancies terminated secondary to other factors not solely related to FGR (such as abruptio placenta, etc.) and pregnancies with incomplete data were excluded.

The subjects were divided into two subgroups:

a. Less than 29 weeks age of gestation
b. More than or equal to 29 weeks age of gestation

Each subject was classified into two stages:

1) Doppler stage during the diagnosis of fetal growth restriction and
2) Doppler stage during the time of delivery

The subjects may move from one stage of fetal growth restriction to another, but these subjects were counted in both stages of classification. Hence, all the subjects were counted in every stage that they were in and all the subjects were accounted for at the end of the study. When the data collected presented with a skewed distribution, (more subjects on the group of fetuses with growth restriction at more than 29 weeks compared to those at less than 29 weeks), a dichotomous categorization was utilized to ensure statistical significance.

A sample size of at least 66 confirmed patients with valid and complete patient information that were diagnosed with Fetal Growth Restriction among admitted patients from January 1, 2010 – September 30, 2021, was needed to meet the 95% confidence level set by the study. [9] This has a statistically sufficient power to represent the total cases seen in the PCMC Section of Perinatology. The computation was referenced from the 2019 Philippine Statistics Authority (PSA) Registered Live Births in the Philippines Report [3] which equates that the hypothesized percentage (%) frequency of outcome factor is 12.5% (+/- 5%). It has also been calculated using the crude birth rate (CBR) of 15.6 or 16 births per thousand population and has found similar results. The sample size was calculated using a level of significance equal to 5%, and the desired width of confidence absolute limit equal to 7.5%. Adjusted sample size through design effect was adjusted to represent 80% of the total calculated population at a 95% confidence interval. The sample size calculation process for the current study utilized a non-probability sampling which is commonly used to represent the whole population regardless of outcome biases.

All cases were retrospectively identified from the Philippine Children's Medical Center Perinatology Section database between January 1, 2010, to September 30, 2021. The stage-based classification included the following:

1) Severe smallness or mild placental insufficiency (Estimated Fetal Weight <3rd centile, CPR <p5, UA PI>p95, MCA PI <p5, UtA PI >p95)
2) Severe placental insufficiency (UA AEDF)
3) Low- suspicion fetal acidosis (UA REDF, DV PI > p95)
4) High-suspicion fetal acidosis (DV reversed a flow, FHR decelerations)

Maternal demographics, fetal and neonatal data were obtained from the computerized medical records and fellows' endorsement sheets which were supplemented by individual chart reviews and ultrasound results. The demographic data on maternal age, parity, history of smoking and substance abuse, associated comorbidities, indication, and mode of delivery were collected. The outcomes of fetal growth restriction were analyzed based on data obtained from the neonatal intensive-care unit (NICU)

and pediatric ward census of the Section of Neonatology of Philippine Children's Medical Center. The number of admissions to the neonatal unit was determined.

The primary neonatal outcomes were the arterial pH at birth which was categorized into two: pH ≤7.20 and pH >7.20 as well as neonatal mortalities. The secondary outcomes of the study included birthweight, APGAR score, length of stay in the neonatal intensive care unit, respiratory compromise (need for ventilatory support), surfactant use and neonatal complications (necrotizing enterocolitis, infections, polycythemia, persistent pulmonary hypertension, and renal tubular injury).

The most ideal Doppler stage for the determination of the timing of delivery for fetuses below 32 weeks age of gestation was determined. This was based on the doppler stage during the time of delivery which resulted to the least number of neonatal morbidities and mortalities based on the primary and secondary neonatal outcomes.

Statistical analyses were performed using STATA MP Statistical Software, Version 13, College Station, TX: StataCorp LP. A *p*-value ≤0.05 was considered statistically significant. Descriptive statistics were utilized to summarize the study variables and included mean and standard deviation for continuous-level variables; median and interquartile range for ordinal and non-normal, continuous variables; and frequency and percentage for nominal data. Comparative analyses of the demographic and clinical profiles, doppler study findings, indications of caesarean delivery, and the primary and secondary outcomes according to the stages of fetal growth restriction were conducted using Chi-Square Test or Fisher's Exact Test, if the expected frequencies were less than 5.00, for categorical outcomes; Kruskall-Wallis H test for ordinal or non-normally-distributed outcomes; and, Analysis of Variance (ANOVA) for continuous-level, normally-distributed outcomes were employed.

The patients included in this study need not consent as the data were collected from their records. Subject information was kept in a secure database and personal data such as names were coded. The research records and outcomes were stored electronically only. Storage of at least five (5) years is under the purview of the department for the purposes of research and validation purposes, in a manner that is compliant with the data protection policies of the hospital. Risk for data such as data breach, unauthorized access of information and alteration were safeguarded at all costs.

RESULTS

A total of sixty-seven (67) subjects with complete data in the medical records were extracted and included in the study. Of these 67 cases, 21 subjects (31.34%) were between 26 to 29 weeks AOG while 46 cases (68.66%) were 30 to 32 weeks gestation.

Table 1 illustrates the maternal demographic and clinical characteristics of the participants according to fetal growth restriction staging. Results showed that the mean age of the respondents was 34.10 years old (SD=4.76). In addition, most of the participants had a gravidity of 2.00 (IQR= 1 – 3), a parity of 1.00 (IQR=0 – 1), and a parity interval of 5.00 (IQR=3 – 9). It can also be noted that 17.91% of the participants had a history of growth restriction, 28.36% are alcohol drinkers, 38.81% were smokers, and none had used illicit drugs. Results showed that

86.57%), Chronic Hypertensive Vascular Disease (43.28%), and Gestational Diabetes Mellitus (14.93%). Comparative analyses of the demographic and clinical characteristics according to fetal growth restriction staging indicated that these characteristics were not statistically different (p>0.05), except for the proportion of patients with Anti-Phospholipid Syndrome (APS) which was significantly higher

Table 1.
MATERNAL DEMOGRAPHIC AND CLINICAL PROFILES OF THE RESPONDENTS ACCORDING TO STAGE OF FETAL GROWTH RE-

Demographic and Clinical Characteristics	Stage of Fetal Growth Restriction at Diagnosis (N = 67)					Test Statistic[2]	*p*-value (Two-Tailed)
	Stage I (n=46)	Stage II (n=16)	Stage IIII (n=2)	Stage IV (n=3)	Total (N=67)		
Maternal Age ($\bar{x}$, SD)	33.89 (4.46)	33.75 (5.92)	36.00 (4.24)	38.00 (1.00)	34.10 (4.76)	0.83	0.483
Obstetric History (Md, IQR)							
Gravida	2.00 (1 – 3)	2.00 (1 – 3)	3.00 (2 – 4)	4.00 (3 – 6)	2.00 (1 – 3)	6.50	0.090
Parity	1.00 (0 – 2)	0.00 (0 – 1)	1.00 (0 – 1)	1.00 (0 – 1)	1.00 (0 – 1)	1.52	0.678
Term	0.00 (0 – 1)	0.00 (0 – 1)	0.00 (0 – 0)	1.00 (0 – 4)	0.00 (0 – 1)	2.82	0.420
Preterm	0.00 (0 – 1)	0.00 (0 – 0)	1.00 (0 – 1)	0.00 (0 – 0)	0.00 (0 – 1)	2.55	0.467
Abortion	0.00 (0 – 0)	0.00 (0 – 1)	2.00 (0 – 3)	2.00 (1 – 2)	0.00 (0 – 0)	1.45	0.658
Living	0.00 (0 – 1)	0.00 (0 – 1)	0.00 (0 – 0)	1.00 (0 – 4)	0.00 (0 – 1)	3.46	0.326
Parity Interval (Md, IQR; n=45)	6.00 (4 – 9)	4.00 (2 – 10)	3.00 (2 – 4)	4.00 (1 – 13)	5.00 (3 – 9)	2.30	0.513
History of Fetal Growth Restriction (*f*, %)	11 (23.91%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	12 (17.91%)	5.54	0.103
Alcohol Intake (*f*, %)	12 (26.09%)	7 (43.75%)	0 (0.00%)	0 (0.00%)	19 (28.36%)	1.60	0.759
Smoker (*f*, %)	17 (36.96%)	8 (47.06%)	1 (50.00%)	1 (33.33%)	26 (38.81%)	0.37	0.950
History of Substance Abuse (*f*, %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	–
Comorbidities (*f*, %)							
Hypertensive Disorder of Pregnancy	43 (93.48%)	15 (93.75%)	2 (100.00%)	3 (100.00%)	63 (94.03%)	0.34	1.000
Endocrine Disorders	10 (21.74%)	4 (25.00%)	0 (0.00%)	1 (33.33%)	15 (22.39%)	0.86	0.865
Cardiac Disorders	5 (10.87%)	1 (6.25%)	0 (0.00%)	1 (33.33%)	7 (10.45%)	2.22	0.533
Pulmonary Disorders	2 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)	0.94	1.000
Renal Disorders	3 (6.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.48%)	1.43	0.654
Nutritional Disorders	2 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)	0.94	1.000
Reproductive Immune Failure	0 (0.00%)	1 (6.25%)	0 (0.00%)	0 (0.00%)	1 (1.49%)	3.24	0.313
Antiphospholipid Syndrome	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (33.33%)	2 (2.99%)	11.61[&]	0.041

[a] Comparative analyses were conducted using Chi-Square Test, for nominal data; Kruskall-Wallis Test, for ordinal data; or, Analysis of Variance (ANOVA), for continuous data.
[*] Significant at 0.05
[†] Significant at 0.01

The doppler staging of FGR at diagnosis and at delivery is presented in Table 2. It can be noted that at diagnosis, most participants had stage I FGR (68.86%), while majority had stage IV FGR (62.69%) at delivery, indicating that most deliveries waited for doppler progression until the last stage prior to delivery. Results also showed that majority of the FGR had progressed (67.16%), with most progressing by 3 stages (41.79%), and only 16.42% and 8.96% progressing by 2 and 1 stages, respectively. Analysis also showed that the interval of FGR stage progression was 3.41 weeks (SD=1.97) for those with 1 stage progression, 2.71 weeks (SD=1.97) for 2 stage progression, and 2.81 weeks (SD=1.64) for 3 stage progression.

Table 2.
DESCRIPTIVE STATISTICS FOR THE DOPPLER STAGING OF FETAL GROWTH RESTRICTION AT DIAGNOSIS AND AT DELIVERY AMONG THE RESPONDENTS

Characteristics	Frequency (*f*)	Percentage (%)	Mean (SD)
Fetal Growth Restriction Stages at Diagnosis (*f*, %)			
Stage I	46	68.66%	
Stage II	16	23.88%	
Stage III	2	2.99%	
Stage IV	3	4.48%	
Fetal Growth Restriction Stages at Birth (*f*, %)			
Stage I	13	19.40%	
Stage II	10	14.93%	
Stage III	2	2.99%	
Stage IV	42	62.69%	
Progression of Fetal Growth Restriction Staging from Diagnosis to Birth (*f*, %)	45	67.16%	
Number of Stages Progressed in FGR from Diagnosis to Birth (*f*, %)			
1 Stage	6	8.96%	
2 Stages	11	16.42%	
3 Stages	28	41.79%	
Fetal Growth Restriction Stage Progression from Diagnosis to Birth (*f*, %)			
Stage I to Stage II	4	5.97%	
Stage I to Stage III	1	1.49%	
Stage I to Stage IV	28	41.79%	
Stage II to Stage III	1	1.49%	
Stage II to Stage IV	10	14.93	
Stage III to Stage IV	1	1.49%	
Interval of FGR Stage Progression (Weeks; $\bar{x}$, SD)			
1 Stage			3.41 (1.97)
2 Stages			2.71 (1.97)
3 Stages			2.81 (1.64)

Table 3 illustrates the comparative analyses of primary and secondary outcomes according to FGR stages at diagnosis. Results showed that the mean arterial pH at birth was 7.19 (SD=0.12), with most participants having a pH ≤7.20. (53.73%). The mean birthweight was 909.73 grams (SD=286.04), and most participants had extremely low birthweight (59.70%). It can also be noted that the APGAR scores at first (59.70%) and fifth minutes (80.60%) were both within 7 to 9.

Results also indicated that the length of NICU stay was 36.16 days (SD=54.68), and 85.07% had respiratory compromise with 49.25% requiring surfactant use. It can also be noted that the most common neonatal complications were sepsis (79.10%), respiratory distress syndrome (46.27%), pneumonia (35.82%), and necrotizing enterocolitis (20.90%). The prevalence of mortality was 16.42%, with a mean duration of survival of 3.30 days (SD=14.39). Comparative analyses according to FGR stages indicated that arterial pH, length of NICU stay, respiratory compromise, surfactant use, and neonatal complications were not statistically different (p>0.05). Nevertheless, birthweight was significantly different (F=10.96, p=0.001), wherein the mean birthweight was significantly higher among FGR stage I, and further decreases in weight towards the later stages. The birthweight was noted to be significantly highest among stage I FGR ($\bar{x}$=1,116.92, SD=275.21, p=0.025) compared with FGR stage IV ($\bar{x}$=859.93, SD=289.66). The proportion of extremely low birthweight was significantly higher among those with FGR stage III and IV (X^2=12.26, p=0.008).

The prevalence of mortality was also significantly higher (X^2=13.24, p=0.007) among FGR stages III (100.00%) and stage IV (66.67%). Likewise, the proportion of neonates with APGAR scores of 7 to 9 at the first and fifth minutes of life were significantly higher among those with FGR stages I and stage II (p<0.01) than those with stages III and stage IV.

Table 3.
COMPARATIVE ANALYSES OF THE PRIMARY (NEONATAL ARTERIAL PH AT BIRTH) AND SECONDARY OUTCOMES ACCORDING TO STAGE OF FETAL GROWTH RESTRICTION AT DIAGNOSIS

Primary and Secondary Outcomes	Stage of Fetal Growth Restriction at Birth (N = 67)					Test Statistic[2]	*p*-value (Two-Tailed)
	Stage I (n=46)	Stage II (n=17)	Stage IIII (n=1)	Stage IV (n=3)	Total (N=67)		
Arterial pH at Birth ($\bar{x}$, SD)	7.21 (0.13)	7.19 (0.07)	7.23 (0.00)	7.05 (0.05)	7.19 (0.12)	1.65	0.186
pH ≤7.20	24 (52.17%)	9 (52.94%)	0 (0.00%)	3 (100.00%)	36 (53.73%)	3.79	0.359
pH >7.20	22 (47.83%)	8 (47.06%)	1 (100.00%)	0 (0.00%)	31 (46.27%)		
Birthweight (Grams; $\bar{x}$, SD)	1,010.04 (255.76)	748.24 (190.83)	675.00 (0.00)	365.00 (105.00)	909.73 (286.07)	10.96†	0.001
Extremely Low (<1,000 Grams)	21 (45.65%)	15 (88.24%)	1 (100.00%)	3 (100.00%)	40 (59.70%)	12.26†	0.008
Very Low (1,001 to 1,499 Grams)	24 (52.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	26 (38.81%)		
Low (1,500 to 2,499 Grams)	1 (2.17%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	1 (1.49%)		

APGAR Score (*f*, %)							
First Minute						25.46†	0.001
0 to 3	2 (4.35%)	3 (17.65%)	1 (100.00%)	2 (66.67%)	8 (11.94%)		
4 to 6	10 (21.74%)	8 (47.06%)	0 (0.00%)	1 (33.33%)	19 (28.36%)		
7 to 9	34 (73.91%)	6 (35.29%)	0 (0.00%)	0 (0.00%)	40 (59.70%)		
Fifth Minute						20.56†	0.003
0 to 3	1 (2.17%)	1 (5.88%)	0 (0.00%)	1 (33.33%)	3 (4.48%)		
4 to 6	5 (10.87%)	2 (11.76%)	1 (100.00%)	2 (66.67%)	10 (14.93%)		
7 to 9	40 (86.96%)	14 (82.35%)	0 (0.00%)	0 (0.00%)	54 (80.60%)		
Length of NICU Stay (Days; $\bar{x}$, SD)	27.67 (22.77)	65.41 (97.82)	2 (0.00)	12.00 (8.00)	36.16 (54.68)	6.64	0.070
Respiratory Compromise (*f*, %)	38 (82.61%)	15 (88.24%)	1 (100.00%)	3 (100.00%)	57 (85.07%)	1.06	0.853
Surfactant Use (*f*, %)	20 (43.48%)	10 (58.82%)	1 (100.00%)	2 (66.67%)	33 (49.25%)	2.63	0.460
Neonatal Complications (*f*, %)							
Necrotizing Enterocolitis	10 (21.74%)	4 (23.53%)	0 (0.00%)	0 (0.00%)	14 (20.90%)	1.15	1.000
Sepsis	37 (80.43%)	12 (70.59%)	1 (100.00%)	3 (100.00%)	53 (79.10%)	1.85	0.643
Respiratory Distress Syndrome	18 (39.13%)	11 (64.71%)	0 (0.00	2 (66.67%)	31 (46.27%)	4.63	0.159
Pneumonia	15 (32.61%)	7 (41.18%)	0 (0.00%)	2 (66.67%)	24 (35.82%)	2.22	0.568
Pulmonary Hypertension	1 (2.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)	0.46	1.000
Acute Kidney Injury	1 (2.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)	0.46	1.000
Neonatal Mortality (*f*, %)	4 (8.70%)	4 (23.53%)	1 (100.00%)	2 (66.67%)	11 (16.42%)	13.24†	0.007
Duration of Survival (Days; $\bar{x}$, SD)	2.02 (12.38)	6.47 (20.03)	2.00 (0.00)	5.33 (6.11)	3.30 (14.39)	0.41	0.748

[a] Comparative analyses were conducted using Chi-Square Test, for nominal data; Kruskall-Wallis Test, for ordinal data; or, Analysis of Variance (ANOVA), for continuous data.
*Significant at 0.05
†Significant at 0.01

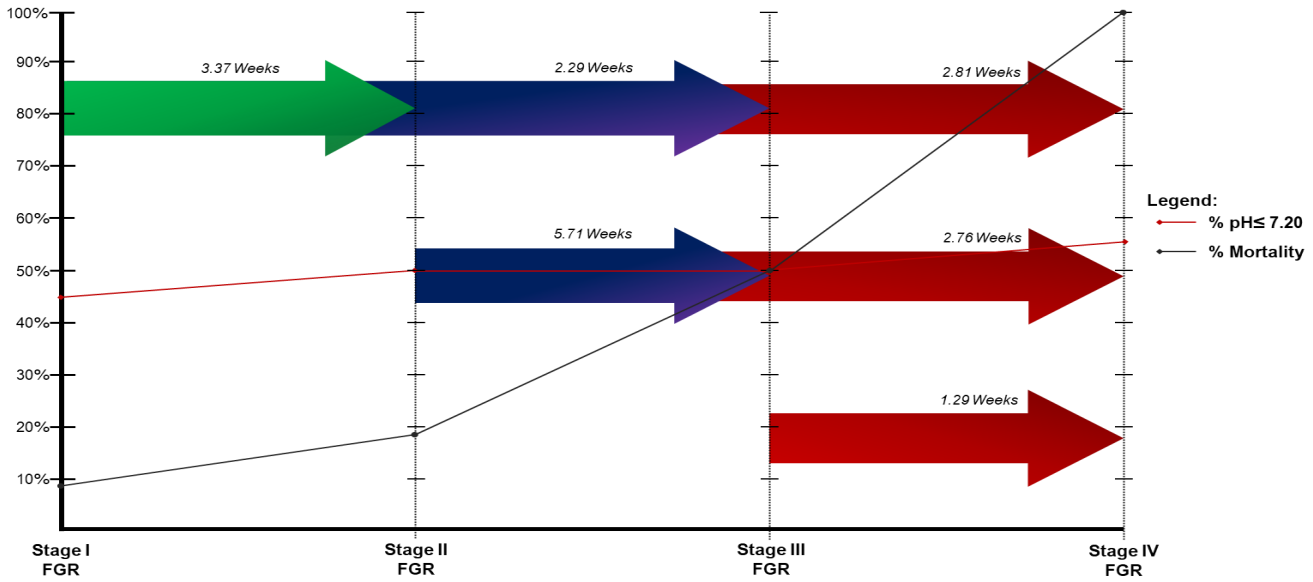

Figure 3. Fetal Growth Restriction Stage Progression and Proportion of Neonatal Complications and Mortality

Figure 3 illustrates the FGR progression and proportion of neonatal complications (pH ≤7.20) and mortality among the subjects. This shows that the FGR stage progression from Stage I to Stage II was at 3.37 weeks, Stage I to Stage III at 2.29 weeks, and from Stage I to Stage IV at 2.81 weeks. In contrast, the FGR progression from Stage II to Stage III was at 5.71 weeks, and it took 2.76 weeks for Stage III to develop to Stage IV. It also took approximately 1.29 weeks for Stage III to progress to Stage IV.

The proportion of neonates with a pH ≤7.20 were 46.25% for Stage I, 50% for Stage II, 50% for Stage III, and 57.14% for Stage IV. The proportion of those affected by neonatal mortality were the following: Stage I (8.70%), Stage II (18.75%) Stage III (50%), and Stage IV (100.00%).

Analyses of the distribution of the different stages of fetal growth restriction according to the age of gestation categories indicated that among those who were at 26 to 29 weeks gestation (n=21), 28.57% were at Stage I FGR, 47.62% were at Stage II FGR, 9.52% were at Stage III FGR, and 14.29% were at Stage IV FGR. In contrast, only two FGR stages were noted among those in the 30 to 32 weeks gestation group, with 86.96% of the (n=46) subjects at Stage I FGR and 13.04% of the cases at Stage II FGR. Although the study initially conceptualized to analyze the results according to age of gestation subgroups (26 to 29 weeks versus 30 to 32 weeks AOG) to provide a more clinically relevant recommendation on the ideal FGR stage to initiate fetal delivery, subgroup analyses were no longer pursued and conducted due to the lack of Stage III and Stage IV FGR cases among those in the 30 to 32 weeks AOG group, which did not permit robust statistical analyses to allow data-driven recommendations.

Discussion

The results of the study highlighted three pertinent results on the evolution of fetal growth restriction at less than 32 weeks gestation. First, fetal growth restriction progressed in most pregnancies by at least 3 stages, and the progression of growth restriction occurred within a 2- to 3.5-week period regardless of the age of gestation. Second, extremely low, and very low birthweights, low APGAR scores, and mortality were significantly higher among FGR stages III and IV at diagnosis. Third, the proportion of subjects with a pH ≤7.20 and neonatal mortality were low at Stage II FGR.

From a clinical practice perspective, these results may be utilized to draw the following recommendations. First, cognizant of the rate of progression of fetal growth restriction at less than 32 weeks age of gestation, more vigilant and frequent Doppler studies may be considered. For those with Stage I, weekly Doppler studies may be conducted, while biweekly doppler studies may be conducted for those with Stage II. In contrast, closer monitoring should be done for the later stages, Stage III FGR may be monitored every 1 to 2 days and Stage IV FGR every 12 hours.

Second, any aberrations from normal doppler study parameters should be carefully considered in timing the fetus' delivery alongside the age of gestation and estimated fetal weight. In the absence of extreme abnormalities in the umbilical artery, such as absent or reverse end-diastolic flow, and/or the ductus venosus, such as absent or reversed A-wave or any complicating maternal condition, pregnancy may be conservatively managed and prolonged until further indications of delivery arise, and at least an estimated birth weight of at least 500 grams is reached to enhance overall and intact survival to prevent neonatal complications. Studies have posited that every 1-day in-utero of fetuses increases neonatal survival by 2% and increasing estimated fetal weight reduces potential complications. [10]

The GRIT Study [11] posited that the uncertainty of clinicians to deliver a growth restricted fetus has affected the appropriateness of the timing of delivery. Thus, a recommendation based on the

current study results was generated based on the presented evidence to facilitate the appropriate timing of delivery of these growth restricted fetuses.

Taking all the primary and secondary neonatal outcomes of the study into account, neonates delivered at Stage I FGR presented with the least neonatal morbidities and mortalities, but pregnancy may still be prolonged beyond this stage since the fetus is still in the compensatory state. Extremely low birthweights, low APGAR scores, and mortality were significantly higher among FGR Stage IV fetuses, resulting to a 100% mortality rate. Statistically, therefore, delivery at Stage 4 is not recommended as this resulted in poor outcomes as seen in the current study. Looking into the primary neonatal outcomes of arterial pH and mortalities seen in Stage II versus Stage III, pH < 7.2 at birth (50% vs 50%) and mortalities (18.75% vs 50%), once delivery of fetuses is prolonged from Stage II to Stage III, there is a 63% increase in the risk of fetal death along with the increase in neonatal morbidities as presented in the secondary neonatal outcomes. Therefore, the recommended timing of delivery of fetuses who are less than 32 weeks AOG with growth restriction is at STAGE II (Umbilical Artery – Absent End Diastolic Flow).

