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A few weeks ago the PAMJE (Philippine Association of Medical Journal Editors) held its annual meeting at the UERM College of Medicine. The day was composed of lectures and panel discussions such as updates on free databases and resources for journal writing, and sharing of best practices by editors of a number of local journals. One highlight was the launching of CENTRAL, which aims to be a directory of websites of local journals that researchers can use, of which The PCMC Journal was tapped to be a member.

All this is to highlight the support that the DOST and PCHRD extend to our Philippine medical journals, as we continue to develop the expertise of our scientists and researchers in disseminating their scientific work to our colleagues here and abroad. And on that hopeful note, we wish you Happy Holidays and best wishes for the coming year!

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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Contents

Instruction to Authors

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 per 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 manuscripts, correspondence and editorial business should be sent to PCMC Journal, Clinical Research Department, Philippine Children's Medical Center, Quezon Ave., Quezon City. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publisher. Accepted manuscripts become the permanent property of the Journal and may not be republished without permission from the Editor. These manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal. Statements or views expressed by an author or authors are not the responsibilities of the editor or publisher.

Cover Letter

A covering letter must accompany all manuscripts with one author designated as correspondent, providing his/her complete address, telephone number, and e-mail address. In order for a manuscript to be considered, reviewed or edited, the following statement must be signed by all the authors: "I/We have been sufficiently involved in this work to take public responsibility for its validity and final presentation as an original publication." Whenever applicable, there should also be a written declaration that the article had written informed consent for publication from the involved subject/s, had conformed to ethical standards and/ or had been reviewed by the appropriate ethics committee. Systematic reviews and case reports do not generally need IRB review. The transmittal letter must include the statement "This paper has not been published and is not under simultaneous consideration for publication elsewhere. I/We hereby confer all copyright ownership/s to the PCMC Journal in the event that this work is published in this journal."

General Guidelines

1. One original and two duplicate manuscripts should be submitted. An electronic copy must also be emailed to crd@pcmc.gov.ph. The manuscript should be typed double-spaced throughout with 1 ¼ cm (½ inch) paragraph indentation, using only one side of each 22x28 cm (8 ½ x 11 inch) opaque bond paper with 3-cm margins (1 ¼ inch) all around. Preferred font styles and sizes are: Times New Roman 12, Arial 11, Tahoma 11, & Verdana 11.

2. The manuscript should be arranged in sequence as follows: (1) Title Page (2) Abstract (3) Text (4) References (5) Tables (6) Figures & Illustrations. A manuscript for an original article should not exceed 25 typewritten pages (including tables, figures, illustrations and references). The text for case reports should not exceed 10 pages, including the visual aids and references.

3. References should be selective and pertain directly to the work being reported.

4. All the sheets of the manuscript should be labelled with the family name of the main/first author (all in capital letters) and page number (in Arabic Numeral) printed on the upper right corner.

Title Page

1. The title should be as concise as possible. Include only the full names of the authors directly affiliated with the work starting with the first name, middle initial if any, and last name. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate; name and location of no more than three institutional affiliations may be included.

2. If the paper has been presented in a scientific in a scientific program or convention, provide a footnote giving the name, location and the date of the meeting.

Abstract

For original articles, the abstract should contain no more than 200 words and should have a structured format consisting of the objective, methodology, results and conclusion. For case reports, the abstract should be from 50 to 75 words and need not be structured. At least 3 keywords, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

Text

1. Generally, the text should be organized consecutively as follows: Introduction, Materials and Methods, Results and Discussion (and Conclusion).

2. All References, tables, figures and illustrations should be cited in the text, in numerical order.

3. Even if commonly employed, all abbreviations should be spelled out once, the first time they are mentioned in the text, followed by the abbreviations enclosed in parentheses. Subsequently, the same abbreviations may be used instead of the long names.

4. All measurements and weights should be in System International (SI) units.

5. Acknowledgements to individuals/groups of persons, or institution's should be included at the end of the text just before the references, Grants and subsidies from government or private institutions should also be acknowledged.

References

1. References in the text should be identified by Arabic Numerals in enclosed parentheses on the same line as the preceding sentence.

2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text.

3. All references should provide inclusive page numbers.

4. Journal abbreviations should conform with those used in the Index Medicus,

5. A maximum of three authors per article can be cited, beyond that,"et al", is added

6. The style/punctuation conforms to that recommended by the ICMJE, which is the ANSI standard styled used by the NLM, and should follow the format of the examples shown below:

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Book

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1. Cite all tables consecutively in the next and number them accordingly. Create tables preferably using a spreadsheet program such as MS Excel with one table per worksheet. Tables should not be saved as image files. The content of tables should include a table number (Arabic) and title in capital letters above the table, and explanatory notes and legends as well as definitions of abbreviations used below. Recommended font is Arial Narrow size 8.