Conclusions and recommendations

Early-onset fetal growth restriction is a significant factor of perinatal mortality and morbidity, and the determination of the ideal timing of delivery with the least number of acidosis and neonatal mortalities is crucial to maximize positive neonatal outcomes. From the study results of the 67 subjects, 46 subjects were classified as Stage I, 17 were classified as Stage II, 1 was classified as Stage III and 3 subjects were classified as stage IV. Close monitoring via doppler studies must be conducted weekly for Stage I, biweekly for Stage II, every 1-2 days for Stage III and every 12 hours for Stage IV to evaluate the fetal status and to decide on the appropriate time to deliver thae fetus cognizant of the different neonatal complications and potential mortalities which may develop. The recommended doppler stage for the delivery of fetuses at less than 32 weeks AOG with growth restriction is at STAGE II (Umbilical Artery – Absent End Diastolic Flow). This recommendation was derived from the proportions of neonatal complications and mortalities, which were low within this FGR stage. With this, hypertension, accounting for 72% of the cases of early onset fetal growth restriction, should be managed promptly and accordingly to prevent the complications inherent in early onset fetal growth restriction. Lastly, it is recommended that future studies should include a larger sample size or a multicenter study to arrive at more statistically powered and conclusive results.

This study has limitations focusing on the study methodology and sample size. In terms of the study design, the study was conducted via a retrospective review of medical records which may lead to certain limitations. First, the retrospective nature of the data collection does not ascertain the causality of the variables under study. Second, several factors may have affected the current results and led to under- or overestimation of the results, despite the researchers' efforts to control these covariates. Focusing on the sample size, the acquired samples was

only 67 which may be inadequate to estimate the outcomes sufficiently and accurately.

The current study cannot provide an evidence-based recommendation on the doppler stage for the delivery of fetuses ≥29 weeks gestation due to the low samples yielded for this specific AOG group. In addition, the current data did not show certain FGR stages among those between 30 to 32 weeks gestations thus, preventing further analyses. Hence, the study results must be interpreted with caution. The study was also conducted in a single institution thus, restricting the generalizability of the results.

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ARTICLE

Intrathoracic masses in children and adolescents: a single tertiary pediatric institution experience

May Priscilla Villarin Cero, Maria Cherry Añana, Beatriz P. Gepte

OBJECTIVES: The Cancer and Hematology Division of the PCMC receives an average of 24 cases of pediatric intrathoracic masses annually. Comprehensive data on the demographic status, clinical profile, management, and outcome are still not available. This study aims to determine the clinical features, diagnosis, management and outcome of children and adolescents with intrathoracic masses from 2017 to 2019.

MATERIALS AND METHODS: Descriptive study design was utilized. Data were collected by doing a chart review. Possible associations between the clinical features and outcome were described.

RESULTS: Sixty-eight (68) cases were referred from January 2017 to December 2019. Mean age at diagnosis is 8.8 years with a 2.4:1 male to female ratio. Severe wasting was seen in 21%. All subjects were symptomatic at presentation, 50% with respiratory compromise. Anterior mediastinal lesions are observed at 82% of cases. Elevated LDH was seen in 50% of the patients. Malignant hematologic lesions are the most common etiology. Steroid pretreatment was given in 40% of patients. Only a small percentage (<20%) underwent definitive treatment. Patients were symptomatic for 18 days on average before consult. It took an average of 18 days for a case to be diagnosed definitively, and 10 days from the diagnosis to start of directed treatment. Mortality rate was high at 57.4%.

CONCLUSION: Patients with intrathoracic mass and malnutrition are 1.4x more likely to die. Diagnosis is the most significant factor associated with death. Observed data can be used as basis to formulate protocols which can streamline the diagnostic and therapeutic approach in these patients.

KEYWORDS: *pediatric mediastinal mass, leukemia, lymphoma*

INTRODUCTION

The Philippine Children's Medical Center (PCMC) is one of the largest tertiary hospitals in the country which caters to pediatric illnesses. In the past three years, the Cancer and Hematologic Division received an average of 24 referrals per year for pediatric thoracic masses. Comprehensive local data on the patient's demographic status, clinical profile, management, and outcome are still not available.

Thus, there is a need to report data on these patients in order to appreciate unique clinical characteristics, challenges in diagnosis, management and outcome.

The estimated incidence of mediastinal masses in the general population is 1 case per 100,000 persons per year (1). There are only a handful of published literature regarding intrathoracic tumors in the pediatric age group worldwide because of the rarity of the condition. Observational studies have a range

of 26 to 204 subjects over a period of 1 to 25 years. Thoracic tumors are mostly located in the mediastinum and are rare in children and adolescents (2). They may have different origins in the embryonic tissues. They can vary from the most benign cysts to the most aggressive malignant lesions (3). The location from where the tumor arises may provide a clue on the nature of the mass. The challenge in the management of these tumors in children starts from the time of consultation, approach to diagnosis, initial administration of emergency measures and definitive treatment to complications. Difficulty in establishing the diagnosis in this subset of tumor arises especially with the need for sedation vis a vis impaired cardiopulmonary function. A careful assessment before an invasive procedure is of utmost importance to minimize the risk of cardiopulmonary collapse (2). Review of previous studies showed T-cell acute lymphoblastic leukemia and Hodgkin's Lymphoma as the most common diagnosis of these thoracic masses (4).

This study aimed to review and describe the different patient related factors and clinical presentations, as well as the diagnostic process, initial management, and outcome of children presenting with intrathoracic tumors in a pediatric tertiary hospital from 2017 to 2019. Possible associations between the clinical features and outcome were examined. Analysis of collated data can provide a basis for formulation of treatment guidelines which may improve the overall outcome of intrathoracic masses in the pediatric age group.

Methodology

This study utilized a retrospective, descriptive and analytical design. Children and adolescents 0-18 years old who were referred to the Cancer and Hematology Division for evaluation and management of intrathoracic masses from January 2017 to December 2019 were eligible for the study. This included charity or service patients only. Since the condition of subjects for inclusion is rare and the number of referrals is small, all subjects were included and sampling was not employed. No subjects were excluded.

Data were collected by doing a chart review of in-patient and out-patient medical records who fulfilled the inclusion criteria. All the private information of these patients were kept confidential. Each patient was assigned a corresponding number for anonymity written on a master list. These numbers served as their code and were used to de-identify the patients.

Patients' data such as demographics, clinical features, and outcome were collected. The information collected was reviewed. The age at the time of referral, gender, nutritional status, and region of origin were collected for demographics. Clinical features such as symptomatology, anatomic location, initial laboratory findings, associated radiologic findings, and the diagnosis were reviewed. Initial treatment modalities used, clinical timeline, and the outcome was noted. Laboratory findings between tumor types was compared. Possible associations between the demographic, clinical parameters, diagnosis, and timelines were explored. Ethical approval to conduct the study was obtained from the PCMC Institutional Research-Ethics Committee.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Frequency and proportion were used to summarize categorical variables, as well as mean, standard deviation and range for numerical variables. Microsoft Excel was used to encode the responses and generate the summary statistics. All valid data were included in the analysis. Missing variables were not replaced nor estimated. For the inferential statistics, Pearson's Chi-square or Fisher's Exact test was used to determine significant differences in proportions across groups, whichever was appropriate. Kruskal-Wallis test was used to determine significant differences in ranks of timelines in days across outcomes. Epi Info for Windows (CDC) was used to generate the statistical analyses.

Results

A total of 68 cases of intrathoracic masses were referred to the Cancer and Hematology Division from January 2017 to December 2019. The mean age of presentation at diagnosis is 8.8 years, with more than half (36/68, 53%) of the patients being less than 10 years of age and the majority (48/68, 71%) males. The male to female ratio is 2.4:1. Almost two-thirds (44/68, 65%) of them had normal nutritional status, while 35% (24/68) of the subjects had malnutrition, with 21% (14/48) being severely wasted. It is expected that majority of the patients were living in the National Capital Region and its neighboring provinces (65/68, 96%), but a small percentage came from as far as the Visayas region (3/68, 4%).

The most prevalent presenting symptom was cough (59/68, 86.8%), with associated dyspnea and easy fatigability in 60.3% (41/68) of patients. clinical evidence of respiratory compromise was noted. Constitutional symptoms such as fever and decreased appetite were reported by 61.8% (42/68) and 35.3% (24/68) patients, respectively. Nine patients (13.2%) were noted to have facial edema upon presentation, of which 6 patients (8.8%) also presented with neck vein engorgement.

Figure 1 shows that the mass was located at the anterior mediastinum for most of the children and adolescents (56/68, 68%). Masses were less commonly seen in the middle mediastinum (7/68, 9%) and posterior mediastinum (11/68,15 %).

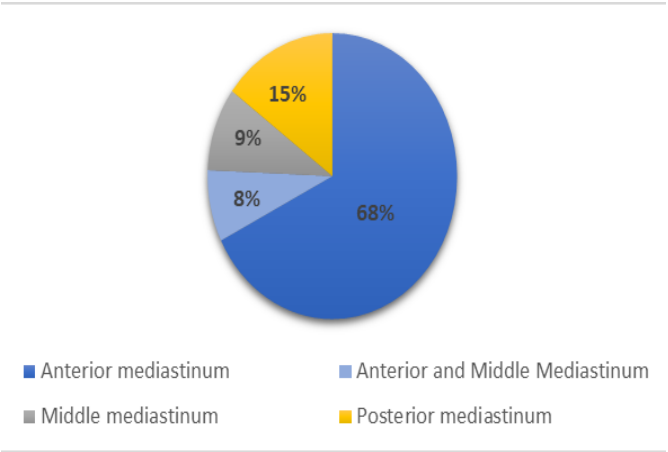

Figure I. ANATOMIC LOCATION OF THE MASS, n=68

Certain laboratory parameters were not requested for some patients. All included subjects had a complete blood count (CBC) while only 93% (63/68) had lactate dehydrogenase (LDH), potassium, and calcium. Only 88% (60/68) had creatinine and 77% (52/68) and 74% (50/68) had phosphorus and blood uric acid determination respectively. Tumor markers for GCT, alpha fetoprotein (AFP) and b-human chorionic gonadotropin (b-hCG) determination were done in only 57.4% (39/68) of patients. The unavailability of uniform laboratory parameters may mask the actual frequencies had all the patients had complete findings.

Half (50%) of them had an elevated LDH value of >500 U/L. Hyperkalemia is present in only 4% (3/68) of the subjects. Potassium and calcium levels were normal in 74% (50/68) and 91% (62/68) of the patients, respectively. None of the subjects present with hypocalcemia. Elevated phosphorus levels were seen in 38% (26/68) while phosphorus level was normal 25% (17/68) of them. Hyperuricemia was seen in only 13% (9/68) of the subjects with normal uric acid level in 60% (41/68) of the patients. Almost three-fourths (74%, 50/68) of the patients had low creatinine level.

Anemia was present in 46% (31/68) of the patients. Leukocytosis was present in 65% (66/68) of the patients with 6% (4/68) having hyperleukocytosis. Thrombocytopenia was present in 18% of the patients (12/68) while 28% (19/68) presented with thrombocytosis. Only 13% (9/68) had bicytopenia, none had pancytopenia.

Table 1 shows that the most common associated radiologic finding was pleural effusion (28/68, 41%), followed by pericardial effusion (14/68, 21%). Parenchymal lung masses (7/68, 10%) and tracheal deviation/compression (10/68, 15%) were less common.

Table 1. ASSOCIATED RADIOLOGIC FINDINGS WITH INTRATHORACIC MASS

	No.	%
Parenchymal lung masses	7	10.3 %
Pleural Effusion	28	41.2 %
Tracheal deviation/compression	10	14.7 %
Pericardial Effusion	14	20.6 %

Table 2 shows the frequency of the masses based on the etiology. More than two-thirds (46/68, 68%) had malignant intrathoracic mass, while less than one-third (22/68, 32%) had masses that were non-malignant. Among patients with a malignant mass, majority (31/46, 67%) were diagnosed to have hematologic malignancies. The most common hematologic malignancy was non-Hodgkin lymphoma (NHL) comprising 22% (15/68) while majority (8/15, 53.3%) of non-hematologic tumors were GCTs. For non-malignant intrathoracic lesions, the most prevalent was tuberculosis (10/22, 45.4%).

Table 2. CLASSIFICATION OF INTRATHORACIC MASSES (n=68)

	No.	%
Malignant Hematologic	**31**	45.6%
T Cell ALL	8	11.8%
Lymphoma		
Non-Hodgkin Lymphoma	15	22.0%
T Lymphoblastic Lymphoma	7	10.3%
ALCL	2	2.9%
DLBCL	2	2.9%
Mature B-Cell	2	2.9%
Hodgkin's Lymphoma	6	8.8%
Not otherwise classified	2	2.9%
Malignant Non-hematologic	**15**	22.1%
Germ Cell Tumors	8	11.8%
Neuroblastoma	5	7.4%
Malignant Peripheral Nerve Sheath Tumor	2	2.9%
Non-Malignant	**22**	32.4%
Tuberculosis	10	14.7%
Pneumonia	6	8.8%
Mature Cystic Teratoma	3	4.4%
Thymoma	2	2.9%
Bronchogenic Cyst	1	1.5%

Table 3 shows the initial diagnostic and therapeutic approach for the patients. Majority of patents was given chemotherapy as initial management (42/68, 62%). Biopsy of the primary tumor was done in 19% (13/68) of the patients while biopsy of extrathoracic lymph nodes was done in 37% (25/68) of the patients. Surgical excision and radiation therapy were done in only 4% (3/68) and 3% (2/68) of the patients, respectively.

Table 3. INITIAL MANAGEMENT OF PATIENTS WITH INTRATHORACIC MASS

	No.	%
Surgical Excision	3	4.4%
Biopsy only	38	
Intrathoracic Mass	13	19.1%
Other sites (Lymph nodes- Cervical, Inguinal)	25	36.8%
Steroid pretreatment	27	39.7%
Chemotherapy	42	61.8%
Radiation therapy	2	2.9%

Table 4 shows the outcome of patients. Majority (39/68, 57.4%) died. Among those who were reported alive were non-malignant (12/68, 17.6%) and were referred back to their respective admitting services, while 13% (9/68) were undergoing treatment at the time the data were gathered. Over 7% (5/68) of the patients were lost to follow up.

Table 4. OUTCOME OF PATIENTS WITH INTRATHORACIC MASS

	Malignant (n=46)		Nonmalignant (n=22)		Total	
	No.	%	No.	%	No.	%
Alive	12	26.1%	12	54.5%	24	35.3%
Not treated	0	0.0%	12	54.5%	12	17.6%
Ongoing treatment	9	19.6%	0	0.0%	9	13.2%
Completed treatment	3	6.5%	0	0.0%	3	4.4%
Died	32	69.6%	7	31.8%	39	57.4%
Lost to follow up	2	4.3%	3	13.6%	5	7.4%

Patients were brought for consultation an average of 18 days (ranging from 2 to 60 days) after symptoms were observed. Diagnosis was confirmed 18 days on average (ranging from 1 to 120 days) after consultation. While treatment was provided 10 days on average (ranging from 1 to 107 days) after diagnosis. It was noted that 7.4% (5/68) of the patients who were brought to a physician for consultation had symptoms for more than 30 days already. Definitive diagnosis was made 30 days after the first consultation for 19% (13/68) of the patients while directed treatment was initiated for more than 30 days in 7.4% of the patients (5/68).

Comparison of laboratory findings between subjects with malignant and non-malignant tumors. Malignant lesions presented with elevated LDH, hyperuricemia, and hypokalemia. Hyperkalemia was seen more in non-malignant lesions. Hyperphosphatemia was seen in similar proportions for both malignant and non-malignant cases. Calcium level is normal in most of the patients and comparable between patients with malignant and benign tumors, as well as creatinine levels. The CBC picture is also comparable between those with malignant and non-malignant lesions in that half of each group has anemia, elevated WBC counts, and normal platelet counts.

Table 5 shows the possible association of clinical parameters and outcome of patients. Higher proportion of death was noted in older children (>10 y/o), as 70% (21/29) of them expired. It was noted that a high proportion of severely wasted patients died (11/13, 85%). In terms of the anatomic location of the mass, those with masses at the posterior mediastinum has the highest proportion of deaths at 70% (7/10). Non-malignant masses also have high proportion of deaths as seven of the eight patients diagnosed with a non-malignant mass died.

Table 5. ASSOCIATION OF CLINICAL PARAMETERS AND OUTCOME

Demographic characteristics	Died (n=39)		Alive (n=24)		Total (N=63)		p-value*
	No.	%	No.	%	No.	%	
Age							
<10 years old	18	55%	15	45%	33	100%	0.207
≥10 years old	21	70%	9	30%	30	100%	
Sex							
Male	28	61%	18	39%	46	100%	>0.999
Female	11	65%	6	35%	17	100%	
Nutritional Status							
Normal	23	56%	18	44%	41	100%	0.287
Wasted	3	60%	2	40%	5	100%	
Overweight	2	50%	2	50%	4	100%	
Severely wasted	11	85%	2	15%	13	100%	
Anatomic location of the mass							
Anterior mediastinum	32	62%	20	38%	52	100%	>0.999
Middle mediastinum	3	43%	4	57%	7	100%	0.412
Posterior mediastinum	7	70%	3	30%	10	100%	0.729
Radiologic findings							
Parenchymal lung masses	3	50%	3	50%	6	100%	0.666
Pleural Effusion	17	63%	10	37%	27	100%	>0.999
Tracheal deviation/ compression	5	56%	4	44%	9	100%	0.721
Pericardial Effusion	8	62%	5	38%	13	100%	>0.999
Diagnosis							
Malignant	32	78%	9	22%	41	100%	0.004
Hematologic	18	69%	8	31%	26	100%	
Non-Hematologic	14	93%	1	7%	15	100%	
Non-Malignant	7	88%	1	13%	8	100%	
* Chi-square test of Fisher's exact test was used, whichever was appropriate.							

Table 6 shows the possible association of nutrition and outcome of patients with intrathoracic mass. In general, it is noted that malnourished patients were 1.4x more likely to die than those with normal nutritional status. All subjects with malignancy and with some form of malnutrition died. Patients with non-malignant lesions and with malnutrition is 2.7x more likely to die. The trend suggested that malnourished patients with wasting had a higher risk of death, but it did not approach statistical significance.

Table 6. ASSOCIATION OF OUTCOME AND NUTRITIONAL STATUS AMONG PATIENTS WITH INTRATHORACIC

	Malignant (n=44)				Nonmalignant (n=19)				Total (N=63)			
NUTRITIONAL STATUS	No. of deaths	%	RR (95% C.I.)	p-value	No. of deaths	%	RR (95% C.I.)	p-value	No. of deaths	%	RR (95% C.I.)	p-value
Normal	21	64%	*Reference*	-	2	25 %	*Reference*	-	23	56 %	*Reference*	-
Overweight	2	100 %	1.57 (1.21-2.03)	0.850	0	0%	0.00 (0.00-?.??)	>0.999	2	50 %	0.89 (0.32-2.46)	>0.999
Wasted	2	100 %	1.57 (1.21-2.03)	0.850	1	33 %	1.33 (0.18-9.86)	>0.999	3	60 %	1.07 (0.48-2.30)	>0.999
Severely wasted	7	100 %	1.57 (1.21-2.03)	0.127	4	67 %	2.67 (0.71-10.05)	0.312	11	85 %	1.51 (1.06-2.154)	0.120
Malnourished (wasted or severely wasted)	9	100 %	1.57 (1.21-2.03)	0.065	5	56 %	2.22 (0.58-8.44)	0.436	14	78 %	1.39 (0.96-2.00)	0.193

Table 7. ASSOCIATION OF CLINICAL TIMELINE AND OUTCOME AMONG PATIENTS WITH INTRATHORACIC MASS (n-63)

Timeline in days, mean ± SD (range)	Died (n=39)	Alive (n=24)	Total (n=63)	p-value
Symptomatology to health seeking behavior	18.4 ± 11.9 (2-60)	18.3 ± 13.2 (2-60)	18.4 ± 12.3 (2-60)	0.981
Consult to diagnosis	17.7 ± 24.9 (1-120)	17.1 ± 23.0 (2-90)	17.5 ± 24.0 (1-120)	0.922
Diagnosis to start of definitive treatment	11.1 ± 17.8 (1-68)	10.5 ± 22.4 (1-107)	10.8 ± 19.5 (1-107)	0.908

Table 7 shows the possible association of the timeline from development of symptoms to treatment and outcome. Timelines for both dead and alive patients are comparable.

DISCUSSION

This study attempted to provide a comprehensive description and analysis of outcomes among pediatric patients with intrathoracic masses from a tertiary pediatric institution in the country. It is limited by its retrospective design, incomplete data sets, and small sample size available for statistical analysis.

The mean age at diagnosis was 8.8 years old, which is younger than that seen in most existing literature (2,5,6,7). In this study, intrathoracic mass was found to be 2.4 times more prevalent in males compared with females. This gender distribution was observed by Kashif et al (2019) in Pakistan, but not by Garey et al (2011) in the United States, which showed equal proportions of boys and girls in their cohort.

Majority of the patients (44/68, 65%) had normal nutritional status while 28% (19/68) presented with malnutrition. Poor nutritional status has been shown to correlate with increased treatment-related side effects and reduced survival (9). Almost one-fifth (21%) of our patients were severely wasted. Other studies in the Asian region showed a higher percentage of undernourished patients as high as 65.6% (3,10). Highest rate of death was seen among those who were severely wasted at 85% (11/13). All malignant cases who were malnourished died. Patients with wasting, especially those with malignancy, exhibit reduced dietary intake, malabsorption or maldigestion of food, or altered energy and nutrition needs (11). Malnutrition appears to contribute to the infectious and immunologic morbidities associated with malignant lesions and adds insult to from treatment modalities.

Majority of the patients (43/68, 63%) came from outside National Capital Region (NCR). Patients from the far northern and southern provinces of Luzon, as well as Visayas were seen. The proximity of the patients' residences may play a role in their health-seeking behavior and the protracted clinical course prior to a definitive diagnosis. Aside from the proximity, availability of health institutions and specialists catering to this subset of patients are limited and is mostly concentrated in the NCR.

All of the subjects were symptomatic at presentation, either with respiratory symptoms or constitutional symptoms, but mostly both. In our cohort, majority presented with respiratory symptoms. Cough, dyspnea and easy fatigability were present in more than 60% of the patients. Nasir et al., (2020) analyzed medical records of 61 pediatric patients in Pakistan who presented with anterior mediastinal mass. In this study, most of the children presented with nonspecific symptoms such as fatigue (63.9%), followed by weight loss. Similarly, this was observed by Garey et al., (2011) in a US study where the mean age of the subjects was 11.3 years.

Compartmentalization of mediastinal masses is often cited as a helpful distinguishing feature that facilitates diagnosis and possible prognosis. Anterior mediastinum lesions were found in 82.4% of our patients (56/68). In this study, majority (46/68, 67.6%) were diagnosed with a malignant lesion. Almost half, 46% (31/68) were diagnosed with a hematologic malignancy which is consistent with most reviewed literature wherein lymphomas and leukemias are the most common lesions found in the anterior mediastinum (7). Middle mediastinum lesions are usually seen in association with anterior

mediastinum tumors and are rarely isolated (5). In our study, four of six patients with middle mediastinum lesions have associated anterior mediastinum lesions. Isolated middle mediastinum lesion was seen in two patients which was eventually diagnosed as T-cell lymphoblastic lymphoma and TB disease. Neurogenic tumors are usually found in the posterior mediastinum. Among our subjects with posterior mediastinal mass, four out of seven are of neurogenic origin (neuroblastoma, malignant peripheral nerve sheath tumor).

There were no significant differences in the blood chemistry results between those with malignant and non-malignant lesions. Elevated LDH (> 500 U/L) was seen in a greater proportion of those with malignant tumors compared with those with non-malignant lesions (57% vs 48%). LDH levels that are two times greater than the upper limit of normal (ULN) poses a risk for tumor lysis syndrome (TLS) and this was seen in 29% of our patients (20/68)

Laboratory parameters such as electrolytes and uric acid were requested for diagnosis and monitoring of a possible TLS. TLS is associated with large tumor burdens, those with high cell proliferation, chemotherapy sensitive tumors, and those with high pretreatment LDH levels (12). The mentioned risk factors are usually associated with hematologic malignancies especially Burkitt's Lymphoma, Tcell ALL, and acute myeloid leukemia (AML) (11).

Hyperkalemia (>5.10 mmol/L) is present in only a small percentage of patients 2% and 11% for malignant and non-malignant lesions respectively. None of the patients presented with hypocalcemia (<1.76 mmol/L) while only one patient presented with hypercalcemia. Hypocalcemia was associated with a poor prognosis among cancer patients (13). Hypercalcemia was also shown to be associated with malignancy, with the risk increasing if it is associated with high levels of lactate dehydrogenase, alkaline phosphatase, WBC, platelet, or CRP. Majority of the patients, comprising 50% of those in both groups showed hyperphosphatemia (>1.45 mmol/L). Only a small portion had hyperuricemia (>448 umol/L), 20% for malignant cases and 10% for non-malignant. A study by Nicholson et al (2021) suggested that combinations of simple blood tests abnormalities could be used to identify patients with cancer. Laboratory parameters included in their study were albumin, alkaline phosphatase, liver enzymes, C-reactive protein, hemoglobin, platelets, and total white cell counts. Our study did not include albumin, alkaline phosphatase, liver enzymes, and CRP.

Anemia was present in 45.6% (31/68) of the patients. In a study by Naeser et al in 2017, high probability of cancer was noted in patients with anemia. This was different from the observation in our study, where only 44% (20/46) of patients with malignancy had anemia at presentation compared to the 50% (11/22) of those with non-malignant lesions. Malignancy-related anemia is multifactorial but is usually associated with tumor infiltration of the bone marrow (18). Other contributory factors include nutrition, the release of inflammatory cytokines, and treatment regimen. Leukocytosis, defined as a WBC count >50,000/mL warrants an investigation especially for clinical signs and symptoms of leukocytosis as it is associated with early morbidity and mortality. Hyperleukocytosis, WBC greater than 100,000/mL can be seen in children with leukemia and lymphoma. In our study, elevated WBC count was present in 65% of the study population.

Four patients who were diagnosed with T-cell leukemia presented with WBC count > 50,000/mL with 3 of the four presenting with hyperleukocytosis (WBC >100,000). Naeem et al. (2015) described in their study that anemia and leukocytosis were equally common. Cancer incidences for patients with normal platelet counts were lower than those reported for patients with thrombocytosis (6). In our cohort, thrombocytosis was seen in 28% of the patients (19/68). It is more common among those who had non-malignant intra-thoracic masses (8/22, 36%) compared to those with malignant lesions (11/46, 24%). On the other hand, thrombocytopenia was seen in 18% (12/68) of the patients. This was found more commonly in patients with hematologic malignancies compared to those non-malignant cases, 20% and 14% respectively.

Malignant lesions (68%, 46/68) were the most common cause of intrathoracic masses in our cohort of patients. This is consistent with several studies done both in Asia and America. Chen et al (2019) reported a diagnosis of lymphoma in 47.5% of children with mediastinal tumors while Kashif et al (2019) reported that 70% of their subjects were diagnosed with malignant lesions (35% T-cell ALL, 30% lymphoma). In one prospective cross-sectional study (5) in Iran however, they reported non-malignant lesions in 51.5% of the subjects. In this study by Alamdaran et al. majority of the thoracic masses were located in the parenchyma and hydatid cyst were the most frequent mass seen. Hematologic malignancies such as T-cell ALL and lymphoma comprised 44% of our cohort and were twice more prevalent compared to non-hematologic malignancies such as GCT and neuroblastoma (15/68, 22%). The majority of patients with hematologic malignancies were diagnosed with NHL (n=9 lymphoblastic lymphoma, n=2 DLBCL, n=2 ALCL), followed by T-cell ALL (n=7) and Hodgkin lymphoma (n=6).

Pleural and pericardial effusion were among the most commonly associated radiologic findings in our cohort of patients (41.2% and 20.6% respectively). Pleural effusion is seen in 31% to 54.5% of other cohorts. Pericardial effusion was seen in 25% to 31% in other studies. The presence of these findings may further impair their respiratory capacity. Tracheal deviation or compression is seen in 15% (10/68) of the population. This was identified as a factor associated with anesthetic complications (8). However, some studies found a poor correlation between symptomatology and radiologic airway compressions (5). They noted that obstruction may be present even without radiologic evidence. Caution should be practiced in these patients; it is probably prudent to presume that those with cardiorespiratory symptoms may be at higher risk for respiratory problems.

Patients with intrathoracic masses may present with significant airway compromise that can be life-threatening hence there is an urgency to establish accurate diagnosis. However, patients in critical condition may not be good candidates for mediastinal surgery requiring general anesthesia. In these cases, a less invasive procedure would be preferable. In many of the clinical reports on mediastinal masses in the pediatric age group, a biopsy of lymph nodes determined the diagnosis and mediastinal tissue biopsy was rarely employed (3,8,10). This observation was also seen in our subset of patients as only 24% (16/68) had either a biopsy or excision of the primary intrathoracic mass. Excision of the

mediastinal mass was done in 14% of those with benign lesions, and none in those diagnosed with malignancy. Mediastinal mass biopsy was done in 24% (11/46) and 9% (2/22) in the malignant group and non-malignant group respectively. Extrathoracic LN (cervical or inguinal) biopsy was done in 40% (27/68) of our patients which helped in establishing the diagnosis. This offered less risk because of minimal sedation and prevention of respiratory compromise. Patients who presented with either leukocytosis or bicytopenia were confirmed to have T-cell ALL through bone marrow evaluation and immunophenotyping. No deaths were reported following sedation and anesthesia for all procedures.

Corticosteroids were used as emergency treatment for patients presenting with life-threatening symptoms. It should be considered that steroid use can compromise the quality of diagnostic material sampled on subsequent biopsies (9). It is also important to note that it imposes a significant risk for tumor lysis syndrome (11). Almost 40% (27/68) of our subjects needed steroid pretreatment at the onset, reflecting the number of patients requiring immediate intervention at presentation. These patients presented with either signs and symptoms of respiratory compromise, bulky disease, or the presence of massive pleural effusions.

Thirty-nine (39) of the 68 patients in this study died with a mortality rate of 57.4% for all cases of intra-thoracic tumors. Different studies reported a mortality rate of 16.4% to 45% in patients presenting with intrathoracic masses (2,3,10,15). Mortality is more than 50% across all etiology, with non-hematologic malignancies having the highest rate. The prognosis of these patients was found to be significantly associated (p value=0.004) with a diagnosis of intrathoracic mass. Based on our observations, the likelihood of death is twice as high in those with malignant lesions.

About 40% (27/68) of patients presented with the advanced stage of the disease as manifested by serious life-threatening symptoms. Kashif et al in 2019 were able to associate the prognosis of these patients with the underlying diagnosis, the delayed presentation to the healthcare facility, and the education status of the head of the patient's family. One study from Japan showed that the median time of symptoms onset to diagnosis was 8.5 days and warning signs leading to admission were noted on average only two days prior to admission (16). Reviews of other available studies do not include specific details on the time frame of symptomatology to specific treatment interventions. This study was not able to show an association between the duration of symptoms to diagnosis, treatment, and outcome. This may be due to the small sample size and the large variability of days across patients. The timeline for all patients, both who died and are still alive, are similar. Our study was only able to give an overview of the average timeline of management in this subset of patients.

Conclusion

Aside from the demographic characteristics of pediatric patients with intrathoracic mass as well as the high mortality rate, this study also highlighted the non-uniformity of diagnostic and treatment approaches in this subset of the population. This may or may not affect the protracted timeline of events from health-seeking behavior to the onset of directed therapy.

From our limited data, we observed that most patients with thoracic masses are in the school-age group, males, with some form of malnutrition. Majority of the patients presented with respiratory symptoms like cough, dyspnea, and chest pain. Most of the masses were located at the anterior mediastinum and are malignant in nature, mainly NHL and Tcell ALL. Steroid pretreatment was given in 40% of the cases indicating the number of cases who were initially seen with severe and life-threatening symptoms. Only a small percentage of these patients underwent directed treatment (<20%) as some expired prior to establishing the diagnosis. Mortality rate is high at 57% and those with malignant lesions were twice more likely to die.

This study had several limitations but it was able to raise awareness regarding the current practice surrounding this kind of case. Diagnostic tests were not obtained uniformly in all subjects. Creating institutional protocols for managing this rare and life-threatening condition may help provide similar and/or comparable data that can eventually translate to better figures for researches in diagnosing and treating these patients. Algorithms for management, or diagnostic and treatment protocols with definite time frames can improve efforts to establish the diagnosis and start directed therapy in the shortest possible time with hopes to augment the high mortality in this subset of patients.

Retrospective studies are usually influenced by recall, reporting, and information bias. It is important to validate the findings of this study with prospective studies. Future prospective studies may include social and economic status in factors that may impact the outcome of the patients. Further studies with larger number of patients, through collaboration among multiple centers, will improve applicability of these results.

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ARTICLE

Evaluation of Prescribing Patterns for Pediatric Community-Acquired Pneumonia in the Outpatient Department of a Tertiary-Care Medical Center in the Philippines

Teresa D. Dacalanio, & Mary Antonette C. Madrid

OBJECTIVES: This study evaluated the antibiotic prescribing patterns in pediatric patients in the Out Patient Department (OPD) of the Philippine Children's Medical Center (PCMC) where it may encourage drug monitoring and improvement in the utilization of antibiotics in the department.

MATERIALS AND METHODS: A descriptive, cross-sectional study involving patient encounters selected using convenience sampling was conducted at the outpatient department of PCMC. All previously healthy pediatric patients aged 3 months to 18 years diagnosed with pediatric community-acquired pneumonia (PCAP) with no known acute and chronic co-morbidities were included. The observed values of the antibiotic prescribing indicators were compared with the optimal values recommended by the World Health Organization (WHO), and the Index of Rational Drug Prescribing (IRDP) was calculated.

RESULTS: A total of 600 patients diagnosed with PCAP were included in the study seen at the PCMC OPD from January 2020 to July 2022. Ninety-six percent of the patient encounters had at least one antibiotic prescribed (SD $\pm$ 0.20). The average number of medicines prescribed per patient encounter was 2.05 (SD $\pm$ 0.85). Of these, 100% were prescribed by generic name and were prescribed from the essential drug list. The most commonly prescribed medications were antibiotics (43.17%) with co-amoxiclav (42.93%), amoxicillin (37.76%), and cefuroxime (7.59%) being the top three commonly prescribed antibiotics.

CONCLUSION: With respect to the IRDP, PCMC scores well with 3.16 where the most rational score is 4. However, this study highlights the high occurrence of prescribing antibiotics in the institution.

KEYWORDS: *Antibiotic prescribing pattern, Outpatient department, Pediatrics, WHO indicators*

INTRODUCTION

While antibiotics remain to be one of the greatest advances in medicine, the method and manner of their use, if not observed properly, could result in problems that might affect the health of humanity as a whole. Currently, the issue of antibiotic resistance has become one of the major concerns of experts in the field of medicine, and this is brought about by the practices in prescribing patterns that involve antibiotics. To give a better perspective, in 2014 alone, 266.1 million courses of antibiotics were dispensed to outpatients in U.S. community pharmacies. This equates to more than 5 prescriptions written each year for every six people in the United States. At least 30% of antibiotics prescribed in the outpatient setting are unnecessary, meaning that no antibiotic was needed at all.

Total inappropriate antibiotic use, inclusive of unnecessary use and inappropriate selection, dosing and duration, may approach 50% of all outpatient antibiotic use. [1] Thus, appropriate antibiotic prescribing must be strongly encouraged among healthcare professionals. Appropriate antibiotic prescribing means antibiotics are only prescribed when needed, and when needed, the right antibiotic is selected and prescribed at the right dose and for the right duration. Appropriate antibiotic prescribing should be in accordance with evidence-based national and local clinical practice guidelines, when available.

Relating to the issue of antibiotic resistance, this study finds it significant to evaluate the prescribing patterns for one of the most common diseases in PCMC where antibiotics are prescribed: Pediatric Community-Acquired Pneumonia (PCAP). According to Philippine Children's Medical Center's (PCMC) 2019 annual report, pneumonia has always been in the top three cases when it comes to admission. It is also in the top three causes of mortality from 2017 to 2019. There have been 517 admitted cases of pneumonia in 2017, 722 in 2018, and 957 in 2019. [2] Nationwide, pneumonia consistently places within the top five causes of mortality from 2017 to 2019. [3, 4, 5]

This study specifically covers the Out Patient Department (OPD) of PCMC because there is no antimicrobial stewardship program, unlike for inpatients where antibiotic surveillance is regularly conducted. With no antimicrobial stewardship program, the OPD of PCMC is more vulnerable to prescribing patterns that might contribute to the aggravation of antibiotic resistance. Consequently, this study assessed the antibiotic prescribing patterns in pediatric patients in the OPD of PCMC where it may encourage drug monitoring and improvement in the utilization of antibiotics in the department. Moreover, this study aimed to describe the antibiotic prescribing pattern in PCAP in the OPD of PCMC and assessed the level of adherence of physicians to the available local clinical practice guidelines in prescribing antibiotics. Ultimately, this study may serve as a reference that may be used to evaluate the need to establish an antimicrobial stewardship program in the OPD of PCMC.

METHODOLOGY

This research used a cross-sectional, descriptive study design with a quantitative approach. This study was conducted at the OPD of PCMC which is manned by resident physicians. PCMC tertiary medical center for children is located in Quezon City, Philippines. It is a referral center for pediatric cases from primary and secondary health facilities nationwide. It also serves as a training institution which offers training programs for medical and allied healthcare providers.

The study population included all previously healthy pediatric patients aged 3 months to 18 years diagnosed with PCAP seen at the OPD of PCMC from January 2020-July 2022 with no known acute and chronic co-morbidities. Six hundred encounters were included as recommended by the World Health Organization (WHO) in investigating prescribing practices of a facility. A convenience sampling was used. [6]

A research assistant reviewed charts of the target population The charts were physical charts obtained from face-to-face encounters of physician and patient at the OPD.

A data collection tool was used to collate the gathered information on 1) patient demographics (i.e., age, sex), 2) prescribing indicators: number of medicines prescribed per patient encounter, percentage of encounters with an antibiotic prescribed, percentage of encounters with an injection prescribed, percentage of drugs prescribed by generic name, and percentage of drugs prescribed from the essential drugs list (EDL), and 3) pharmacologic data (drug class, route, dose, frequency, and duration).[7] The research assistant was trained on the use of the data collection tool and was supervised during data collection.

WHO defines rational use of medicines as giving the right medicine, for the right patient, at the right dose, for the right duration, and at the right (lowest) cost to them and their community. WHO in collaboration with the International Network of Rational Medicine Use (INRDU) has developed a group of indicators to assess the use of antibiotics in health facilities namely, prescribing indicators, facility indicators and patient care indicators [8]. This study focused on the following prescribing indicators[9]: 1) average number of medicines prescribed per encounter which describes the extent of polypharmacy, 2) percentage of encounters with an antibiotic prescribed which describes the frequency of antibiotic prescribing among healthcare providers, 3) percentage of encounters with an injection prescribed which describes the frequency with which injectable forms of medicines are prescribed, 4) percentage of drugs prescribed by generic name which describes the tendency of healthcare providers to prescribe medicines using generic name, and 5) percentage of drugs prescribed from the EDL which describes the prescribing practices conformance to the drug use policy.

The observed values of the antibiotic prescribing indicators were compared with the optimal values recommended by the WHO. An index system developed by Zhang and Zhi was used to compute for the optimal index for each indicator [10]. The optimal index for all indicators was set at 1. The values closer to 1 indicated rational drug use. The Index of Rational Drug Prescribing (IRDP) was calculated by adding the index values of all prescribing indicators [10]. The optimal values and indices are seen in Table 1.

Table 1. Optimal Values and Indices of the Drug Prescribing Indicators

Prescribing Indicator	Optimal Value [11]	Optimal Index [12]
Average number of medicines prescribed per encounter	1.6 – 1.8	1
Percentage of encounters with an antibiotic prescribed	20 – 26.8	1
Percentage of encounters with an injection prescribed	13.4 – 24.1	1
Percentage of drugs prescribed by generic name	100	1
Percentage of drugs prescribed from the EDL	100	1

Based on the index system of Zhang and Zhi [10], the calculation of non-polypharmacy, rational antibiotic and injection safety indices, the following formula was used:

$$Index = \frac{Optimal\ Value}{Observed\ Value}$$

While the generic name and essential drugs list indices were computed using the following formula:

$$Index = \frac{Observed\ Value}{Optimal\ Value}$$

All the observed indices were compared with the optimal indices indicated by the WHO. The institution's IRDP was calculated by adding all of the observed indices and was likewise compared with the optimal IRDP.

RESULTS

This study complied with the Data Privacy Act of 2012 and National Ethical Guidelines for Health and Health-related research. Patient data was kept confidential by controlling access to digital and physical documents. On data analysis, each chart was identified by a specific number, and names and/or initials of patients were not used.

After thorough data cleaning, a total of 600 patients diagnosed with PCAP were included in the study. Among these, majority were male (61.33%) and belonged to the age group 1 to 5 years (57.17%).

Table 2. Clinico-Demographic Data of Patients with PCAP seen at the OPD of PCMC, January 2020 – July

Sex	**N (%)**
Male	368 (61.33)
Female	232 (38.67)
Age	**N (%)**
3 to 12 months	163 (27.17)
1 to 5 years	343 (57.17)
>5 years	94 (15.67)

The average number of drugs given per patient was 2.05 (SD $\pm$ 0.85). Of the total 1332 prescribed drugs, the most common were antibiotics (43.17%) followed by antipyretics (26.80%), then vitamins and minerals (12.16%).

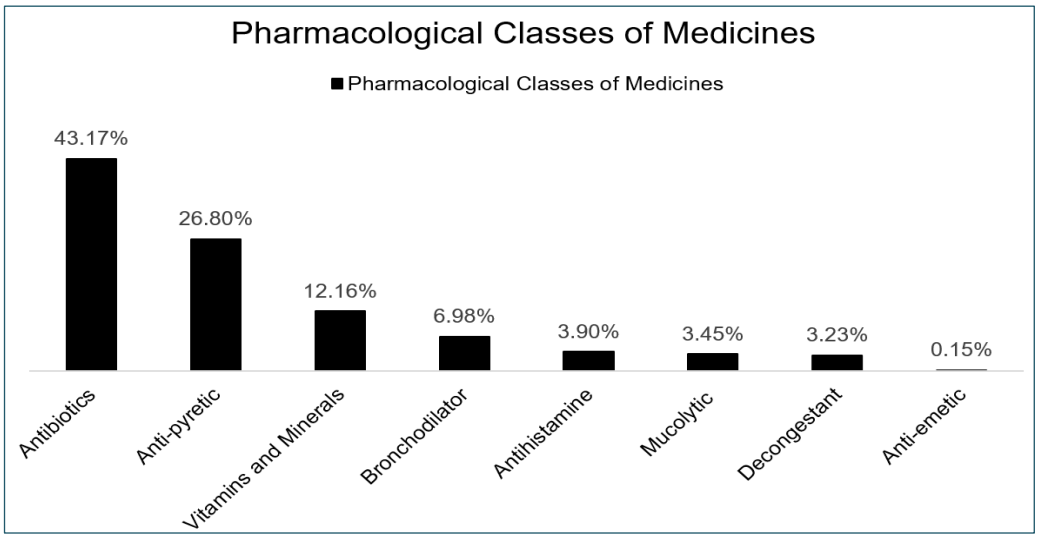

Figure 1. Pharmacological Classes of Medicines prescribed at the OPD of PCMC, January 2020 – July 2022

The most prescribed antibiotic was co-amoxiclav (42.93%) followed by amoxicillin (37.76%) then cefuroxime (7.59%) (Figure II).

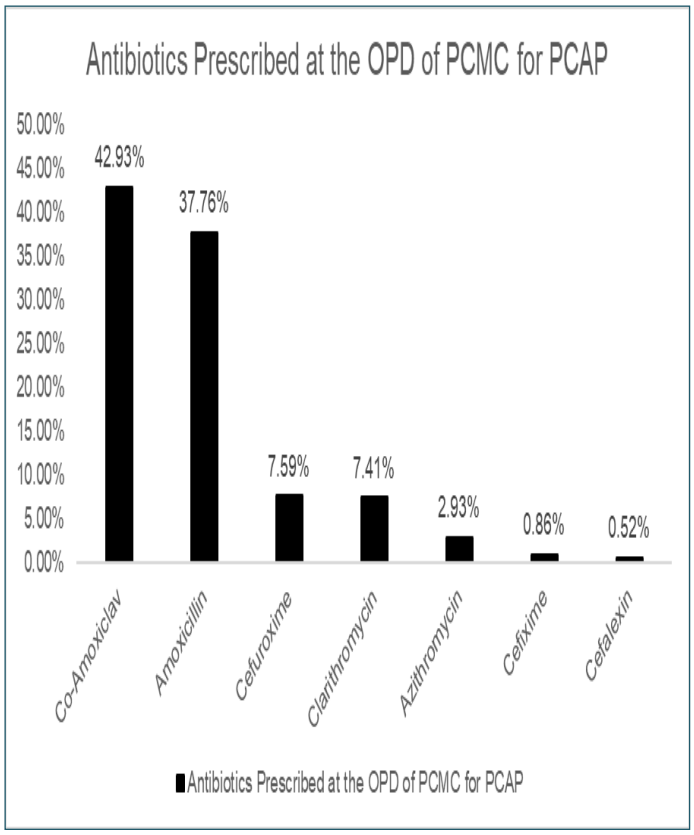

Figure 2. List of Antibiotics Prescribed at the OPD of PCMC for PCAP, January 2020 – July 2022

The average number of medicines prescribed per encounter was 2.05 (SD $\pm$ 0.85). Of the 600 patient encounters, 96% had at least one antibiotic prescribed (SD $\pm$ 0.2) and none had an injection prescribed (Table 3). All medications were prescribed by generic name and were from the essential drugs list.

In this study, a zero occurrence of prescribing of injection was not included in the computation for IRDP since the observed value serves as the denominator in arriving at the injection safety index. A zero denominator would yield an undefined value therefore, this indicator has been removed from this study's IRDP and 4 would be the most rational index. The calculated IRDP of PCMC was 3.16. Rational antibiotic index had the lowest values (0.28) followed by polypharmacy index (0.88) (Table 4). Moreover, the generic name index and essential drugs list index attained the optimal index.

Prescribing	Observed	Optimal
Average number of medicines prescribed per encounter	2.05	1.6 – 1.8
Percentage of encounters with an antibiotic prescribed	96	20 – 26.8
Percentage of encounters with an injection prescribed	0	13.4 – 24.1
Percentage of drugs prescribed by generic name	100	100
Percentage of drugs prescribed from the EDL	100	100

Table 3. Drug Prescribing Indicators at the OPD of PCMC with their corresponding Indices

Drug Prescribing indicator	PCMC Index	Optimal Index
Polypharmacy index	0.88	1
Rational antibiotic index	0.28	1
Injection safety index	-	1
Generic name index	1.00	1
Essential drugs list index	1.00	1
IRDP	**3.16**	**5**

Table 4. IRDP

Discussion

Our results indicate that the common prescribed antibiotics at the OPD of PCMC for children diagnosed with PCAP are co-amoxiclav, amoxicillin and cefuroxime. The findings in this study are consistent with other studies where amoxicillin was the most common antibiotics prescribed to manage PCAP [13,14] In some studies among Asian countries, there is an overuse of broad-spectrum therapy[15-18]. This antibiotic prescribing pattern at our institution as well as in the entire country remains to be studied since as of this writing, the author has yet to encounter any research tackling the overuse of broad-spectrum therapy. This prescribing pattern may be attributed to the fact that PCAP Clinical Practice Guidelines (CPG) recommend the use of the above-mentioned antibiotics in treating PCAP.

As evident from the results of this study, the most prescribed antibiotics at the OPD of PCMC for PCAP patients, namely 1) co-amoxiclav; 2) amoxicillin; and 3) cefuroxime, are consistent with the recommended antibiotics under the PCAP CPG. It is worth noting that in this study, out of the three most prescribed antibiotics for PCAP patients, only Co-Amoxiclav did not meet the PCAP CPG recommended dosage. Results actually show that prescriptions for co-amoxiclav are underdosed at 40mg/kg/day whereas the PCAP CPG recommends 80-90mg/kg/day [19]. It is important to follow the proper dosage and duration of antibiotics to prevent the consequences of under- and over-dosing. Aside from adherence to the local CPG, it is also important to look into local antibiotic resistance pattern in order to prescribe the proper antibiotic for each patient.

The results of this study also show that the average number of medicines prescribed per encounter is higher than the acceptable range (2.05 vs 1.6-1.8) based on reference values developed for the WHO [11]. Aside from the high average number of medicines prescribed per patient, the data gathered for this study also show that the percentage of encounters with antibiotics prescribed exceeds the acceptable range as well. These indicators point to polypharmacy which is prescribing more medicines than are clinically indicated or the use of an excessive number of inappropriate medicines. Polypharmacy must be addressed because polypharmacy consequently increases health care costs while also prolonging the duration of treatment due to possible adverse reactions and drug interactions [12].

There was also no encounter in PCMC where an injection was prescribed. This is a good prescribing indicator because it eliminates injections which, if used irrationally, may be a cause for public health concern. This is because injections have contributed to increasing hospital waste where waste management systems are not fully efficient, incurs necessary pain to patients and likewise exposes them to the possible spread of infections like HIV/AIDS, hepatitis, and abscesses and promote microbial resistance, muscle contractures, and nerve injury [12].

Furthermore, PCMC prescribes generic drugs in all of the encounters included in this study as shown by the observed value of 100. This is beneficial to patients because generic prescribing has been found to reduce the cost of medicines and prevent errors and confusion in writing and dispensing prescriptions [20]. Similarly, the percentage of medicines prescribed from the essential drugs list in this study shows a 100 observed value, meaning that all prescriptions consist only of medicines coming from the essential drug list [21]. Corollary, this indicates

that the prescribers in PCMC are well aware of the essential drug list for children.

Interestingly, analyzing the data with respect to the Index of Rational Drug Prescribing (IRDP), it may be said that PCMC as an institution scores well with 3.16 where the most rational score is 4. However, PCMC's IRDP must be accorded an in-depth examination because while the numerical value of PCMC's IRDP point to it being rational, closer scrutiny of the individual indices making up the IRDP would show that PCMC scores low on the index of rational prescribing of antibiotics. This means that there is a high occurrence of prescribing antibiotics in the institution. The danger here is that children are actually at risk of mortality due to otherwise treatable infections due to the development of resistance to antibiotics [12].

We were able to provide information on PCMC's rational pediatric prescribing which can be the baseline for future assessments in terms of monitoring prescribing trends and addressing the situation if needed. However, this must still be regarded as a purely descriptive study, where data might not be able to encapsulate and consider all the factors present such as how appropriately medications were prescribed with regard to specific diseases. This study also did not investigate other factors which can contribute to the choice of antibiotics, such as previous intake of antibiotics, and the level of resistance of organisms in the area. Therefore, this study offers a first step toward improved adherence to recommendations, which may help lower management costs and delay the evolution of resistant microbes. Large, well-designed multicenter trials are therefore required to assess the efficacy of guidelines in childhood PCAP and the degree to which they are followed.

Conclusion

The prescribing pattern for PCAP in the OPD of PCMC is rational as evident from the high IRDP (3.16 out of 4). However, it is important to note that there is a high occurrence of antibiotic prescribing in the institution at 96% with a corresponding low rational antibiotic index of 0.28. Based on these findings, we recommend that further studies be done to investigate the factors contributing to the over-prescribing of antibiotics in PCMC.

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ARTICLE

Resilience among Pediatric healthcare workers during the COVID-19 pandemic in a tertiary hospital

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Objectives: Healthcare-workers are at the center of the pandemic, dealing with cases while being at risk of acquiring the infection themselves, causing work-related stress. Despite this, they continue reporting for duty. This paper aims to determine the factors that affect resilience of pediatric healthcare-workers in close contact with patients suspected with COVID infection and its association to sleeping disturbance during the first two years of COVID – 19 pandemic in a tertiary hospital in the Philippines.

Methodology: This is a cross-sectional study. Healthcare-workers who render bedside patient care for those suspected or with COVID-19 infection, not diagnosed with any mental health illness, and fit the inclusion criteria were chosen through purposive sampling and asked to answer questionnaires with demographic survey, BRS and PSQI tool.

Results: Among 89 participants, females were predominant (60.67%). Majority were in the 30-39 age group (44.94%) and are nurses (40.45%) or doctors (39.33%) who were single (76.40%). Many have normal resilience as measured from their BRS scores with an average PSQI per category equal to or exceeded 5.00. The correlation coefficient was at -0.338 (p-value 0.001) between the BRS and PSQI scores, indicating that a significant negative correlation exists between the two scores.

Conclusion: Normal resilience was reported in the majority of the healthcare-workers. All study participants had poor sleep quality as determined in the overall average PSQI score. A negative correlation between resilience and sleep quality was observed, denoting that poor sleep quality can be associated with lower resilience, and vice versa. However, temporality cannot be assumed with this study.

Keywords: *resilience, sleep disturbance, COVID-19, pediatric healthcare workers*

INTRODUCTION

The novel coronavirus disease (COVID-19) was officially reported in December 2019 in Wuhan, Hubei Province, China. [1] Since then, it has spread worldwide and many countries still suffer from high cases despite worldwide efforts to vaccinate the population to create herd immunity. Community quarantines were employed in hopes to decrease the rate of transmission all over the world [2] however, new variants are being discovered pushing incidence and transmission rates to increase despite the world's efforts to contain the virus. In the center of this pandemic are the healthcare workers who deal with the increasing number of cases and are at high risk of infection due to the nature of their work hence they experience high levels of work-related stress. Because of the ever-changing health protocols, there is heavy workload causing excessive fatigue, tension, and exhaustion.

[1] Despite this, there are still healthcare workers who chose to continue their work in the frontlines. This paper aims to identify the factors that affect resilience among pediatric healthcare workers in direct contact with patients suspected with COVID infection and its association with sleeping disturbance during the first two years of the COVID – 19 pandemic in a tertiary hospital in the Philippines.

Resilience is the ability of an individual to manage stress and handle difficulties. Stress is defined in this study as a biological and psychological response felt from confronting an event one deems to be harmful or incapable of overcoming. A stressor is the threat one perceives as the cause of the stress. Not everyone who suffers from adversity may have negative psychological effects, some are able to overcome misfortunes and adapt and one of the reasons why they are able to do so is because they are resilient. Resilience may vary depending on different variables like culture, ethnicity, values, environment, skills developed, etc. in every individual. Development of resilience mostly depends on what is needed to successfully thrive in one's environment or situation.[3] However, with the ever-changing health protocols, there is heavy workload causing excessive fatigue, tension, and exhaustion.[1] There are evidence that as one's resilience increases, they are less prone to have sleep disturbances. Resilient people are more patient and adapt better to circumstances which results to better sleep quality. Resilience is a positive indicator for physical and mental health and those with higher resilience have better sleep quality.[3] Based on research on previous outbreaks, there were reports of emotional and psychological distress in healthcare workers which led to increased risk of sleep disturbance.[4,5] A meta-analysis of 17 studies on healthcare workers in China regarding sleep disturbances and quality of healthcare workers during the COVID-19 pandemic concluded that sleep disturbances were common in healthcare workers and the there is a heavy mental burden on them during COVID-19 pandemic.[1] Poor sleep quality may decrease a person's attention span, decision-making ability, and work efficiency which may ultimately lead to poor response to an outbreak. Sleep disturbances include disorders of initiating and maintaining sleep, excessive somnolence, disorders of sleep-wake schedule, and dysfunctions associated with sleep.[6] A social media survey in the United States conducted for healthcare workers also revealed that they have poor sleep, some have insomnia, and over half reported burn out calling for sleep interventions for frontline healthcare workers.[7] In another study conducted in the Philippines, anxiety related to the COVID-19 pandemic was prevalent in the nursing workforce possibly affecting their well-being and work performance, and those with high personal resilience and good social and organizational support reported lower levels of anxiety and stress. [8]

There is a relationship between resilience and sleep quality. As resilience increases, there is better sleep quality in adults.[3] This study will measure the ability of the pediatric healthcare workers in a tertiary hospital in the Philippines to cope with stressful events like the COVID-19 pandemic and determine the factors that might affect their resilience.

Materials and Methodology

This research is a cross – sectional study. The target population is the group of pediatric healthcare workers in PCMC in direct contact with patients suspected and/or confirmed to have COVID-19 infection during the COVID-19 pandemic. In the said institution, not everyone works in direct contact with patients. Some are employed to do bedside care while others do not handle patients and perform solely administrative work. Among those who render patient care bedside, not everyone is in contact with those who are suspected or have COVID-19 infection. Only a select few are assigned to wards with patients who are suspected or infected with COVID-19 infection, i.e., isolation ward, triage, and/or emergency room. Only medical technologists, radiologic technologists, nurses, and doctors who render patient care bedside for those suspected or have COVID-19 infection previously or currently assigned at the COVID ward, triage, and/or ER from April 2020 until present were included. Those diagnosed with mental health illnesses, taking medications, and/or undergoing counseling for the past 6 months were excluded from the study.

The sample size was computed using the formula $n = \frac{Z^2 P(1-P)}{d^2}$ where n is the sample size, Z is the statistic corresponding to level of confidence which is 95%, P is expected prevalence obtained from a similar study which is 45.1% and d is the precision set at 5%. The total population in the institution to be tested which included all medical technologists, radiologic technologists, nurses, and doctors was set at 582. The calculated sample size needed for this study was 231 participants.

Data gathering became problematic because some healthcare workers did not agree to participate in this study while others had disclosed mental illnesses prior to answering the questionnaires and were immediately excluded. Due to the nature of the work, there was difficulty in collecting data from employees who did not go on duty during the time of collection, i.e., those who are on the night shift, since data collection was done only during the day. Out of the 582 total population set in the beginning, there is no data on how many healthcare workers render patient care bedside for those who are suspected or have COVID-19 infection previously or currently assigned at the COVID ward, triage, and/or ER from April 2020 until present. The total population set during the computation of the sample size may be more than the actual number of healthcare workers eligible to participate in the study. Hence, there was difficulty in meeting the said sample size. Identification of subjects was done through purposive sampling within the set data collection period.

The data was gathered by individually asking healthcare workers who fit the inclusion criteria and are willing to answer the questionnaires. They were chosen based on their eligibility according to the inclusion criteria set by the investigator. Once the participants consented in participating in the research, they were asked to answer a general demographic survey and two validated tools that will give the following information:

a) Demographic (age, sex, marital status, occupation, duration of exposure to COVID-confirmed patients)

b) BRS scores

c) PSQI scores

Those participants who did not disclose their mental illness prior to the data collection and answered that they have mental health problems and/or are taking psychotropic medications were excluded from the data processing and analysis.

The BRS has been validated through pretesting across different countries which showed that the tool is acceptable, reliable, and valid across nationalities, cultures, and socio-demographics. In studies done to review and validate resilience measurement scales, BRS tool was among the top 4 that scored high in the validation. The tool scored high on content validity, internal consistency, construct validity, reproducibility reliability, and interpretability among all resilience measurements.[9] This questionnaire has a Cronbach alpha of 0.71 which means that this tool's internal consistency is within the acceptable level of reliability. Pearson correlation of BRS was able to replicate the correlational direction and magnitude of other well-established scales. The confirmatory factor analysis indicated that with a two-factor structure, it met all criteria for a good model fit without correlating the error terms between items.[10] It is in the public domain and may be used in research as long as the authors are properly cited and acknowledged in the paper.

The PSQI tool has been validated and is accepted as a screening tool worldwide for sleep disturbance. It has a sensitivity of 89.6% and specificity of 86.5% and has been translated into 48 languages. It has an internal consistency and reliability coefficient (Cronbach's alpha) of 0.83 for its seven components.[11]

Since the expected participants in this study are healthcare workers in a tertiary hospital i.e., nurses, radiology technologists, medical technologists, and doctors, who are at least college graduates who are expected to have basic English literacy, there is no need to translate both tools into the native language. Although self-administered questionnaires can be empowering, they may also convey inaccuracy when it comes to understanding what is written. Participants may also purposely modify their responses during the data collection knowing that they are part of a study which is called the Hawthorne effect. Such hindrances were addressed by establishing rapport with the participants and being present for possible questions during the data collection.

Upon processing and analysis of the data collected from the questionnaires, those participants identified to have poor resilience with sleep disturbance were informed and advised to consult with a specialist who can help them address their problems. Results from the questionnaire answered by the participants were kept at a designated place for storage, kept confidential, and will be disposed of after 5 years from the publication of the research.

The study was presented to the Philippine Children's Medical Center Institutional Review Board, Ethics Committee and was only pursued upon their approval. Data Privacy Act was implemented in handling all collected data. All soft copy files are password protected and saved in a separate USB which only the researcher has access to, to ensure data privacy and will be deleted and disposed of after 5 years. Each participant was assigned control numbers. After analyzing the data and participants with significant findings have been contacted, the paper-based questionnaires will be kept in an allocated place and will be kept for 5 years then shredded afterward.

Microsoft Excel was used for data entry and documentation using tables. Quantitative variables were summarized as prevalence, means and standard deviation. Using SPSS version 26, one-way ANOVA was done to explore the difference in resilience among different categorical variables, i.e., age, sex, marital status, and occupation while the association between the sleep quality and resilience of pediatric healthcare workers was measured using the Pearson correlation. The level of significance was set at 95%.

RESULTS

A total of 89 participants were included in the study. The following tables describe the results obtained from these participants. From the profile of pediatric healthcare workers, a predominance of female participants was observed, which was 54 or 60.67% of the overall study population. Most of the participants also were in the 30-39 age group (40 out of 89 participants, 44.94%), and a considerable percentage of the study population included nurses (36 out of 89 participants, 40.45%) and doctors (35 out of 89 participants, 39.33%). Most were also single (68 out of 89 participants, 76.40%).

Table 1. Profile of Pediatric Healthcare Workers in direct contact with patients suspected with COVID-19 infection at PCMC

Characteristics		Frequency (%)
Sex	Male	35 (39.33)
	Female	54 (60.67)
Age	20-29	39 (43.82)
	30-39	40 (44.94)
	40-49	3 (3.37)
	50-59	7 (6.74)
	60-69	1 (1.12)
Occupation	Medical Technologist	6 (6.74)
	Radiologic Technologist	12 (13.48)
	Nurse	36 (40.45)
	Doctor	35 (39.33)
Marital Status	Single	68 (76.40)
	Married	21 (23.60)

In Table 2 are the disaggregation of resilience score categories across the demographic variables. Most of the study participants have normal resilience across categories as measured from their BRS scores. From the breakdown of BRS score classifications per category of the demographic variables, females are more resilient with 36 (62.07%) participants having normal resilience and 7 (41.18%) people having high resilience. Among the age groups, those with ages 30-39 years old had the most normal resilience (25 out of 58, 43.11%) and high resilience (12 out of 17, 70.59%). According to occupation, nurses have the most persons with normal resilience (24 out of 58, 43.1%) and high resilience (9 out of 17, 52.94%). Majority of those who had normal resilience were single with 46 out of 58 persons (72.41%) and 13 out of 17 (76.47%) persons with normal resilience were also single.

Breaking down the results of the PSQI and BRS by the demographic variables, it is generally observed that PSQI was generally poor among all categories of the demographic variables, as the average PSQI per category which ranged from 5.00 to 7.60. Higher average PSQIs were seen in the male sex (7.09), age of 30-39 (7.6), were nurses(7.58), and were single(7.04). Of these average PSQIs, the average score of the category of those aged 30-39 had the highest average PSQI at 7.60 with a standard deviation of 3.68.

Table 2. Breakdown of results for each category based on their answers in the tools

Variables	Resilience, n (%)			
	Low	Normal	High	Ave PSQI (SD)
Sex				
Male	3 (21.43)	22 (37.93)	10 (58.82)	7.09 (4.69)
Female	11 (78.57)	36 (62.07)	7 (41.18)	6.83 (2.79)
Age				
20-29	10 (71.43)	24 (41.38)	5 (29.41)	6.59 (3.70)
30-39	3 (21.43)	25 (43.10)	12 (70.59)	7.60 (3.68)
40-49	---	3 (5.17)	---	6.33 (4.04)
50-59	1 (7.14)	5 (8.62)	---	5.33 (2.80)
60-69	---	1 (1.72)	---	5.00 (---)
Occupation				
Med.Tech.	1 (7.14)	5 (8.62)	---	5.17 (3.37)
Rad.Tech.	1 (7.14)	8 (13.79)	3 (17.65)	6.00 (4.77)
Nurse	3 (21.43)	24 (41.38)	9 (52.94)	7.58 (3.49)
Doctor	9 (64.29)	21 (36.21)	5 (29.41)	6.89 (3.36)
Marital Status				
Single	13 (92.86)	42 (72.41)	13 (76.47)	7.04 (3.51)
Married	1 (17.14)	16 (27.59)	4 (23.53)	6.57 (4.08)

Pearson correlation was run to determine the relationship between the PSQI and BRS scores of the study participants. The correlation coefficient was calculated at -0.338 with a p-value of 0.001, indicating that a significant, negative, but weak correlation exists between the two scores. This indicates that poor sleep quality (indicated by a high PSQI score) is associated with lower resilience (indicated by a lower BRS) in the context of the study population.

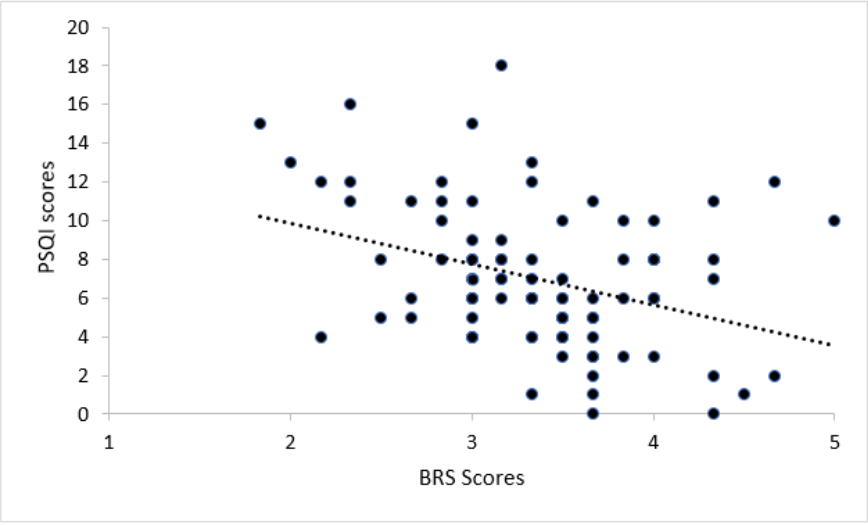

Figure. Pearson Correlation Coefficient of results showing linear correlation between BRS and PSQI scores.

Lastly, an analysis of variance (ANOVA) test was done to determine if there are any significant differences between the categorical variables which can affect sleep quality (measured by the PSQI) and resilience (measured by the BRS). From the F and p-values generated from the analysis, no statistically significant differences were found between groups for each category of the variables for which the test was run since all p-values were more than 0.05.

Table 3. Analysis of Variance (ANOVA) of factors which may affect sleep quality and resilience

Factors	BRS		PSQI	
	F	p-value	F	p-value
Age	2.123	0.085	1.161	0.334
Sex	0.001	0.971	0.763	0.385
Occupation	1.451	0.617	1.330	0.082
Marital Status	2.168	0.145	0.002	0.968

Discussion

Among the participants, there was predominance of females, aged 30-39 years old, nurses, who are single. These percentages are the same with the results of surveys in the world showing that more females are employed in the healthcare business.[12] According to Philippine data from 2019, there were more females aged less than 40 years old nurses in the healthcare profession industry which is parallel with the results of this paper.[13] The marital status predominant which is single, may be because majority of the participants are on the younger side. Also, there has been an increase in the number of healthcare professionals seeking higher paying jobs abroad.[14] The older nurses may have already migrated to a different country and may contribute to the reason there are younger participants in this study.

Resilience has been a topic of focus for healthcare workers during the COVID-19 pandemic. A systematic review of evidence has found that there are factors that affect resilience among healthcare workers, particularly work engagement, social support, and anxiety or depression [15]. The study also found moderate resilience scores for healthcare workers around the world, which was also validated through the findings of this study. Normal resilience score was the majority in the study participants. The same results of normal resilience were seen in the data from the predominantly female, single, aged 30-39 nurses which may also be because they were also most of the participants.

Resilience can also depend on social resources to thrive under different circumstances. Therefore, a study coined the term “national resilience” to note that resilience can also occur as a collective effort or a country-wide phenomenon [16]. In this study which measured and determined the antecedents of national resilience in Filipino adults during the COVID-19 pandemic, older age, religious beliefs, and holding a more right-wing political attitude tend to have a higher level of perceived national resilience, for the following reasons: (1) older individuals had many experiences which allowed them to have greater confidence in the capacity of the nation to recover amid crisis; (2) religion is a stronghold that Filipinos consider especially during times of personal or collective crisis; and (3) having a more conservative political view can make one more responsive and attuned to negative stimuli. [17] Generally, Filipinos are among the most resilient healthcare workers which may be due to cultural

[17] Generally, Filipinos are among the most resilient healthcare workers which may be due to cultural, social and based on political and religious beliefs which may be the reason why there is a predominance of participants with normal to high level of resilience in this study. A higher level of national resilience is strongly linked to lesser psychological distress in the country's population [17], and it is for this reason that coping strategies to boost the resilience not only of healthcare workers but of the totality of the national population can be considered by policymakers.

Preserving the resilience of healthcare workers especially during times of distress such as the COVID-19 pandemic should be highly considered in health, safety, and wellness programs in healthcare facilities. An abundance of studies emphasized the need for healthcare worker leaders to recognize that these workers need to be more widely understood and that restricting organizational resilience can lead to adverse patient safety impacts and worsen staff retention [18]. A study recommended strategies for supporting the mental well-being and resilience of healthcare workers especially during distressing times such as the COVID-19 pandemic [19], including the development of a modern-day hierarchy of needs to primarily support the physical and psychological needs of the healthcare workers before finally addressing and supporting patient and community needs, allowing healthcare workers to seek psychological help without stigma or repercussion, development of individualized emotional support plans, limiting shift work, and the implementation of training and education strategies on mental health awareness in healthcare facilities.

The study findings also demonstrated how sleep quality can be a factor which can be independently associated with resilience in the healthcare worker population. In healthcare workers, a generally poor quality of sleep can be observed as they also work in shifts, which disrupts the normal circadian rhythm. In fact, a study on the impact of shift work on sleep quality among healthcare workers mentioned that working during consecutive night shifts, consecutive day shifts, and between evening and day shifts led to more restricted sleep schedules [20], consequently adversely affecting their sleep quality.

Working during the COVID-19 pandemic is also shown to have a negative impact on sleep quality of healthcare workers, as mentioned in several studies which also used the PSQI for their scoring tool. In these studies, poor sleep quality was also found to be positively correlated with anxiety [21, 22] and a higher risk of developing anxiety-related symptoms [23, 24]. These studies explain that reasons for poor sleep quality among healthcare workers during the pandemic can be attributed to post-traumatic stress disorder (PTSD), depression, anxiety, high workload, and stress-induced sleep problems, which has been the common experience of all healthcare workers in caring for COVID-19 patients as collectively mentioned by these studies.

We showed that poor sleep quality is also associated with poor resilience. This is further proven by the results of the Pearson coefficient run using the data collected which revealed that a negative but weak correlation exists between the two scores used to evaluate each participant. Moreover, regardless of the demographic characteristics, sleep quality is still poor in the healthcare worker population.

Based on the results of the analysis of variance done, there was no statistically significant differences found between groups for each category of the variables and the resilience of a healthcare worker.

Conclusion

This study was a single-center cross-sectional study which revealed that there is a predominance of females, age of 30-39, and the nurse and doctor occupations were observed. Normal resilience was also reported in majority of the healthcare workers. All the study participants had poor sleep quality as determined in the overall average PSQI score. A negative correlation between resilience (as measured by the BRS) and sleep quality (based on PSQI scores) was observed, which denotes that poor sleep quality can be associated with lower resilience, and vice versa. However, temporality cannot be assumed in this study.

Healthcare program planners can consider the addition of coping strategies as well as training and education strategies on increasing the resilience of healthcare workers, since more resilient workers are better equipped in delivering the optimal quality of healthcare services to their patients. Improving sleep quality among the workers in this study population is also recommended for the hospital management, to consider limiting shift work hours, and developing more equitable work rotation schedules so that they can compensate for the high restriction in their sleep schedules.

Future studies can expand by doing the same objectives in healthcare workers in different settings, to better see the dynamicity of resilience as a multi-faceted phenomenon, and how sleep quality can be affected by different environmental and socio-demographic conditions. A multi-center study may also be done to increase the number of participants and possibly apply stratification of the samples. A different study design of a larger scale may also be employed to be able to establish temporality between resilience and sleep disturbance.

A limitation of this study is the lack of randomized sampling. In using purposive sampling, the researcher was only able to interview subjects who were on duty at a specific time that was convenient for the interviewer to perform data collection. Because the researcher did not meet the sample size, stratification of the participant's answers was not possible. Enlarging the scope of this paper to a multi -center study might help. This paper, likewise, is unable to remove the factor of the nature of the work – with all the participants going on night duties which may cause sleep disturbance all on its own. Another limitation is that the research design cannot establish temporality between sleep disturbances and resilience in healthcare workers. This may be a recommendation for another possible research topic.

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ARTICLE

Efficacy of intravenous Lidocaine in controlling emergence agitation in children for surgery under Sevoflurane anesthesia: a meta-analysis

Niña Kashka E. Pamintuan, & Ana Maria de la Cerna

BACKGROUND: Emergence delirium is a state of mental confusion and agitation after wakening from anesthesia that may result in traumatic injuries to the child. Limited drugs have been studied or used to prevent this occurrence.

OBJECTIVE: To determine the efficacy and safety of intravenous lidocaine in controlling emergence agitation (EA) in children undergoing surgeries done under general anesthesia compared to placebo or other intravenous anesthetics.

METHODOLOGY: This study is a meta-analysis, where published articles were obtained using PubMed, Cochrane Library, Clinical Trials, and Google Scholar up to August 2022. The primary outcome measure includes incidence of emergence delirium while secondary outcomes are postoperative pain and adverse effects comparing lidocaine and other intravenous drugs. The latter includes nausea and vomiting, untoward airway events and local anesthetic toxicity (LAST). Review Manager 5.4 was used for statistical analysis.

RESULTS: There were a total of 6 articles included for quantitative and qualitative analysis. The overall incidence of emergence agitation (RR=1.03, 95% CI [0.50, 2.13], P=0.94) and adverse events were higher in the Lidocaine group, although the differences were not significant. Subgroup analysis by comparator showed significant increased risk of developing EA with Lidocaine compared to other intravenous drugs (RR=2.06, 95% CI [1.32, 2.32], P=0.002). The risk for developing postoperative pain is decreased with Lidocaine compared to placebo and other drugs.

CONCLUSION: Intravenous lidocaine given to children undergoing general anesthesia with sevoflurane increased their risk for emergence delirium, compared to both placebo and other intravenous anesthetics.

KEYWORDS: *lidocaine, emergence agitation/delirium, children, pediatric, anesthesia, sevoflurane anesthesia, general anesthesia*

INTRODUCTION

First described in the early 1960s, emergence agitation (EA), also referred to as emergence delirium (ED) or emergence excitement is defined as a state of mental confusion, agitation and disinhibition particularly upon wakening from anesthesia [1]. This manifests as hyperexcitability, crying, restlessness, self-injury and hallucinations despite attempts to reorient the patient through verbal or other means [2, 3].

Its incidence varies from 20-80%, more commonly seen in children aged 2-7 years old [4, 5] who undergo painful surgical procedures under general inhaled anesthesia [5]. Suggested risk factors include rapid awakening in an unknown environment, agitation during anesthetic induction, preoperative anxiety, airway obstruction, environmental disorders, use of pre-anesthetic medication, anesthetic technique, type of anesthetic used (volatile, intravenous) and postoperative pain [6].

This may last from a few minutes to as long as thirty minutes and may resolve spontaneously. However, though short in duration, it may cause a great deal of stress for both parents and healthcare personnel. Emergence agitation may result in traumatic injuries to the child, pulling out of intravenous lines and drains, self-extubation and emotional trauma for the caregiver [7]. There is limited literature on the pathophysiology of emergence agitation in children. Some say that it is because of increased sympathetic tone and prolongation of the excited state during anesthesia recovery [13]. Others say that it is due to differential recovery rates in brain function due to differences in clearance on emergence [13]. Elevated lactate and glucose concentrations in the parietal cortex due to sevoflurane anesthesia, and the occurrence of clinically silent sevoflurane-induced epileptogenic activity have also been proposed [13]. A functional MRI was used by the team of Bouxveraoux et al, to explain the mechanisms underlying the alteration of consciousness during anesthesia [15,16]. It was found that during emergence from general anesthesia, thalamocortical connectivity in sensory networks, and activated midbrain reticular formation are preserved. However, delayed recovery of subcortical thalamoregulatory systems could contribute to defects in cortical integration of information, which could lead to confusion or an agitated state [9, 15]. Thus, various medications namely, midazolam, ketamine, alpha 2 agonists and propofol, have been studied to reduce the incidence of this complication. Of these, propofol is the preferred drug for the prevention and treatment of emergence agitation [13]. According to the study of Auoad et. al with children, 1 mg/kg propofol at the end of surgery after discontinuation of sevoflurane decreases the incidence of agitation [17]. However, propofol, along with the mentioned drugs, poses some undesirable side effects including delayed postoperative awakening, hypotension, bradycardia and asystole [13].

Lidocaine is a tertiary amine derived from xylidine. This drug is commonly used for local anesthesia, often combined with epinephrine [20]. It can also be given intravenously for advanced airway management as an adjuvant to tracheal intubation by obtunding the hypertensive response to laryngoscopy [20]. Other uses of lidocaine besides reduction in pain are reduction of nausea, ileus duration, opioid requirement and length of stay in hospital [14]. Aside from minimizing the patient's pain on emergence by sodium channel blockade, Lidocaine diminishes the nociceptive signaling to central nervous system through inhibition of G-protein mediated effects and reducing sensitivity and activity of spinal horn neurons particularly targeting glycine and NMDA receptor-mediated [14]. Additionally, in a journal by Dunn et. al, systemic lidocaine blocks excitatory responses in wide dynamic range neurons in the rat spinal cord through a mechanism probably involving strychnine-sensitive glycine receptors [14]. Its other mechanism of action includes blockade of muscarinic, nicotinic and dopaminergic receptors, enhancement of gamma-aminobutyric acidinergic pathways, inhibition of opiate receptors, anti-inflammatory properties and inhibition of release of substance P, a potent NK1 agonist [18, 19]. Toxicity from perioperative lidocaine is exceedingly rare [14]. Among the dreaded adverse effects of the provision of local anesthesia is local anesthetic systemic toxicity (LAST) manifesting as cardiac and central nervous system symptoms. Drowsiness was reported in 2 of 18 patients who received perioperative lidocaine infusion for abdominal surgery.

There are anecdotal reports that patients who receive perioperative lidocaine appear to be sleepier during emergence from anesthesia. Also, it is thought that the apparent delayed awakening results from patients being less responsive to the endotracheal tube [14]. Perioperative lidocaine has been shown not to affect time to PACU discharge [14]. These findings are supported by the retrospective study by Both et. al. It explores the use of perioperative intravenous lidocaine administration in children undergoing laparoscopic procedures. This analysis did not reveal any adverse effects in pediatric patients receiving intravenous lidocaine for surgeries done under general anesthesia [9]. Given its superior safety profile compared to older local anesthetic agents [20] and easy accessibility, lidocaine shows immense potential for reduction of emergence agitation. Several clinical trials have shown that Lidocaine can significantly reduce the incidence of emergence agitation in children who underwent surgery under general anesthesia [8, 9], while others state it has no effect [10,11]. Other studies have used it as an adjunct for prevention of emergence agitation and showed favorable results [4, 12]. To date, no meta-analysis has been conducted with regards to this topic.

The general objective of this study is to determine the efficacy and safety of intravenous lidocaine in controlling emergence agitation in children undergoing surgeries done under general anesthesia compared to placebo or other intravenous anesthetics. Specifically, to determine whether there is a difference in the incidence of emergence agitation, postoperative pain and adverse events among pediatric surgical patients done under general anesthesia via sevoflurane given intravenous lidocaine versus placebo or other intravenous anesthetics.

The adverse events that were considered include nausea and vomiting, untoward airway events and LAST.

Materials and Methodology

This meta-analysis followed the recommendations of the PRISMA-P 2020 statement and Cochrane Collaborations for systematic reviews and meta-analysis. Included journals were obtained through PubMed, Cochrane Library, Clinical Trials and Google Scholar from August 2022. The search terms were “randomized controlled trial”, “clinical controlled trial”, “Lidocaine”, “emergence agitation/ delirium”, “adjuvant”, “children”, “pediatrics”, “anesthesia”, “general anesthesia” and “sevoflurane anesthesia”.

The studies reviewed were randomized controlled trials that assessed the safety and effectiveness of intravenous lidocaine in decreasing the incidence of emergence agitation among children of any age group under 18 years of age with American Society of Anesthesiologist (ASA) functional classification I-II undergoing surgery under general anesthesia via sevoflurane. These include lidocaine dosed at 1-2mg/kg intravenous bolus either at induction or prior to extubation which may be followed by an infusion at 1.5mg/kg/hr or not. This intervention was compared to a placebo or other intravenous anesthetics. Studies wherein lidocaine given through local or aerosolized, other forms of general anesthesia and articles that included children with central nervous system, hepatic or renal dysfunction, developmental delay or preceding psychological or psychiatric disorders were excluded. The primary outcome measure is the incidence of emergence agitation assessed using any emergence agitation scoring

scale such as the PAED scale or other 4- or 5- point The secondary outcome measures are as follows: 1) postoperative pain scores using scoring tools for pain, and 2) adverse events including nausea and vomiting, untoward airway events and LAST.

The presence of emergence agitation is defined by: a) Cravero 5-point emergence agitation scoring system, with five steps from obtunded and unresponsive to wild thrashing behavior requiring restraint [22]. A score of more than 4 is indicative of emergence agitation; b) Cole 5-point scale with five categories: asleep, awake and calm, irritable or consolable crying, inconsolable crying, and severe restlessness [4]. A score of more than 4 is indicative of emergence agitation; c) PAED score with 5 criteria scored using a 5-point scale. The maximum achievable score is 20 [22]. A score of more than 10 is indicative of emergence agitation; and d) WATCHA 4 -point scale which is a simpler tool to use in clinical practice and may have a higher overall sensitivity and specificity [22]. A score of more than 4 is indicative of emergence agitation.

On the other hand, the presence of postoperative pain is defined by the following pain scoring systems: a) Children's Hospital of Eastern Ontario pain scale (CHEOPS) which is an observational scale for measuring postoperative pain in children aged 1-7 years. This scale includes six categories of pain behavior: (cry, facial, verbal, torso, touch, and legs). A score ranging from 0 to 2 or 1 to 3 is assigned to each activity and the total score ranges between 4 and 13 [23]. A score of more than 6 will denote pain in the child; b) objective pain scale (OPS) incorporates four pain behaviors (crying, movement, agitation, and verbalization) and blood pressure change. Each of these categories is scored from 0 to 2 [23]. A score of more than 6 will denote pain in the child; and c) children and infants postoperative pain scale (CHIPPS) is used for those less than 6 years old or unable to understand the visual pain scale. A score of more than 4 will denote pain in the child.

Data was extracted by two authors and cross-checked by another independent author for accuracy and completeness. Assessment for risk of bias was performed using the Review Manager program. The following biases were assessed: selection bias, performance bias, detection bias, reporting bias, attrition bias, and other author-reported bias. Each criterion was assessed as having low, unclear, or high risk for bias. Risk of bias assessment was performed independently by two review authors. Conflict resolution was done through consensus. A third reviewer who is a content expert was called upon if disagreements are not resolved.

Review Manager (RevMan) 5.4 was used for statistical analysis. Risk ratio was used to compare the incidence of emergence delirium, postoperative pain and adverse effects between Lidocaine versus placebo and other drugs. Under adverse effects, the incidence of nausea and vomiting, untoward airway events and LAST between the said comparators were included. Subgroup analysis was performed for incidence of emergence delirium by comparator and dose. Random effects model was used as there was substantial heterogeneity, graded as I^2 of >60%, seen in the groups.

Results

A total of nine hundred eighty-four (984) studies were identified through electronic databases and hand searches (Figure 1). One hundred forty-five studies were included in the title and abstract screening after removing duplicates. Of these, only twenty-two studies met the criteria for full-text review. From these twenty-two studies, fourteen were excluded: six studies had incomplete data, one study had no available full text article and seven studies had different routes of administration of comparator drug. In all, a total of six studies were included for meta-analysis.

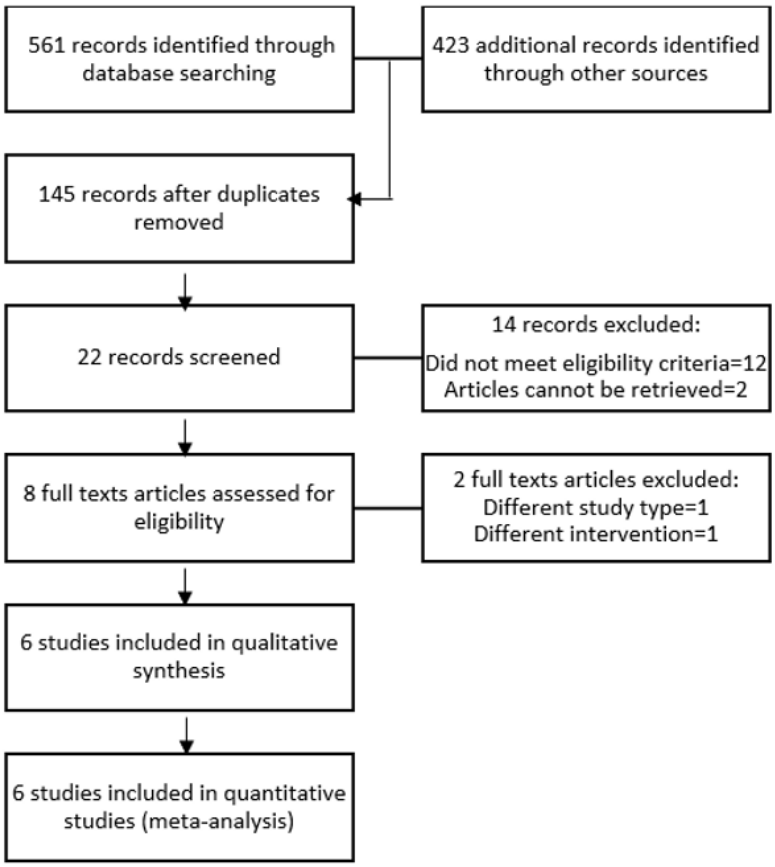

Figure 1. Prisma Flow Diagram

Description of the included studies

Six (6) randomized controlled trials published from 2005 to 2022 that assessed the effectiveness of intravenous lidocaine in decreasing the incidence of emergence agitation postoperatively, compared with placebo and other intravenous drugs such as Propofol, Esmolol and Magnesium sulfate in children with age range of 2 to 14 years, classified ASA I – II under general anesthesia were included. Table 1 shows the studies' population, sample size, intervention and comparator, primary and secondary outcomes.

Table 1. Characteristics of Included Studies (n=5)

Primary Author	Year	N	Type of study	Age , ASA status, type of surgery	Intervention (Dose and Administration)	Comparator	Primary Outcome	Secondary Outcome
Jang, Y	2005	85	RCT	2-7 years old; ASA 1 and 2; Lower abdominal surgery	1.5mg/kg Lidocaine (over 30-45s) 5 minutes before discontinuation of anesthetic	Saline	EA score (5-point score by Cravero; >4)	CHEOPS, modified Aldrete postanesthesia score
Lee, J	2007	120	RCT	3-9 years old; ASA 1 and 2; tonsillectomy and adenoidectomy	1% 1mg/kg or 2% 2mg/kg at 1 minute (over 10s) after beginning of spontaneous respiration (before extubation)	Saline	Arousal Excitement (5 point scale by Cravero; >4)	Sedation score (UMSS>2), incidence of cough
Echevarria, G	2018	92	RCT	2-12 years old; ASA 1 and 2	IV lidocaine (1.5 mg/kg intravenous lidocaine over 5 min followed by 2 mg/kg/h) prior to intubation	Saline	POV	EA (WATCHA scale > 3), Time to extubation, postop pain, plasma concentration
Ji, J	2019	84	RCT	3-9 years old, ASA 1 and 2; Strabismus surgery	Lidocaine 1.5mg/kg after the gas was turned off and the patient started to move voluntarily	Esmolol 0.5mg/kg; Saline	Cole 5 point score (EA) >4	Objective pains score (OPS) and RASS
Manouchehrian, N	2022	102	RCT	3-14 years old; ASA 1 and 2	At the end of the surgery, two minutes before endotracheal extubation, 2% Lidocaine 1mg/kg	Propofol 0.5mg/kg	Laryngospasm	Agitation nausea and vomiting, shivering
Manouchehrian, N	2022	62	RCT	3-14 years old; ASA 1 and 2	After intubation, 2% Lidocaine 1mg/kg	Magnesium sulfate 15mg/kg	Laryngospasm	Agitation nausea and vomiting, agitation, sedation score

Five (5) studies were assessed as having low risk of bias and one (1) study was assessed as having unclear risk/some concerns mainly due to unspecified information on allocation concealment (Fig 2).

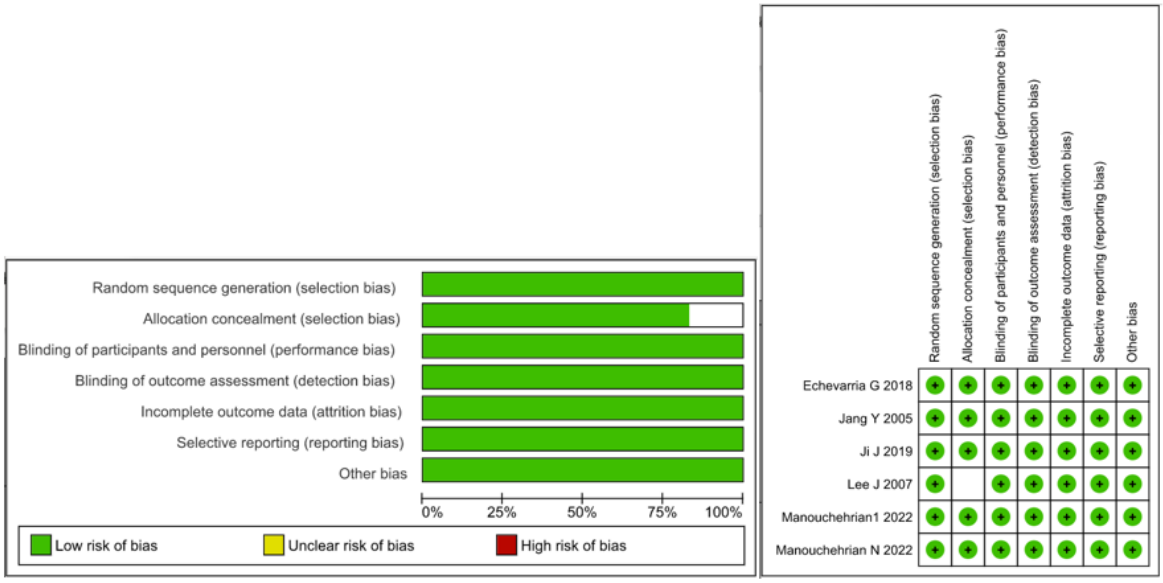

Figure 2. Cochrane risk of bias assessment.

Effect of Interventions

1. Incidence of Emergence Agitation

Data for the incidence of emergence agitation were available for all six (6) studies. There was a total of five hundred forty-three (543): two hundred seventy-three (273) patients in the lidocaine group and two-hundred seventy (270) patients in the comparator group. Forest plot showed increased risk of developing EA in patients given Lidocaine compared to comparators (RR=1.03, 95% CI [0.50, 2.13], P=0.94) however, not statistically significant. Considerable heterogeneity was observed when these studies were pooled (□2= 34.1, I2=86%, P<0.00001) (Fig 3).

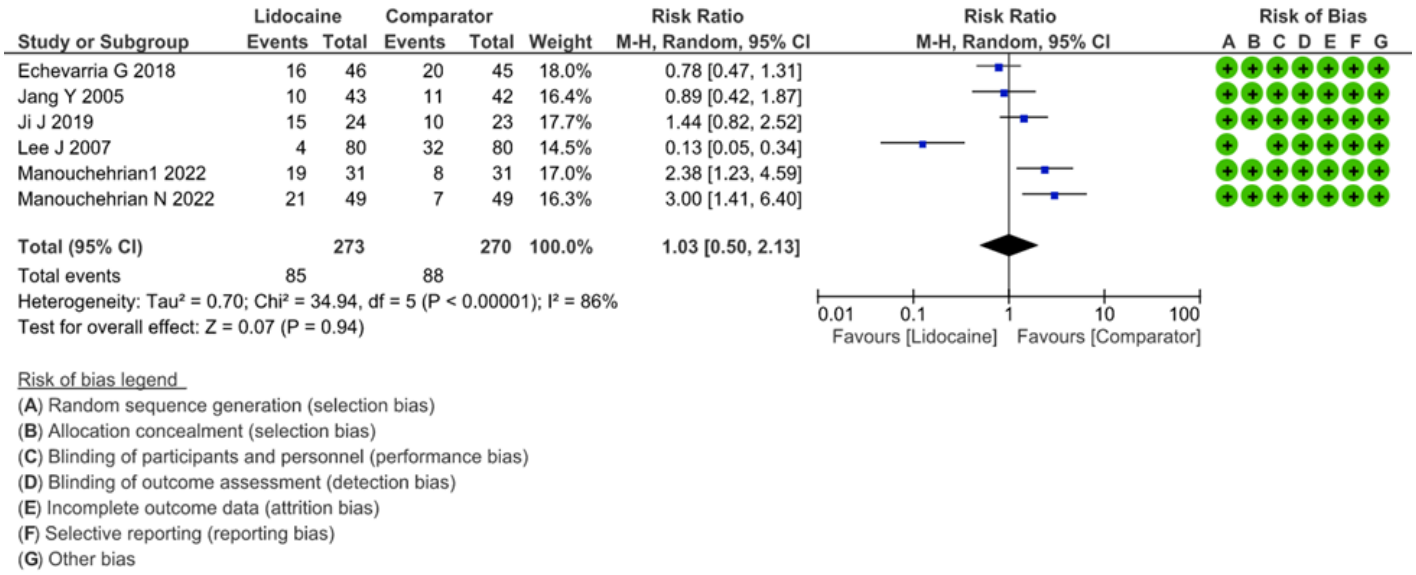

Figure 3. Incidence of Emergence Agitation (EA): Lidocaine vs. Comparator

a. Subgroup Analysis by Comparator

Differing types of comparators can influence the treatment effect [10, 11]. Subgroup analysis between placebo vs other intravenous anesthetics, namely Propofol, Esmolol, and Magnesium Sulfate. The test for subgroup differences yielded a $p<0.05$, hence significant. No significant difference was seen in the incidence of ED with the use of Lidocaine vs placebo. On the other hand, three studies showed favor to comparators. There was twice the increased risk of developing ED in the Lidocaine group vs comparators (RR=2.06, 95% CI [1.32, 2.32], P=0.002). Moderate heterogeneity was observed but not significant (χ^2=2.58, I2=30%, P=0.24) (Fig 4).

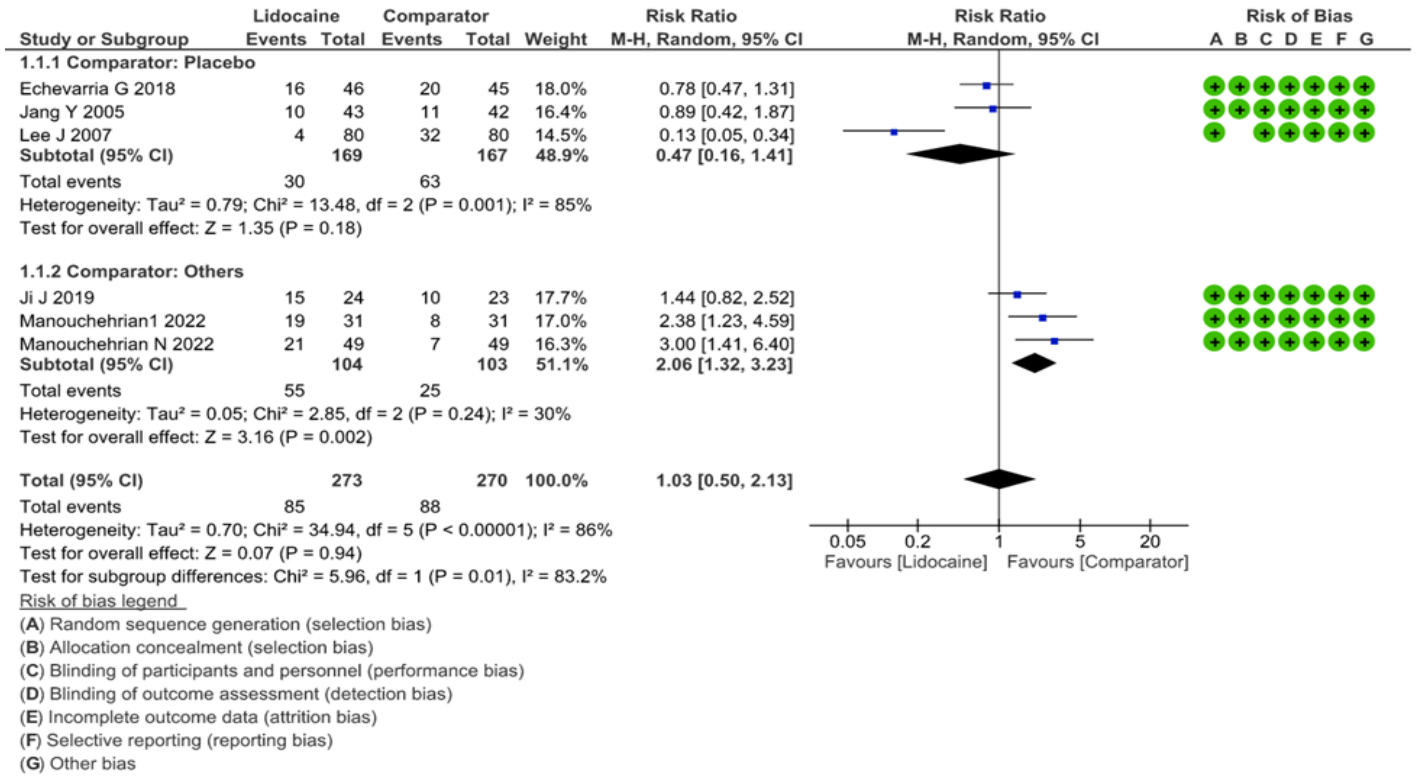

Figure 4. Incidence of Emergence Agitation (EA) by Compara-

b. Subgroup Analysis by Dose

Multiple studies have used different doses of Lidocaine to determine if it will decrease EA, however, conflicting results were found [10]. Hence, we did a subgroup analysis of differing dose of Lidocaine. The groups were divided into two: dose of $\leq$1.5mg/kg which included three studies and dose of >1.5mg/kg which included two studies. These cut off doses of intravenous lidocaine were based on the study of Both, et. al on pediatric patients done in 2018 (9).

Forest plot shows the mean effect of pooled trials was in favor of Lidocaine for both doses (Overall RR=0.90, 95% CI [0.46, 1.79], P=0.30) (Figure 6). Due to significant substantial heterogeneity, there was contradicting mean effect in each dose. It was observed that less than or equal to 1.5mg/kg dose of Lidocaine had increased risk of developing EA (RR=1.22, 95% CI [0.58, 2.55], P=0.60) while greater than 1.5mg/kg dose of Lidocaine showed a decreased risk of developing EA (RR=0.25, 95% CI [0.01, 4.41], P=0.35). These

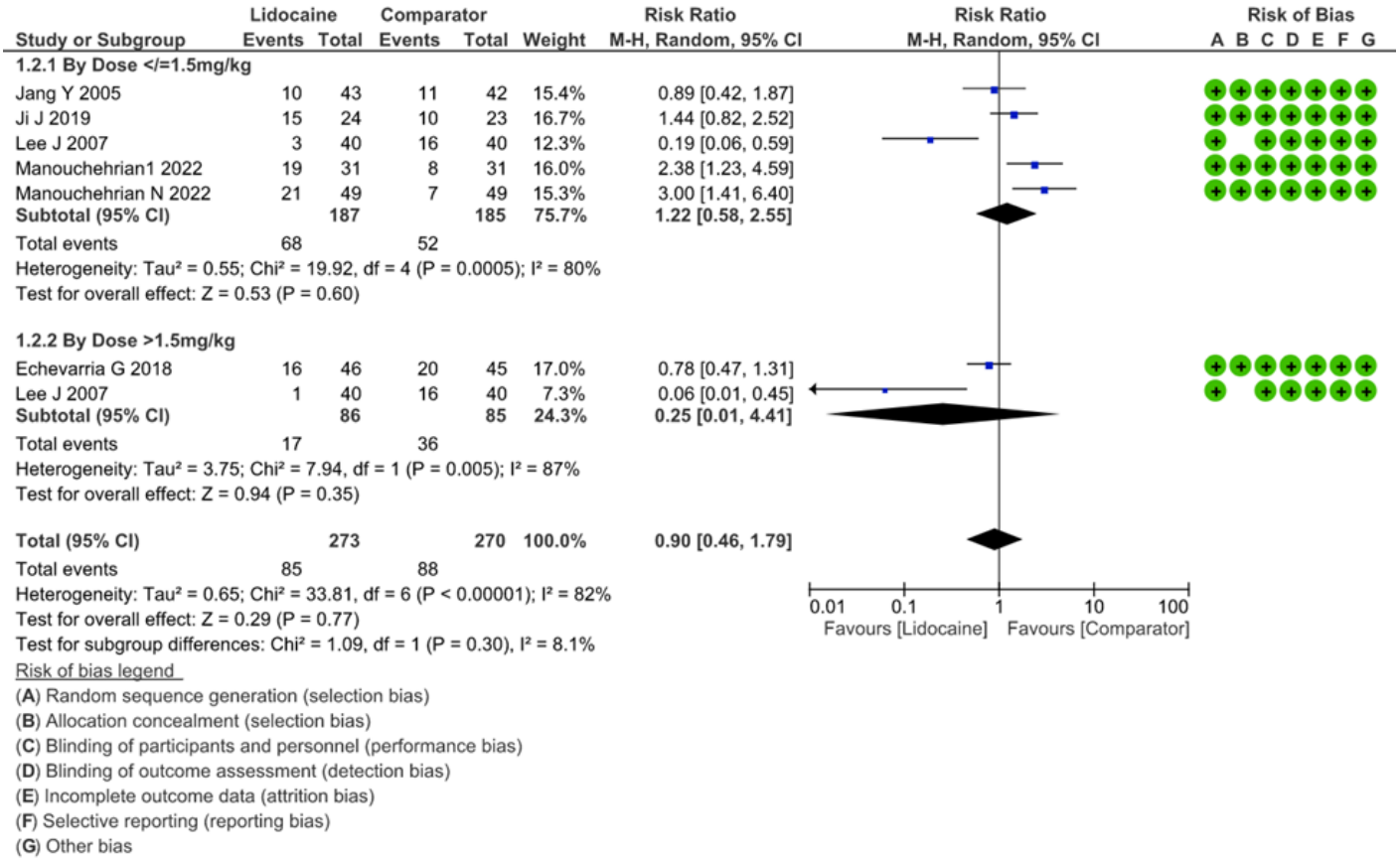

Figure 5. Incidence of Emergence Agitation (EA) by Dose

2. Incidence of Postoperative Pain

Three (3) studies compared the incidence of postoperative pain in children with the use of Lidocaine vs comparators. These studies showed that there were fewer episodes of postoperative pain with the use of Lidocaine compared to placebo and other drugs (Jang 2005: RR=0.78, 95% CI [0.42-1.47], Ji 2019 RR=1.05, 95% CI [0.62-1.76]. However, the results were not statistically significant (Fig 6).

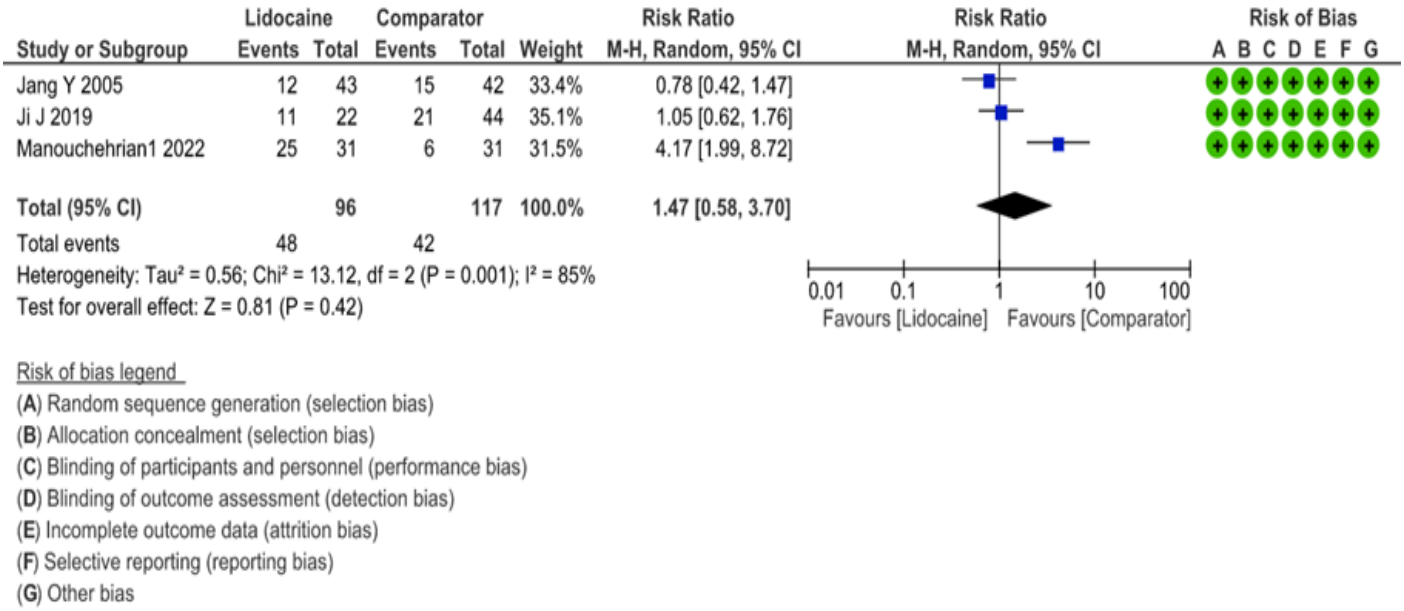

Figure 6. Incidence of Postoperative Pain: Lidocaine vs Comparators

3. Incidence of Adverse Effects

Five (5) studies had data on adverse events with the use of Lidocaine compared to other drugs. Forest plot shows that the use of Lidocaine increased the risk of incidence of adverse effects compared to placebo and other comparators (RR=1.21, 95% CI [0.39, 3.75], P=0.74). This was, however, not statistically significant. Substantial heterogeneity was also seen in this group which was significant (□2=47.95, I2=94%, P<0.00001) (Fig 7).

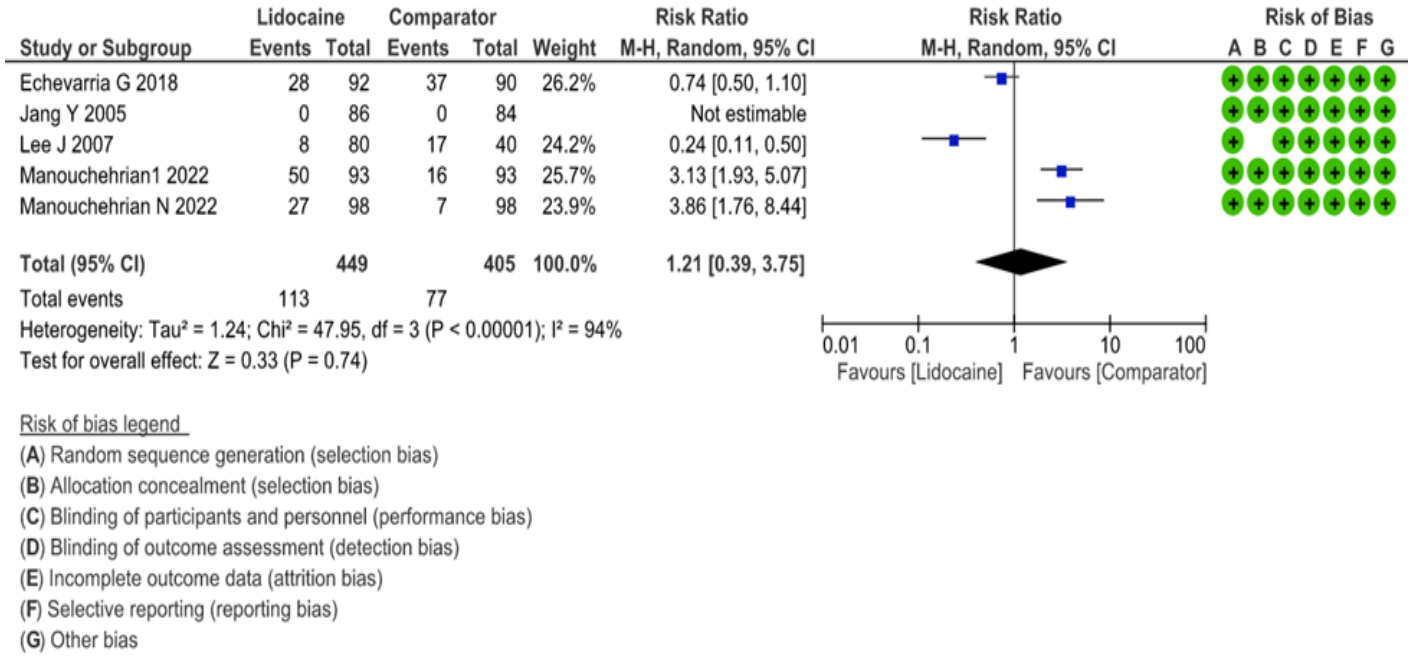

Figure 7. Incidence of Adverse Effects: Lidocaine vs Comparators

Figure 8 showed the breakdown of the mean effect per adverse effect type. The overall effect showed that there was an increased risk of developing adverse effects with the use of Lidocaine (RR=1.49, 95% CI [0.62, 3.57], P=0.85).

Four (4) studies noted the incidence of nausea and vomiting in children if Lidocaine was used compared to placebo and other drugs. Subgroup 1.4.1 showed there was an increase in the likelihood of developing nausea and vomiting from the use of Lidocaine compared to other comparators (RR=1.73, 95% CI [0.52, 5.79], P=0.37). There was also a note of significant substantial heterogeneity in this group (□2=22.41, I2=91%, P<0.00001).

Three (3) studies mentioned untoward airway events, particularly laryngospasm. This subgroup (1.4.2) still favors comparators as there is an increased likelihood of developing untoward airway events with the use of Lidocaine (RR=1.37, 95% CI [0.17, 10.83], P=0.76). Significant substantial heterogeneity was also observed (□2=20.41, I2=90%, P<0.00001).

The two subgroups previously discussed did not show any statistical significance for each type of adverse effect. There were also three (3) studies that described LAST in their paper. No studies reported any incidence of LAST in the course of their study.

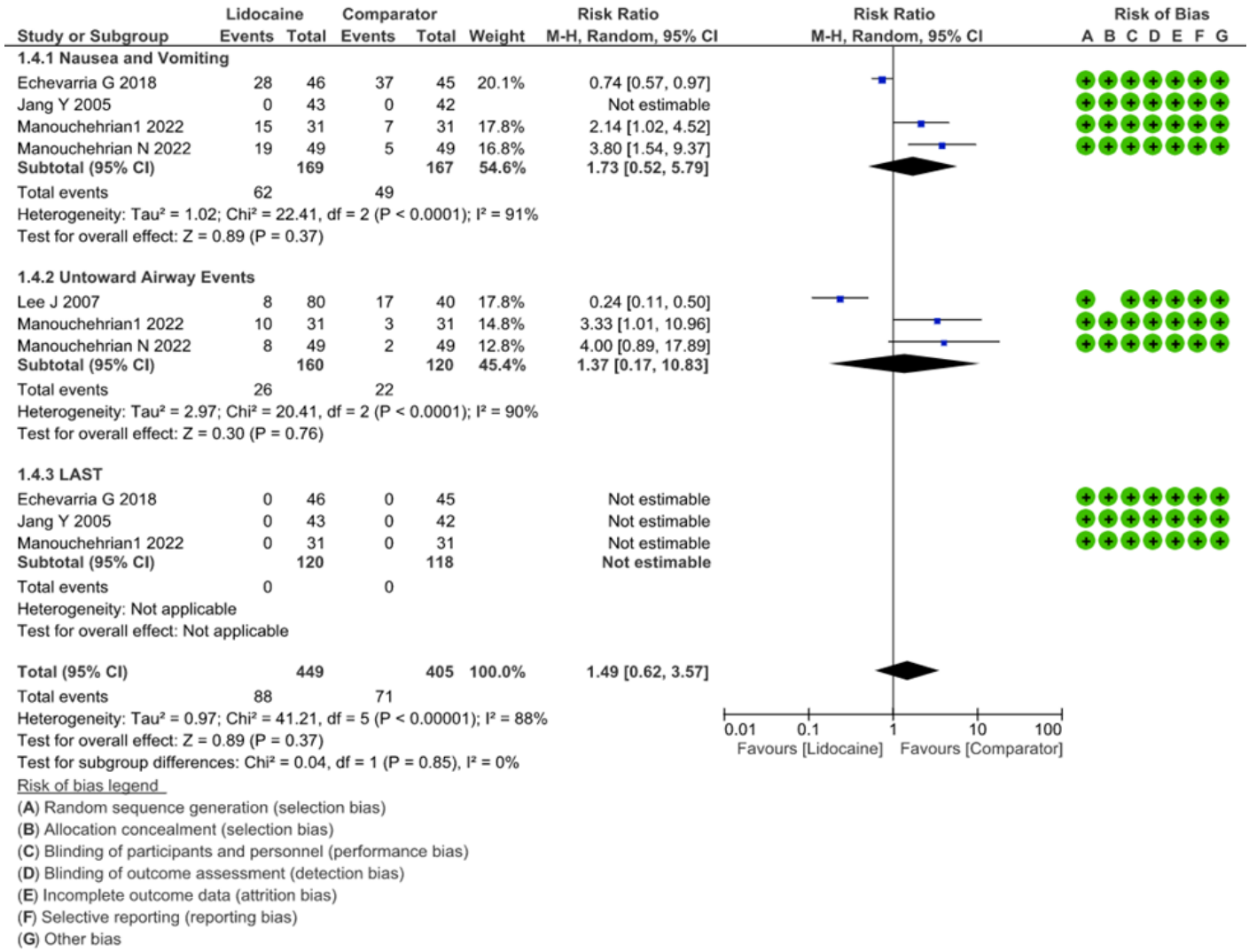

Figure 8. Subgroup Analysis of Adverse Effects: Lidocaine vs Compar-

4. Sensitivity Analysis

This analysis was performed to account for possible sources of heterogeneity. The results of the sensitivity analysis are shown in Table 3. This showed that the pooled effect did not change when the studies with results opposite the direction of the pooled effect were excluded.

Table 2. Sensitivity analysis: Incidence of Emergence Agitation

Study	RR	95% CI	I-squared
Including all (6) RCTs	1.03	0.50, 2.13	86%
Removing Manouchehrian_1 2022	0.83	0.38, 1.84	86%
Removing Manouchehrian 2022	0.86	0.38, 1.96	86%
Removing Lee 2007	1.44	0.87, 2.4	69%

Discussion

This meta-analysis aimed to determine the efficacy and safety of intravenous lidocaine in controlling emergence agitation in children undergoing surgeries done under general anesthesia compared to placebo or other intravenous anesthetics. This was based on studies mentioning the effectivity of using Lidocaine in decreasing the said event in children. However, this study has found the opposite. This study revealed that there was an increased risk of developing emergence agitation with the use of Lidocaine compared to placebo and other drugs. This finding was, however, not statistically significant and the data was heterogeneous. Subgroup analysis was done to look for possible causes of heterogeneity according to type of comparators and different doses of Lidocaine.

In the subgroup analysis by comparator, the studies have compared the effect of Lidocaine with placebo and other drugs namely, Propofol, Esmolol and Magnesium sulfate in preventing emergence agitation. The result showed decreased incidence of EA if Lidocaine was compared to a placebo but an increased incidence of EA if compared to the drugs previously mentioned. Only the latter showed statistical significance.

Many studies have investigated the benefit of using Propofol in preventing emergence agitation including a meta-analysis done by Gupta et. al [27]. On the other hand, Magnesium is a predominantly intracellular cation which has a central nervous system depressant property [28] which addresses the prolonged excited state during anesthesia recovery - hypothesized to be the pathophysiology of emergence agitation [13]. Another drug included in the comparators is Esmolol. This is a beta antagonist which is said to block cortical arousal alleviating agitation [12]. Hence, the following drugs' mechanism of action can explain the seen superior benefit of the comparators over lidocaine.

A subgroup analysis by dose was also done as this may have caused the heterogeneity between the studies. However, the results were contradicting. A dose of less than or equal to 1.5mg/kg showed an increase in developing EA as opposed to a decrease in risk when greater than 1.5mg/kg dose was used. These did not eliminate heterogeneity and the findings were not statistically significant. It can be inferred that increasing Lidocaine's dose will show a more pronounced effect [13] provided that it is within the drug's toxicity dose. Future studies have yet to determine the minimum effective concentration to lessen emergence agitation. Other possible causes of heterogeneity are timing and manner of drug administration. These were, unfortunately, not standardized in each study, therefore, cannot be grouped together.

There was an overall increased risk of experiencing an adverse effect with the use of Lidocaine compared to comparators, although statistically not significant. In particular, there was an increased likelihood of experiencing nausea, vomiting and untoward airway events (laryngospasm and stridor) with the use of Lidocaine. This finding can again be explained by the inherent properties of the comparator drug. It is established that Propofol has intrinsic properties in preventing postoperative nausea and vomiting [28] while Magnesium has the ability to relax muscles and increase flaccidity which decreases airway reactivity hence laryngospasm [27]. No events of LAST were noted for all studies reviewed.

There are several analyses with significant statistical heterogeneity which cannot be resolved by subgroup analyses. Adverse events reported in individual studies were not uniform, and there were limited studies on specific comparators that further analyses cannot be performed on them. Another possible source of the heterogeneity is the different surgical procedures used in the individual studies. This study also did not explore the difference in timing and manner of dose administration since the data available were not standardized. It was also noted that the enrolled trials had small sample sizes which may affect the results.

There also seems to be a publication bias as seen with the funnel plot of the incidence of emergence agitation, even when analyzed by comparator and dose.

Conclusions

Intravenous lidocaine given to children undergoing general anesthesia with sevoflurane increased their risk for emergence agitation, compared to both placebo and other intravenous anesthetics. It, however, may contribute to decreasing postoperative pain in the said group. The risk of adverse effects is also possibly increased with the use of lidocaine hence, caution should be exercised with this subset of patients.

This study recommends adding more studies favorably those with larger sample sizes, good quality databases and high-quality RCT's with evidence on the effectivity of lidocaine on emergence agitation in children undergoing inhalational general anesthesia. It is also recommended to include future studies investigating the effect of lidocaine focusing on standardized timing and mode of dose administration.

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ARTICLE

Modified pediatric nutrition screening tool to identify malnutrition and those at risk for malnutrition among patients aged 6 to 18 years old admitted at Philippine Children's Medical Center

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OBJECTIVE: To determine the reliability and validity of the modified pediatric nutrition screening tool in identifying malnutrition and risk of malnutrition among admitted pediatric patients aged 6 to 18 years old.

METHOD: The Modified Pediatric Nutritional Screening Tool (PNST) was used to assess 130 admitted patients aged 6 to 18 years old. Evaluation of anthropometric measurements, body weight changes, clinical conditions and dietary intake were done within 48 hours of admission. Intraclass correlation coefficient was used to determine reliability of the tool among different raters while chi square test was used to determine correlation of the tool with the Screening Tool for the Assessment for Malnutrition in Pediatrics (STAMP).

RESULT: The comparison of the modified PNST measurements by two observers showed no significant difference with p value of 0.078. All PNST criteria except clinical condition were associated with risk of malnutrition based on STAMP. The overall modified PNST criteria is significantly associated with risk of malnutrition based on STAMP.

CONCLUSION: The modified PNST accurately identifies malnutrition and risk of malnutrition among admitted patients aged 6-18 years old. The criteria used in the modified PNST were strongly associated with risk for malnutrition measured using previously validated tools and demonstrates a good interobserver reliability. It is recommended to be used as routine screening in the hospital setting for early identification of malnutrition and risk for malnutrition.

KEYWORDS: *Malnutrition, Risk of Malnutrition, Nutrition Screening Tool, Pediatrics*

INTRODUCTION

Malnutrition has always been considered a major burden across the world and is considered one of the leading causes of morbidity and mortality [1]. It is associated with impaired cognitive development, higher risk of infection and complications, and delay in recovery among sick children [2]. Among hospitalized patients, it is correlated to longer hospital stay and an increased risk of infectious complications.

Likewise, admitted patients are at risk of developing malnutrition [3]. Prevalence of malnutrition is usually underreported among hospitalized pediatric patients [7]. This is problematic as it may lead to delays in diagnosis and management resulting in an unfavorable outcome. To address this issue, there are various nutritional screening tools developed to accurately determine the prevalence of malnutrition on admission and to identify those at risk of malnutrition during hospital admission [3].

Among these tools are Screening Tool for the Assessment for Malnutrition in Pediatrics (STAMP), Subjective Global Nutritional Assessment, Nutritional Risk Score (NRS), Pediatric Nutritional Risk Score (PNRS), Pediatric Yorkhill Malnutrition Score (PYMS), Screening Tool for Risk on Nutritional status and Growth (STRONGkids), and Pediatric Digital Scaled Malnutrition Risk screening Tool (PeDiSMART) [3], [7], [8]. Though there are many methods available for nutritional evaluation, there is no consensus yet of which among the screening tools is most suitable for use among hospitalized pediatric patients. Hence, selection of nutritional screening tool has become preferential based on the user's interest, subject of the intended population, simplicity and ease of use [3,4].

Locally, a Pediatric Nutrition Screening Tool which focuses on four parameters namely anthropometric measurements, history of weight loss, clinical or medical condition and food intake has been developed in a study done by Olay in 2013. In their study, a simple and concise screening tool was developed to identify malnutrition and risk for malnutrition among admitted patients at Philippine Children's Medical Center (PCMC). The tool was made to cater to Filipino children as it was based on the Food Guide Pyramid recommended by the Philippine Society of Pediatric Gastroenterology and Nutrition. The tool was validated and compared with STAMP since the author found its parameters comparable to the said tool. However, the tool only caters to admitted patients aged 1 to 5 years.

There is also no other locally available pediatric nutrition screening tool to identify patients who are malnourished or at risk for malnutrition among admitted patients 6 to 18 years old. Hence, the previously developed tool was modified to cater to the other pediatric age group that is not covered by the said study. The modified tool aims to be administered on admission to promote early identification and management of malnutrition as well as active surveillance of those who will be identified to be at risk for malnutrition. Also, it intends to highlight the importance of administering a nutritional screening tool as part of routine admission to identify those with malnutrition and to catch early those patients who are at risk of malnutrition. Timely diagnosis of malnutrition will allow immediate multidisciplinary management and referral to gastroenterology and nutrition as well as dietary services to prevent nutritional deterioration and nutrition related complications especially among those who are at risk of longer hospital stay.

METHODOLOGY

This is a cross sectional study design. All admitted pediatric patients aged 6 to 18 years old with an expected hospital stay of at least 24 hours were invited to participate in the study. This included COVID confirmed cases, those who were admitted for procedures and patients with co-morbidities such as malignancy, cerebral palsy, or other chronic diseases. Patients with large variation in hydration status which may affect the baseline weight on admission such as those patients with fulminant cardiac, renal, and liver failure presenting with edema on the time of admission were excluded from the study [9]. An informed consent was solicited by the primary investigator and co-investigators from the parents or any legal representative of the patients while an informed assent was requested from participants who were aged 12 years old and above.

The computed recommended sample size based on the sample size requirements for estimating intra-class correlations with desired precision for this study is 120 subjects [9]. This recommendation factored in a potential dropout rate of 10%. However, for this study, there were 130 participants aged 6 to 18 years old included in the study.

The Modified Pediatric Nutritional Screening Tool for Ages 6 to 18 years old was derived from Olay's study wherein a Pediatric Nutrition Screening tool was developed and validated to identify malnutrition and risk of malnutrition for hospitalized patients aged 1 to 5 years old at Philippine Children's Medical Center. The four parts of the tool namely Anthropometrics, Body Weight Change, Clinical Condition and Dietary Intake were retained.

The first part, anthropometrics, was revised to cater to the target population in the study which was 6 to 18 years old. In the original pediatric nutrition screening tool, they made use of weight for height, weight for age and length for age to objectively measure the participants' anthropometrics. In the modified tool, body mass index (BMI) for age and height for age based on the World Health Organization Growth Chart were used. The scoring system in the second and third part namely body weight change and clinical condition were retained. For the last part, dietary intake, it was revised based on the daily recommended food intake according to the Food and Nutrition Research Institute for ages 6 to 18 years old.

This part of the tool made use of the World Health Organization Growth Charts namely Height for Age and Body Mass Index for Age to provide an objective analysis of the patient's anthropometrics. A score of 2 was set for z score of less than -3 which indicates severe malnutrition, 1 for z score of less than -2 which indicates moderate malnutrition and 0 for z score of less than -1 which indicates absence of malnutrition. A score of at least 1 indicates presence of malnutrition.

The second part investigated the history of weight loss due to present illness in the past 4 weeks. A time interval of 4 weeks was retained from the original tool since studies show that weight loss within a month signifies nutritional risk in children [9]. A score of 1 is given if the answer is yes and 0 if the answer is no.

The next parameter is the clinical or medical condition of the patient on admission. This may be divided into three different conditions based on severity adapted from Olay's study which was adapted from the American Academy of Pediatrics and American Dietician Association [9]. Conditions involving mild stress factors are labeled as Grade 1 conditions. This included those who are admitted for diagnostic procedures, minor infection not necessarily requiring hospitalization, other episodic illnesses, or minor surgery. Moderate Stress factors such as those with severe but not life-threatening infection, routine surgery, fracture, chronic illness without acute deterioration, or inflammatory bowel disease were grouped under Grade 2 conditions. Lastly, severe stress factors, such as those with immunodeficiency, malignancy, severe sepsis, those who will undergo major surgery, multiple injuries, acute deterioration of chronic disease and major depression are considered grade 3 conditions [9].

The last part of the tool includes the quality, quantity and frequency of food intake based on the daily nutritional food guide recommended for Filipino children and adolescents aged 6 to 18 years old

based on the Nutritional Guidelines for Filipinos published by the Food and Research Institute. This part of the questionnaire was consulted and checked by the hospital's in house nutrition specialist prior to use in the study. A 24-hour food recall was asked from the primary caregiver and from the cooperative patient. This was compared to the recommended daily food intake per age group which is answerable by yes or no. A score of 1 was given for no answers while 0 was given for yes answers.

The data collection was done by the primary investigator and co-investigators. The first part was the administration of the modified pediatric nutrition screening tool. This was followed by the assessment of anthropometric measurements including weight (in kg), height (in cm) and body mass index (kg/m^2).

Part 1: Administration of Pediatric Nutritional Screening Tool

On admission, a modified pediatric nutritional screening tools was performed by the primary investigator and co-investigators for patients aged 6 to 18 years old. The modified pediatric nutritional screening tool was derived from a local study by Olay et al in 2013 which aims to identify malnutrition and risk of malnutrition among admitted patients aged 1 to 5 years old [9]. In this study, the tool was modified to cater the rest of the pediatric population which were not catered by the said pediatric nutrition screening tool. Admitted patients aged 6 to 18 years old who fulfilled the inclusion criteria were invited to participate in the study. The modified pediatric nutrition tool consisted of the following parameters:

- Anthropometric measurements, namely Height-for-Age and BMI-for-Age, were expressed as z scores based on the WHO Growth Chart. Each item is equivalent to a score of either 0, 1 or 2 which correlates to severe, moderate and none. Any patient with a score of at least one in this parameter was classified as malnourished.

- History of weight loss due to sickness in the past 4 weeks is answerable by yes or no with an equivalent score of 1 or 0. A score of 1 was given to those who answered yes and 0 for those who answered no.

- Clinical or medical condition on admission is classified according to grading system. Conditions classified as Grade 1 include conditions with mild stress factors such as admission for diagnostic procedures, minor infection not necessarily requiring hospitalization, other episodic illnesses, or minor surgeries. Grade 2 conditions were those with moderate stress factors. These conditions included severe but not life-threatening infection, routine surgery, fracture, chronic illness without acute deterioration, or inflammatory bowel disease. Lastly, grade 3 conditions were those with severe stress factors such as those with HIV, malignancy, severe sepsis major surgery, multiple injuries, acute deterioration of chronic disease and major depression. Grades 3, 2 and 1 were equivalent to a score of 2, 1 and 0.

Dietary intake which included the quality, quantity and frequency of the patient's food intake was based on the patient's 24-hour recall diet. This was based on the daily nutritional food guide recommended for Filipino children and adolescents aged 6 to 18 years old based on the Nutritional Guidelines for Filipinos published by the Food and Research Institute. Each item was answerable by yes or no. A no answer was equivalent to a score of 1 while yes was equivalent to 0.

The overall risk of malnutrition during admission was obtained by adding the scores of these four parameters. The cut off scores for the high, medium, and low categories from the original tool used by Olay were retained in this study. An overall score of more than or equal to 4 was considered high risk, a score of 2 to 3 was medium risk and a score of 0 to 1 was considered as low risk.

Part 2: Anthropometric Measurements

The weight and height of all subjects were assessed upon admission. To ensure accurate measurement of data, standard equipment was used for all participants. For the weight, a calibrated beam scale was used. To ensure accuracy of data, subjects was measured on barefoot with only light minimal clothing on. The measurement was in metric units (kg) and was recorded to the nearest 0.1 kg. In obtaining the height, a stadiometer with the child barefoot with heels, buttocks, shoulders and back of head against it with arms hanging freely at the sides was used for older children who were cooperative and those who were able to stand on their own. For those who could not stand or for non-cooperative patients, a length board was used. The measured height was in centimeters and was rounded off to the nearest 0.1 cm. The body mass index in kg/m^2 was derived from the weight and height of the participant. This was translated into standard deviation scores based on the World Health Organization's BMI-for-Age Growth Chart. The patient's height was also translated into standard deviation (SD) based on the World Health Organization's Height-for-Age Growth Chart.

An informed consent was asked from the parents of patients who wished to participate in the study. For participants aged 12 years old and above who were cooperative and could make decisions, an assent form was requested. The study made sure that the confidentiality of the research data was secured, and that the anonymity of all participants was kept. All the information gathered was strictly used for the sole purpose of this study. Only the lead primary investigator, secondary investigators, co-investigators, and the members of the ethical board review have access to the information gathered. All the documents containing the gathered information were kept and archived by the primary investigator in a secured box and will be kept for a minimum of three years upon completion of research. After three years, the documents will be shredded and disposed of. For electronic records, these will be deleted or overwritten. The primary investigator made sure to completely remove deleted records to keep all data confidential.

For patients who consented to participate in the study, after each interview and screening process, the results were discussed with the parents, legal guardians and to the cooperative patients. Those who were assessed as malnourished or who were considered at risk for malnutrition were advised referral to the hospital's Dietary and Gastroenterology service for nutritional build up and appropriate intervention.

Reliability of the Modified Screening Tool

The assessments done by the primary and co-investigators using the modified pediatric nutrition screening tool in the same pediatric patients aged 6 to 18 years old admitted at Philippine Children Medical Center in identifying malnutrition and risk of malnutrition were compared to determine the reliability of the said tool.

The correlation between Modified Pediatric Nutritional Screening Tool (PNST) and Screening Tool for the Assessment of Malnutrition among Pediatrics (STAMP) was determined by comparing the outcomes of both tests. In the study by Olay et al, STAMP was used to compare the modified pediatric nutrition screening tool since its contents was said to be comparable with the parameters being measured in the proposed tool [9].

STAMP is a validated nutrition screening tool which was developed from Royal Manchester Children's Hospital in Great Britain used for early identification of malnutrition and nutrition risk to provide appropriate intervention. It is a tool which is divided into 4 steps which assesses diagnosis with nutritional consequences, nutritional intake, evaluation of nutritional status and lastly, overall risk of malnutrition [10].

The first step in the tool is diagnosis which asks regarding co-existing condition with nutritional consequence. A score of 3 was given to those with definite nutritional implications, including bowel failure, intractable diarrhea, burns, major trauma, Crohn's disease, cystic fibrosis, liver disease, major surgery, multiple food allergies and intolerances, oncology on active treatment, renal disease or failure and inborn errors of metabolism. A score of 2 was given to those with possible nutritional implications such as those with behavioral eating problems, cardiology, cerebral palsy, cleft lip and palate, coeliac disease, diabetes, gastroesophageal reflux, minor surgery, neuromuscular conditions, psychiatric disorders, respiratory syncytial virus (RSV), and single food allergy or intolerance. A score of 0 was given to those with no nutritional implications such as those who underwent day care surgery and those who were admitted for investigations [10].

The second step assessed the child's nutritional intake. A score of 3 was given for those with no intake, 2 if with decreased or poor intake and 0 if there was no change or if the patient has good intake [10].

The third step involved assessment of the weight and height of the patient which makes use of centile quick reference tables provided in the screening tool to determine the centile difference between weight versus height. A score of 3 was given if there was more than 3 centile spaces, if there was more than or equal to 3 columns apart or if weight was less than 2nd centile. A score of 1 was given if there were more than 2 centile spaces or if it was equal to 2 columns apart. A score of 0 if there was 0 to 1 centile spaces or columns apart [10].

The last step was the determination of overall risk of malnutrition. The scores from steps 1 to 3 were added to estimate the overall risk of malnutrition. The participant was considered as high risk if the total score for steps 1 to 3 was more than or equal to four, medium risk if 2 to 3 and low risk if 0 to 1 [10].

Patient demographics and characteristics were summarized using frequency and proportion for categorical variables and mean with standard deviation for continuous variables. Intraclass Correlation Coefficient was used for reliability analysis wherein the assessment of two raters were compared if they correlated with each other. For validity testing, chi-square and fisher test was used to determine if each parameter of the modified pediatric nutrition screening tool demonstrated association with the nutritional risk assessment done using STAMP.

STATA 14 was used for data analysis and a p-value <0.05 was considered significant.

RESULTS

A total of 130 patients were included in the study with a mean age of 11.3 years. There were 69 (53.1%) males and 61 (46.9%) females. Their mean weight was 35.5 kg, and their mean height was 140.8 cm.

Table 1. ***Demographic Characteristics of Patients***

	Frequency (n=130)	Percentage
Sex		
Male	69	53.1
Female	61	46.9
	Mean ± SD	**Range**
Age (years)	11.3 ± 3.5	6 - 18
Weight (kg)	35.5 ± 14.7	11.3 – 74.4
Height (cm)	140.8 ± 16.9	93.0 – 177.0

Using the modified PNST scoring, 2 of the 130 patients (1.5%) were identified as low risk for malnutrition while 45 (34.6%) were at moderate risk and 83 (63.9%) were high risk. The average PNST score was 4.3 ± 1.9.

Table 2. ***Distribution of Patients According to Modified PNST Scoring***

	Frequency (n=130)	Percentage
PNST Scoring		
Low risk	2	1.5
Moderate risk	45	34.6
High risk	83	63.9
Mean ± SD =	4.3 ± 1.9	

Table 3 shows the distribution of patients according to diagnosis and overall risk for malnutrition using the STAMP criteria. There were 79 (60.8%) of patients who were at high risk and 51 (39.2%) at medium risk for malnutrition based on the STAMP criteria.

Table 3. ***Distribution of Patients According Overall Risk for Malnutrition based on STAMP criteria***

	Frequency (n=130)	Percentage
Overall Risk of Malnutrition		
Low Risk	0	0.0
Medium Risk	51	39.2
High Risk	79	60.8

As seen in Table 4, all PNST criteria, except clinical condition, were significantly associated with risk for malnutrition based on STAMP (all p values <0.05). An increasing number of patients with z-scores of <3 were seen with an increased risk of malnutrition using modified PNST. Similar findings were also noted with the presence of body weight change. The overall modified PNST criteria was also significantly associated with the risk of malnutrition based on STAMP (p<0.000001). As much as 88.0% of high-risk patients identified in STAMP were also high-risk in modified PNST.

Table 4. Association *of the Different Modified PNST Criteria with Risk of Malnutri-*

	Medium Risk (n=51)	High Risk (n=79)	Total (n=130)	P value
HFA				
<z-3	47 (92.2)	55 (69.6)	102	0.008[a]
<z-2	3 (5.9)	14 (17.7)	17	
<z-0/Z-1	1 (2.0)	10 (12.7)	11	
BMI for age				
<z-3	49 (96.1%)	38 (48.1%)	87	
<z-2	2 (3.9%)	21 (26.6%)	23	<0.000001[a]
<z-0/Z-1	0 (0.0%)	20 (25.3%)	20	
Body Weight Change				
Yes	5 (9.8%)	44 (55.7%)	49	<0.000001
No	46 (90.2%)	35 (44.3%)	81	
Clinical Condition				
Grade 1	2 (3.9%)	1 (1.3%)	3	
Grade 2	17 (33.3%)	19 (24.0%)	36	0.221*[a]
Grade 3	32 (62.7%)	59 (74.7%)	91	
Dietary Intake (rice)				
Yes	35 (68.6%)	28 (50.6%)	75	0.048
No	16 (31.4%)	51 (49.4%)	55	
Dietary Intake (meat/fish/ chicken)				
Yes	32 (62.7%)	28 (35.4%)	60	0.002
No	19 (37.3%)	51 (64.6%)	70	
Dietary Intake (fruits/ vegetables)				
Yes	45 (88.2%)	48 (60.8%)	93	0.001
No	6 (11.8%)	31 (39.2%)	37	
Dietary Intake (milk)				
Yes	46 (90.2%)	65 (82.3%)	111	0.212
No	5 (9.8%)	14 (17.7%)	19	
Overall PNST score				
Low	2 (3.9%)	0 (0.0%)	2	<0.000001[a]
Moderate	36 (70.6%)	9 (11.4%)	45	
High	13 (25.5%)	70 (88.6%)	83	

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

[a] Fisher's Exact test

Table 5 shows the comparison of the modified PNST measurements by two observers. There was no significant difference (p value = 0.078) in the ratings done by different observers. Kappa statistics for inter-observer agreement also showed substantial agreement (0.63. p<0.001). This means that modified PNST scoring has good reliability.

Table 5. ***Comparison of the Inter-Observer Measurements of Modified PNST***

	Mean ± SD	Range	p-value (mean difference)
Reader 1	4.3± 1.9	1 – 13	*p value = 0.078*
Reader 2	4.4 ± 1.9	1 – 13	
% agreement = 92.0% Kappa = 0.63, substantial agreement *p value* = <0.001			

DISCUSSION

Malnutrition can be defined as a lack, excess or imbalance of energy, protein, and other nutrients results in quantifiable negative consequences on tissue/body form (body shape, size, and composition), function, and clinical outcome [14]. The length of the hospital stay is reduced, and infection-related problems are avoided with proper and adequate nutritional support [15] [16]. The danger of nutritional depletion must be diagnosed as soon as possible, ideally before admission, to start the proper nutritional intervention at an early stage to prevent malnutrition, particularly hospital-acquired malnutrition. A comprehensive nutrition-focused quality improvement program has been shown to lower the per-patient healthcare cost, according to a recent study about medical costs associated with malnourished hospitalized patients [17]. However, due to the lack of an easy-to-use nutritional screening instrument that has been fully validated, routine nutritional screening is infrequently performed on pediatric patients [18]. In the current study, factors of anthropometrics, body weight change, clinical conditions and dietary intake were seen to be significantly associated in identifying malnutrition and risk for malnutrition.

Another screening tool proposed to be used by healthcare workers was STAMP (Screening Tool for the Assessment of Malnutrition in Pediatrics). A different cohort of 238 kids was recruited for the evaluation phase, while a total of 122 kids were recruited for the development phase. Some of the identified predictors of nutrition risk included low percentile weight for age, reported weight loss, and disparity between weight and height percentile. STAMP was created by combining these indicators with the anticipated nutritional risk of clinical diagnosis. When compared to the classification of nutrition risk made by a licensed dietitian, STAMP evaluation revealed fair to moderate reliability (p-value= 0.541; 95% CI 0.461 to 0.621). The estimated sensitivity and specificity were 91% (86-94%) and 70% (51-84%) respectively [22]. According to the findings from the initial study's development phase, the objective data on weight and height was the best indicator of dietary risk hence anthropometric measurements are frequently employed as a criterion for determining under- and over-nutrition. However, a complete picture of nutrition risk in a clinical setting cannot be obtained from anthropometric measurements alone, thus, additional information, such as dietary intake and underlying clinical condition and management, are also necessary.

Other factors such as inadequate dietary intake was also found to be predictors of undernutrition in the current investigation [22].

Results for nutrition status can be accurately determined using anthropometric data based on well -established universal growth standards [23]. Likewise, the impact of disease or illness that increases dietary requirements should also be considered when assessing nutritional requirements and malnutrition among hospitalized children [22]. Also, weight loss or gain may be aggravated in hospital premises because of different factors such as the disease condition itself and the hospital food services offered [22]. A unique factor used in this screening tool is the Filipino based dietary intake which would appropriately assess the patient's nutritional intake. Among the different dietary intakes, protein was significantly associated with a high risk of malnutrition [9].

Conclusion and Recommendations

The Modified Pediatric Nutritional Screening Tool provides an accurate method to identify malnourished and nutritionally at-risk pediatric patients aged 6 to 18 years old. The criteria used in the modified PNST were strongly associated with risk for malnutrition measured using previously established and widely used tools. Modified PNST also demonstrated good interobserver reliability. Based on these findings, the modified PNST is strongly recommended to be used in the hospital setting to early identify children who require nutritional support and intervene accordingly. Further studies are recommended to determine the accuracy and reliability of the modified PNST in hospitalized children with specific health conditions that can predispose them to malnutrition. Moreover, since the study only investigated the reliability of the modified PNST as well as its correlation with Screening Tool for the Assessment of Malnutrition among Pediatrics (STAMP), a follow up research of on sensitivity and specificity of the tool may be done.

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ARTICLE

Factors Associated with the Development of Tumor Lysis Syndrome Among Pediatric Cancer Patients at the Philippine Children's Medical Center

Maria Carmela Gabrielle L. Tingne, Anne Lolita B. Tomas – Abadilla, & Maria Beatriz P. Gepte

BACKGROUND: Tumor lysis syndrome (TLS) is an oncologic emergency resulting from cancer chemotherapy; delays in its recognition could be life-threatening. Early recognition of associated risk factors and its management may help prevent its occurence.

OBJECTIVES: To identify the risk factors for TLS among cancer patients at the Philippine Children's Medical Center.

METHODS: This was a retrospective case-control study. Categorical variables were compared using chi-square test and continuous variables were compared using independent t-test. The association between TLS and patients' characteristics was determined through logistic regression analysis.

RESULTS: Medical records of 712 patients with cancer seen between 2016-2020 were reviewed. Children with (n=35) and without (n=137) TLS were selected as cases and controls and matched for age and cancer type. Factors associated with TLS are underweight patients with BMI < 18.5 (cOR 0.33, 95% CI 0.11-0.98); patients with both hepatomegaly and splenomegaly were four times more likely to develop TLS (cOR 3.946, 95% CI 1.2-12.94) while patients with lymphadenopathy were twice more likely to develop TLS (cOR 2.309, 95% CI 1.02-5.21). Patients with elevated WBC, low phosphorus and high uric acid at baseline have increased odds of developing TLS.

CONCLUSIONS: After group matching for age and cancer type, factors associated with increased odds of TLS among pediatric cancer patients in PCMC are hepatosplenomegaly, lymphadenopathy, elevated WBC, low potassium level, low phosphorus and high uric acid at baseline with higher fluid balance.

KEYWORDS: *tumor lysis syndrome, pediatric cancer, risk factors for TLS*

INTRODUCTION

Tumor lysis syndrome (TLS) is an oncologic emergency characterized by a group of metabolic derangements caused by the massive and abrupt release of cellular components into the blood following the rapid lysis of malignant cells. [(1)] The consequences of these derangements are potentially severe and include acute kidney injury, cardiac arrhythmias, seizures and even death. [(2)]

Tumor lysis syndrome can be diagnosed using the Cairo-Bishop Definition of TLS, which was developed in 2004. It can occur spontaneously or after starting chemotherapy. There are two types: clinical tumor lysis syndrome (CTLS) and laboratory tumor lysis syndrome (LTLS). Laboratory tumor lysis syndrome is diagnosed with the presence of two or more of the following abnormalities in a patient with cancer or undergoing treatment for cancer within 3 days prior to and up to 7 days after the initiation of

treatment: uric acid ≥ 476 umol/L or 25% increase from baseline, potassium ≥6 mmol/L or 25% increase from baseline, phosphorus ≥2.1 mmol/l or 25% increase from baseline and calcium ≤1.75 mmol/l or 25% decrease from baseline. Clinical tumor lysis syndrome on the other hand is diagnosed when a patient with laboratory tumor lysis syndrome has at least 1 of the following: creatinine ≥1.5x the upper limit of normal, cardiac arrhythmia, sudden death and seizure. [2]

The incidence of TLS is higher among hematologic malignancies, because of high rate of cell turnover and sensitivity to cytotoxic therapies. [3] It has been classically associated with bulky and rapidly dividing hematologic malignancies occurring most frequently in high-grade Non-Hodgkin Lymphoma and acute leukemia and less commonly in chronic leukemia and multiple myeloma. [4] There is a reported incidence of 5.2 to 23% in patients with Acute lymphocytic leukemia, 18% in AML with white blood cell count >75,000 and 26.4% B-cell acute lymphoblastic leukemia. [5]

In solid tumors, case reports of TLS have become increasingly common over the previous decade and are mostly seen in adult cases, although there are very limited data available in the pediatric population. Spontaneous TLS in solid tumors has been observed in the following: breast cancer, gastric cancer, germ cell tumors, gastrointestinal adenocarcinoma, squamous cell lung cancer, and metastatic castrate-resistant prostate cancer. [6]

Prevention is the best treatment for TLS. Treatment and prevention include hypouricemic agents, electrolyte management and adequate hydration. Patients who will not respond to hydration and medical management may need renal replacement therapy. [4] Intractable fluid overload, hyperkalemia, hyperuricemia, hyperphosphatemia, or hypocalcemia and renal failure are indications for renal dialysis. [2]

This study aims to identify patients who are at risk for the development of tumor lysis syndrome in hematologic malignancies and solid tumors so that prophylactic measures may be implemented before the initiation of therapy, to minimize the clinical consequences of tumor lysis syndrome. [1]

METHODOLOGY

This case control study was performed to determine the factors associated with the development of tumor lysis syndrome in children with cancer. It was conducted at the Philippine Children's Medical Center, a tertiary pediatric hospital in Quezon Avenue, Quezon City. It included all patients who were newly diagnosed to have either hematologic or solid tumor malignancy from January 2016 to December 31, 2020. Patients who started chemotherapy prior to admission at our institution were excluded. Initial laboratory results of white blood cell count, serum lactate dehydrogenase, calcium, potassium, phosphorus, uric acid and creatinine were recorded.

The diagnosis of tumor lysis syndrome was based on the Cairo-Bishop criteria. Laboratory tumor lysis syndrome was diagnosed in the presence of two or more of the following laboratory abnormalities within 3 days prior and up to 7 days after the initiation of treatment: uric acid ≥476 umol/L or 25% increase from baseline, potassium ≥6 mmol/L or 25% increase from baseline, phosphorus ≥2.1 mmol/L or 25% increase from baseline and calcium ≤1.75 mmol/L or 25% decrease from baseline.

Clinical tumor lysis syndrome on the other hand was diagnosed when a patient with laboratory tumor lysis syndrome has at least 1 of the following: creatinine ≥1.5x the upper limit of normal, cardiac arrhythmia, sudden death and seizure. Data on patients who fulfilled the criteria for TLS were collated and analyzed. Charts with incomplete data were excluded from the study.

All charts of admitted patients with newly diagnosed hematologic malignancy and solid tumor were retrieved and included in the study. The patients' charts were reviewed and the following demographic and clinical data were recorded: age, sex, weight, height, BMI (for patients above 6 years old), type of malignancy, initial and subsequent laboratory results up to 7 days after starting chemotherapy of white blood cell count, serum potassium, calcium, uric acid, phosphorus, creatinine as requested by hematologist-oncologist and/or nephrologist-in-charge. For solid tumors, the size and location as well as presence or absence of metastasis, enlarged palpable lymph nodes and their location by physical examination were noted. For hematologic malignancies, presence of enlarged palpable nodes and their distribution, presence or absence of mediastinal mass, organomegaly based on physical examination and/or imaging upon admission were recorded. Clinical monitoring for kidney function status such as daily urine output and fluid balance aside from the aforementioned laboratory parameters were also documented. Details of management such as chemotherapy or medications, method of hydration and further interventions with their corresponding outcomes were likewise collated.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Odds ratios and the corresponding 95% confidence intervals from Firth logistic regression were computed to determine the association between patient profile and TLS. Fisher's exact test was used to compare outcomes of those with TLS vs without TLS. All valid data were included in the analysis. Missing data were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

A total of 712 charts of new patients with malignancy were reviewed. Children with (n=35) and without (n=137) TLS were selected as cases and controls, respectively, with group matching for age and cancer type (Table 1). The group matching was based on data that TLS occurs more frequently in hematologic malignancies than in solid tumors. The highest risk of developing TLS is observed in patients with lymphoproliferative disorders with high proliferative rates and high tumor sensitivity to chemotherapy. [4,7] Age was also used to match patients since most malignancies are classified as high risk for patients aged 10 years and above this was done to minimize confounding in this comparison between TLS and non-TLS. The overall median age was 6.5 (range 0.08-18) years, and 134 (77.91%) had hematologic type of malignancy. Majority of the patients were males (60.47%) and had BMI of < 18.5 kg/m^2 (61.86%).

Among the hematologic types of malignancy, the three most common subtypes were B- cell acute lymphocytic leukemia, ALL (37.75%), acute

myelogenous leukemia, AML (13.95%) and T-cell acute lymphocytic leukemia, ALL (9.88%). Hepatoblastoma was the most common type of solid tumor (4.65%). Sixteen (9.3%) had a mediastinal mass. Hepatomegaly and splenomegaly were found in 72 (41.86%) and 10 (5.81%) patients, respectively while 14 (8.14%) patients had both. Cancer had metastasized to the brain in 3 (1.7%) and to other sites in 8 (4.65%) patients.

The following profiles were associated with TLS as shown in table 1: Patients who were underweight or BMI < 18.5 with a cOR 0.33, 95% CI 0.11 -0.98, p = 0.045, were more likely to develop TLS compared to patients with normal BMI. Compared to those with normal BMI, those with BMI <18.5 were less likely to have TLS (cOR 1.235, 95% CI 0.24-6.36, p = 0.801 and cOR 0.33, 95% CI 0.11-0.98, p= 0.45). There is no association with TLS and BMI for overweight or obese compared to normal BMI (cOR 1.235, 95% CI 0.24-6.36, p = 0.801 and cOR 0.529, 95% CI 0.1-2.81, p = 0.455). After matching for age and cancer type, we observed that patients with both liver and spleen organomegaly were four times more likely to develop TLS (cOR 3.946, 95% CI 1.2-12.94, p = 0.023) while patients with palpable lymphadenopathy in either cervical, axillary or inguinal area were twice more likely to develop TLS (cOR 2.309, 95% CI 1.02-5.21, p = 0.044).

Table 1. Deamographic and clinical profile of pediatric cancer patients

	Total (n=172)	With TLS (n=35)	No TLS (n=137)	Crude Odds Ratio (95% CI)	p-value
	Median (Range); Frequency (%)				
Age, years					
<10	102 (59.3)	19 (54.29)	83 (60.58)	1.0 (Reference)	-
≥10	70 (40.7)	16 (45.71)	54 (39.42)	1.296 (0.62–2.71)	0.491
Sex					
Male	104 (60.47)	21 (60)	83 (60.58)	1.0 (Reference)	-
Female	68 (39.53)	14 (40)	54 (39.42)	1.033 (0.49–2.18)	0.932
BMI, kg/m^2 [n=97]					
<18.5	60 (61.86)	10 (43.48)	50 (67.57)	**0.33 (0.11–0.98)**	**0.045**
18.5 to 23	21 (21.65)	8 (34.78)	13 (17.57)	1.0 (Reference)	-
23 to <27.5	7 (7.22)	3 (13.04)	4 (5.41)	1.235 (0.24–6.36)	0.801
≥27.5	9 (9.28)	2 (8.7)	7 (9.46)	0.529 (0.1–2.81)	0.455
Type of malignancy					
Hematologic	134 (77.91)	29 (82.86)	105 (76.64)	1.0 (Reference)	-
Solid tumor	38 (22.09)	6 (17.14)	32 (23.36)	0.715 (0.28–1.82)	0.483
Specific type of malignancy				-	-
Hematologic	134 (77.91)	29 (82.86)	105 (76.64)		
AML	24 (13.95)	2 (5.71)	22 (16.06)		
Anaplastic large cell lymphoma	1 (0.58)	1 (2.86)	0		
APML	3 (1.74)	0	3 (2.19)		
B Cell ALL	65 (37.79)	11 (31.43)	54 (39.42)		
B Lymphoblastic lymphoma	1 (0.58)	0	1 (0.73)		
Burkitt's lymphoma	3 (1.74)	3 (8.57)	0		
CML	8 (4.65)	2 (5.71)	6 (4.38)		
Hodgkin lymphoma	5 (2.91)	0	5 (3.65)		
Infantile leukemia	1 (0.58)	0	1 (0.73)		
JMML	3 (1.74)	0	3 (2.19)		

Large B Cell lymphoma	1 (0.58)	0	1 (0.73)		
NHL	2 (1.16)	0	2 (1.46)		
T cell ALL	17 (9.88)	10 (28.57)	7 (5.11)		
Solid tumor	38 (22.09)	6 (17.14)	32 (23.36)		
Hepatoblastoma	8 (4.65)	2 (5.71)	6 (4.38)		
Medulloblastoma	1 (0.58)	0	1 (0.73)		
MMGCT	3 (1.74)	1 (2.86)	2 (1.46)		
Neuroblastoma	6 (3.49)	0	6 (4.38)		
Non-seminomatous GCT	4 (2.33)	1 (2.86)	3 (2.19)		
Osteosarcoma	2 (1.16)	0	2 (1.46)		
PNET	1 (0.58)	0	1 (0.73)		
Retinoblastoma	4 (2.33)	0	4 (2.92)		
Rhabdomyosarcoma	4 (2.33)	0	4 (2.92)		
Wilms' tumor	5 (2.91)	2 (5.71)	3 (2.19)		
Metastasis					
Brain	3 (1.74)	0	3 (2.19)	0.541 (0.03–10.72)	0.687
Liver	0	0	0	-	-
Lungs	13 (7.56)	3 (8.57)	10 (7.3)	1.308 (0.37–4.65)	0.679
Others	8 (4.65)	1 (2.86)	7 (5.11)	0.757 (0.13–4.54)	0.760
With mediastinal mass	16 (9.3)	6 (17.14)	10 (7.3)	2.676 (0.93–7.7)	0.068
Organomegaly					
None	76 (44.19)	12 (34.29)	64 (46.72)	1.0 (Reference)	-
Liver only	72 (41.86)	13 (37.14)	59 (43.07)	1.171 (0.5–2.73)	0.715
Spleen only	10 (5.81)	4 (11.43)	6 (4.38)	3.572 (0.93–13.72)	0.064
Liver and spleen	14 (8.14)	6 (17.14)	8 (5.84)	**3.946 (1.2–12.94)**	**0.023**
Lymphadenopathy (cervical, axillary and inguinal)	101 (58.72)	26 (74.29)	75 (54.74)	**2.309 (1.02–5.21)**	**0.044**

Statistical test used: Firth logistic regression

The initial laboratory readings of patients are summarized in Table 2. Majority had normal potassium (121 or 70.35%), calcium (125 or 70.35%), serum creatinine (133 or 77.33%) and phosphorus (115 or 66.86%) levels. Of the parameters, cases and controls significantly differed in terms of WBC, potassium, calcium, creatinine, and uric acid. For every unit increase in WBC, the odds of TLS increases by 0.3% (cOR 1.003, 95%CI 1.001-1.01, p = 0.006). The median baseline calcium (2.4 mmol/L vs. 2.33 mmol/L) and uric acid (745 mmol/L vs. 356 mmol/L) levels were greater in children with TLS than in those without. The odds of TLS increased more than four-fold (cOR 4.70, 95% CI 1.14-19.3) with every mmol/L rise in baseline calcium, but when categorized, there was no significant association detected. TLS odds increased by 0.5% (cOR 1.005, 95% CI 1.003-1.01) with each mmol/L increment in uric acid. The median baseline serum creatinine level (54 umol/L vs 40 umol/L) was higher while the potassium level (3.3 mmol/L vs 4.1 mmol/L) and phosphorus level (1.29 mmol/L vs 1.51 mmol/L) were lower in children with TLS than in those without. Moreover, low phosphorus levels were more frequent in children with TLS (median of 1.29 vs 1.51). Patients

with high creatinine are four times more likely to develop TLS than those with normal creatinine (cOR 4.054, 95% CI 1.69-9.75, p = 0.002). Patients with low baseline phosphorus were eight to nine times as likely to develop TLS (cOR 8.68, 95% CI 3.44-21.92, p < 0.001).

Table 2. Initial or baseline laboratory profile of pediatric cancer patients and associated with tumor lysis syndrome

	Total (n=172)	With TLS (n=35)	No TLS (n=137)	Crude Odds Ratio (95% CI)	p-value
	Median (Range)				
WBC count, x10^9/L	18.7 (0.6 to 758.2)	75.7 (3.1 to 758.2)	17.3 (0.6 to 630.9)	**1.003 (1.001–1.01)**	**0.006**
Potassium, mmol/L	4 (1.7 to 6.8)	3.3 (1.7 to 5.5)	4.1 (2.3 to 6.8)	**0.368 (0.2–0.66)**	**0.001**
Low	31 (18.02)	17 (48.57)	14 (10.22)	**8.948 (3.69–21.7)**	**<0.001**
Normal	121 (70.35)	14 (40)	107 (78.1)	1.0 (Reference)	-
High	20 (11.63)	4 (11.43)	16 (11.68)	2.022 (0.62–6.57)	0.241
Calcium, mmol/L	2.35 (1.65 to 3.49)	2.4 (1.76 to 3.49)	2.33 (1.65 to 3.43)	**4.7 (1.14–19.3)**	**0.032**
Low	23 (13.37)	3 (8.57)	20 (14.6)	0.641 (0.19–2.15)	0.472
Normal (8.4–10.2)	125 (72.67)	26 (74.29)	99 (72.26)	1.0 (Reference)	-
High	24 (13.95)	6 (17.14)	18 (13.14)	1.319 (0.49–3.55)	0.584
Serum creatinine, umol/L	43 (12 to 1051)	54 (19 to 1051)	40 (12 to 146)	**1.023 (1.01–1.04)**	**0.003**
Low	13 (7.56)	0	13 (9.49)	0.174 (0.01–3.03)	0.231
Normal	133 (77.33)	23 (65.71)	110 (80.29)	1.0 (Reference)	-
High	26 (15.12)	12 (34.29)	14 (10.22)	**4.054 (1.69–9.75)**	**0.002**
Phosphorus, mmol/L	1.5 (0.13 to 2.77)	1.29 (0.13 to 2.5)	1.51 (0.77 to 2.77)	**0.219 (0.07–0.64)**	**0.006**
Low	27 (15.7)	15 (42.86)	12 (8.76)	**8.68 (3.44–21.92)**	**<0.001**
Normal	115 (66.86)	14 (40)	101 (73.72)	1.0 (Reference)	-
High	30 (17.44)	6 (17.14)	24 (17.52)	1.857 (0.67–5.18)	0.237
Uric acid, mmol/L	383 (96 to 2379)	745 (217 to 2379)	356 (96 to 1011)	**1.005 (1.003–1.01)**	**<0.001**
LDH, U/L	1000 (45 to 51730)	2016 (337 to 51730)	970 (45 to 35480)	1 (0.99–1.0001)	0.05

Statistical test used: Firth logistic regression

Chemotherapy was given to 170 patients in the study (98.84%) and 34 (97.14%) had TLS with one patient having spontaneous tumor lysis even prior to giving of chemotherapy. There were 155 patients who received hyperhydration (90.12%) and 93 patients (54.07%) and 105 patients (61.05%) of the total were given hypouricemic agents and electrolyte management respectively; most were given in combination with each other (Table 3). Only four (11.43%) patients with TLS underwent dialysis.

Table 3. Treatments received by newly diagnosed cancer patients and their TLS

	Total (n=172)	With TLS (n=35)	No TLS (n=137)
	Frequency (%)		
Chemotherapy	170 (98.84)	34 (97.14)	136 (99.27)
Hydration	155 (90.12)	35 (100)	120 (87.59)
Hypouricemic agent	93 (54.07)	31 (88.57)	62 (45.26)
Electrolyte management	105 (61.05)	33 (94.29)	72 (52.55)
Dialysis	4 (2.33)	4 (11.43)	0

The median onset of TLS was 2 days (range 0-6) from chemotherapy initiation (Table 4). In-hospital mortality rate was greater among cases (14%) than controls (7%) but did not reach statistical significance. Patients with TLS are more likely to develop fluid overload at 499 (CI -2225-5500, p value – 0.011).

	Total (n=172)	With TLS (n=35)	No TLS (n=137)	p-value
	Median (Range); Frequency (%)			
Days from chemotherapy initiation [n=28]	[n=28] 2 (0–6)	[n=28] 2 (0–6)	-	-
Urine output during chemotherapy, cc/kg/hr	3.35 (0.11 to 12)	3.02 (0.11 to 9.1)	3.4 (1 to 12)	0.064*
Fluid balance during chemotherapy	275 (-2225 to 5500)	499 (-2225 to 5500)	200 (-540 to 2824)	**0.011***
Final status				0.192†
Alive and discharged	157 (91.28)	30 (85.71)	127 (92.7)	
Expired	15 (8.72)	5 (14.29)	10 (7.3)	

Statistical test used: * - Mann-Whitney U test; † - Fisher's exact test.

Indicators for TLS clinical and laboratory criteria are shown in Table 5. The median creatinine level in umol/L was 42 (range of 12-1051) and it was higher in patients with TLS than without (54 vs 40). Majority of the patients had normal serum creatinine levels (74.42%). Patients who had high creatinine were more likely to develop TLS as compared to those who did not develop TLS (40% vs 8.76%). One patient had cardiac arrhythmia and also one patient had seizure. Both had TLS.

About 52 (30.23%) had potassium of ≥ 6 mmol/L or at least 25% increase from baseline and majority had TLS (25 or 74.29%). The median potassium level in mmol/L was 4.2 (range of 2.2-35) and it was higher in patients with TLS than without (5 vs 4.1). Most of the patients had normal potassium levels (65.7%), and majority do not have TLS (73.72%). Eleven (6.4%) had calcium levels of ≤1.75 mmol/L or at least 25% decrease from baseline and more frequently seen in patients with TLS (28.57% vs 0.73%). The median calcium level in mmol/L was 2.2 (range of 0.62-3.49) and it was higher in patients without TLS (2.26 vs 2.08). Forty-eight (27.91%) has phosphorus levels of ≥ 2.1 mmol/L or at least 25% increase from baseline and more frequently seen in patients with TLS (91.43%). The median phosphorus level in mmol/L was 1.5 (range of 0.54-4.35) and it was higher in patients with TLS (2.26 vs 1.4). Twenty (11.63%) had uric acid >476 umol/L or at least 25% increase from baseline and it was more frequent in patients with TLS (42.86% vs 3.65%). The median uric acid in mmol/L was 245 (range of 69-1510), and it was higher in patients with TLS (434 vs 222).

Table 5. Indicators for Laboratory and Clinical TLS Criteria

	Total (n=172)	With TLS (n=35)	No TLS (n=137)
	Median (Range); Frequency (%)		
Clinical criteria (any one)			
Creatinine	42 (12–1051)	54 (19–1051)	40 (12–146)
Low	18 (10.47)	1 (2.86)	17 (12.41)
Normal	128 (74.42)	20 (57.14)	108 (78.83)
High	26 (15.12)	14 (40)	12 (8.76)
Cardiac arrhythmia	1 (0.58)	1 (2.86)	0
Sudden death	0	0	0
Seizure	1 (0.58)	1 (2.86)	0
Laboratory criteria (any two)			
Potassium ≥6 mmol/L or at least 25% increase from baseline	52 (30.23)	26 (74.29)	26 (18.98)
Potassium	4.2 (2.2–35)	5 (2.2–6.6)	4.1 (2.5–35)
Low	14 (8.14)	2 (5.71)	12 (8.76)
Normal	113 (65.7)	12 (34.29)	101 (73.72)
High	45 (26.16)	21 (60)	24 (17.52)
Calcium ≤1.75 mmol/l or at least 25% decrease from baseline	11 (6.4)	10 (28.57)	1 (0.73)
Calcium	2.25 (0.62–3.49)	2.08 (0.62–2.75)	2.26 (1.82–3.49)
Low	42 (24.42)	20 (57.14)	22 (16.06)
Normal (8.4–10.2)	116 (67.44)	12 (34.29)	104 (75.91)
High	14 (8.14)	3 (8.57)	11 (8.03)

Phosphorus ≥2.1 mmol/l or at least 25% increase from baseline	48 (27.91)	32 (91.43)	16 (11.68)
Phosphorus	1.5 (0.54–4.35)	2.26 (0.69–4.35)	1.4 (0.54–2.5)
Low			
Normal			
High			
Uric acid ≥476 umol/l or at least 25% increase from baseline	20 (11.63)	15 (42.86)	5 (3.65)
Uric acid	245 (69–1510)	434 (69–1510)	222 (75–450)
Low	32 (18.6)	3 (8.57)	29 (21.17)
Normal	98 (56.98)	7 (20)	91 (66.42)
High	42 (24.42)	25 (71.43)	17 (12.41)

Discussion

Risk factors for TLS can either be patient or tumor related. In this study, subjects were matched according to age and diagnosis i.e. hematologic malignancy versus solid oncologic tumors. It was found out that TLS is associated with the following: hepato-splenomegaly with TLS occurring four times more than those without any organomegaly; lymphadenopathy increased the odds of TLS two times more than those without. Other factors associated with developing tumor lysis syndrome were having a higher baseline WBC count as well as low potassium levels, higher creatinine, low phosphorus, high uric acid at baseline as well as higher fluid balance during the chemotherapy. On the other hand, there was decreased risk of TLS in patients with BMI of less than 18.5 (cOR 0.33 95% CI 0.11 – 0.98, p-value 0.045) compared to normal BMI range.

Patient related factors such as organomegaly and lymphadenopathy appear to significantly increase the chance of developing tumor lysis syndrome. These findings are also consistent with the findings in the study by Gopekumar et al in 2018, which analyzed the outcomes of tumor lysis syndrome in children with leukemia and lymphoma. In a univariate analysis, the presence of a mediastinal mass, generalized lymphadenopathy, hyperuricemia and hyperleukocytosis were significantly associated in the development of TLS. However, in the multivariate analysis, only the presence of hyperuricemia reached statistical significance.[8]

Laboratory features of patients who developed tumor lysis syndrome were increased serum creatinine levels as well as hyperphosphatemia.[9] However, in this study, an increased risk of TLS was observed among patients with low to normal baseline phosphorus and high baseline calcium levels.

This is similar to the 10-year review by Ahn et al. in 2011 on 396 children who were diagnosed with acute leukemia and non-Hodgkin lymphoma, which showed a four-fold increase in the risk of developing TLS in patients with hypophosphatemia.[24] This may be explained by the use of phosphorus in the synthesis of cellular components for the tumor cells to proliferate and then eventually lysed by chemotherapy causing the extracellular phosphorus to be shifted into the cancer cells thus causing hypophosphatemia. Another explanation for this may be a possible proximal tubular dysfunction from competitive inhibition of tubular reabsorption of phosphorus by some unidentified metabolites of malignant cells. Therefore, hypophosphatemia can be an indication of high tumor burden or high cell proliferation rate which is a major predictor of TLS. [10,11]

Other tumor related factors such as high baseline serum uric acid and high levels of white blood cells were also noted to have increased the risk for TLS. In this study, those who developed TLS had a median baseline white blood cell count of 75,000/mL while those who did not develop TLS had a median baseline of 17,300/mL. The elevated serum LDH level however did not show a significant increase (cOR 1, 95% CI 0.99–1.0001, p 0.05) in the risk of developing TLS. In several studies however, elevated initial levels of serum LDH that indicate tumor bulk is considered a very significant risk factor in developing TLS. [10,12,13,14] Other factors such as presence of a mediastinal mass did not increase the risk for TLS (cOR 2.676, 95% CI 0.93 – 7.7, p 0.068). These are cases of T cell ALL and Diffuse Large B-cell Lymphoma. This is in contrast to a study by Nasir et al that reported the presence of mediastinal mass as the most significant factor for mortality and tumor lysis syndrome. There were 61 children with mediastinal masses that were included in the study; 72.1% had T cell lymphoblastic leukemia with anterior mediastinal masses. [15] Numerous other studies have shown these characteristics to be significant risk factors but results of this study may suggest that these factors may not be statistically significant in this matched control study but is clinically significant.

There are more cases of TLS seen in patients with hematologic malignancies than in those with solid tumors. Among the hematologic malignancies, most were cases of ALL. As seen in Table 1, acute lymphoblastic leukemia with B cell immunophenotype followed closely by T cell immunophenotype had the most cases of TLS, which is consistent with findings of Abdel-Baser et al. in 2012 wherein, T-cell immunophenotyping was the strongest predictor of TLS.[13]

In solid tumors, tumor lysis syndrome although rare, an increase in cases has been seen recently. In a comprehensive review of literature by Findakly et al. in 2020 on tumor lysis in solid tumors in both adult and pediatric population, it was recognized that the recent advancement in cancer therapy has brought about increase in the incidence of tumor lysis in solid tumors, previously thought to be rarely associated. This observation is important because the increasing mortality in TLS from solid tumors rose to as high as 35% compared to 1.9% rate reported for patients with ALL and NHL. [16] Another review by Criscuolo et al in 2015, also showed a less frequent occurrence of tumor lysis syndrome in solid cancers, and is usually associated with bulky and high chemosensitive diseases; spontaneous events prior to chemotherapy are seen mostly as case reports. [17]

In this study, a total of 35 solid tumor cases were identified. Six (17.1%) had TLS; 2 had hepatoblastoma, 2 had Wilms' tumor, and 2 had germ cell tumors. Four of the six cases were already advanced with metastasis to the lungs and bone marrow. Solid tumors are considered low risk to develop tumor lysis syndrome as classified in Cairo Bishop and most are case reports. Although TLS is rare, cases of TLS seen in hepatoblastoma, germ cell tumors, neuroblastoma and even rhabdomyosarcoma in children have been reported. [12,16,18]

The following interventions were given to those who were assessed to have a higher risk of TLS development in pediatric cancer patients: hyperhydration, the use of hypouricemic agents and electrolyte management such as giving of aluminum magnesium oxide and phosphate-binding medication (sevelamer) for hyperphosphatemia. This practice is based on the treating physician's knowledge as guided by the Cairo-Bishop Criteria : that patients who are at high risk in developing TLS are identified and aggressive management to prevent TLS are given early in the course of treatment. Four cases out of the 35 (11%) cases with TLS progressed to acute kidney injury needing dialysis despite hyperhydration, hypouricemic agents and other oral agents. These are cases of Burkitt's lymphoma, hepatoblastoma and 2 cases of B cell ALL. All had elevated creatinine, phosphorus and uric acid with seizures and cardiac arrythmia after the giving of chemotherapy.

There were 5 deaths out of the 35 cases that had TLS (14.3%), which is higher compared to 10 out of 137 deaths (7.3%) in non-TLS patients. The causes of death were mostly multifactorial and due to multiple organ failure wherein tumor lysis syndrome may have contributed as well. In patients with no TLS, causes of death were mostly from hemorrhage (intracranial) and sepsis.

Tumor lysis syndrome developed more frequently in patients after receiving chemotherapy (31/35, 88%) than spontaneously prior to chemotherapy (4/35, 11%). With this result, it is recommended to closely monitor the levels of uric acid and serum electrolytes in patients being treated with chemotherapy. It is suggested to give aggressive hydration, electrolyte management and monitoring as early as 48 hours prior to initiating any treatment. This is also congruent with recommendations in a study by Adeyinka et al in the management tumor lysis syndrome that Intravenous fluid should be initiated 48 hours before the start of chemotherapy and should be continued for 48 hours after chemotherapy. This allows volume expansion and increase glomerular filtration rate that can help in the excretion of the solutes associated with tumor lysis syndrome. [9,15]

Conclusion and Recommendations

After group matching for age and cancer type, the following were associated with increased odds of TLS among pediatric patients with malignancy at PCMC: liver and spleen organomegaly, lymphadenopathy, elevated baseline WBC, low potassium level, low phosphorus and high uric acid at baseline with higher fluid balance on monitoring. While the following factors did not increase the odds of developing TLS: sex, elevated LDH, creatinine, presence of mediastinal mass and presence of metastasis.

The current study was limited by its retrospective nature. It did not present the actual prevalence of tumor lysis syndrome in our institution since a lot of cases were not included in the analysis

due to incomplete data. A prospective cohort study is more ideal as it will allow assessment of subjects at baseline. The data collection will be more accurate with regard to exposures, confounders and endpoints. Nonetheless, this study provided a baseline estimate for TLS cases and their profile in our institution that may be used as a comparison in further research.

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