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Figures or graphs should be identified by Roman Numeral/s with titles and explanations underneath. The numbers should correspond to the order in which the figures/graphs occur in the text. It is recommended that figures/graphs also be submitted as image files (preferably as .jpeg or.gif files) of high resolution. All identifying data of the subject/s or patient/s under study such as name, case numbers, etc., particularly in case reports should be removed.

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1. All illustrations/photographic prints should be submitted in duplicate and placed in a separate envelope.
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Contact Information

For comments, questions, and concerns, contact:

Paul Matthew Pasco, MD, MSc

Editor-in-Chief

The PCMC Journal

Philippine Children's Medical Center

Quezon Ave., Quezon City

Tel No. 8588-9900 local 1308

crd@pcmc.gov.ph

www.pcmc.gov.ph/research

ARTICLE

Association between training culture and burnout among residents and fellows during the Covid-19 pandemic in a pediatric tertiary hospital

Alvin C. Agustin, Soraya A. Alvarado

OBJECTIVE: Medical trainees have increased burnout compared to the general population. This may be attributed to physiological stress, increased workload, work demands, and the training culture. This study evaluated the association between the current training culture of the residents and fellows and prevalence of burnout at the Philippine Children's Medical Center.

MATERIALS AND METHODS: Two validated survey instruments were utilized in this study: the Organizational Culture Assessment Instrument (OCAI) to assess the current and preferred training culture among the trainees, and the Maslach Burnout Inventory (MBI) to evaluate the prevalence of burnout among participants.

RESULTS: Ninety-two (pediatric residents = 50; fellows = 42) trainees were included in the study. Whereas the current identified training culture in the institution was the market or compete culture, respondents preferred the clan or collaborative culture. Majority of trainees scored high among the 3 domains of burnout: 72% for emotional exhaustion, 64% for depersonalization, and 57% in personal accomplishment. Market culture was significantly associated with emotional exhaustion and depersonalization.

CONCLUSION: The prevalence of burnout among medical trainees is a significant issue that requires attention. It is essential to implement programs to decrease burnout and shift towards a supportive training culture. This study suggests a gradual shift towards a clan culture, which can help promote collaboration, mentorship, and mutual support among trainees. Such changes will not only improve the well-being of trainees, but also enhance the quality of patient care.

KEYWORDS: *training culture, burnout, trainees*

INTRODUCTION

Culture is defined as a set of shared attitudes, values, goals, and practices that characterizes a particular group or community[1]. Culture influences the performance, engagement, and competitiveness of an organization[3]. In the hospital setting, medical residents and fellows-in-training are considered part of an organization as they share the same objectives and principles in their training program. Bing-You in 2019, reported that a clan culture was the current culture preferred by medical residents[4]. A clan culture denotes a familial atmosphere where the emphasis is on people, with everyone being highly regarded. The primary focus of this culture is to facilitate effective communication among its members[5].

Burnout syndrome is increased feelings of emotional exhaustion and development of negative attitude and feelings towards oneself and to other people, leading to physical exhaustion, depersonalization, and work inefficiency[6]. Physicians experience a higher rate of burnout compared to the general population[7], with the highest prevalence observed among medical trainees[8]. The recent pandemic and new changes in the pediatric residency and fellowship training are difficult times which can take a significant physical, mental, and emotional disadvantage to the medical trainees[9]. The endpoint is residents and fellows will quit[10]. According to a study conducted at the Philippine General Hospital (PGH) Department of Pediatrics, 89.83% of pediatric residents experienced high levels of burnout during the COVID-19 pandemic, compared to 36.5% among their trainees during 2016[11]. Similarly, a study done last 2015 at the Philippine Children's Medical Center (PCMC) revealed that only 18% of pediatric residents experience high levels of burnout[12]. Over the past two years since the onset of the COVID-19 pandemic, the PCMC residency training program has witnessed a decline in the number of applicants and an increase in trainee attrition. In 2021, 41% of first-year residents resigned, while 29% of them discontinued their training within the first six months of 2022. To provide support to the residents and fellows amidst the pandemic, regular psychosocial assistance was offered in the form of group activities and inspirational messages through a Viber group.

Organizational culture, including the "training program" culture provides guidelines and identity in the workplace[13]. There are 4 types of organizational culture: the market or complete culture, which focuses on completing work and getting things done. The hierarchy culture emphasizes authority and obedience. Medical residents' perception of a hierarchy culture is negatively associated with effective feedback[4], furthermore, studies have shown a correlation between hierarchy culture and workplace bullying among nurses[14]. The clan culture is friendly and collaborative, promoting teamwork and conflict management.

With regards to patient care, clan culture improves overall quality of care, relationship, and communication within co-workers[15-16]. Moreover, there is a positive and significant relationship between clan culture and intention to stay among healthcare workers[17]. Lastly, the adhocracy or create culture, focuses on innovation, entrepreneurship, and creative solutions. Burnout in healthcare is influenced by situational, personal, and work-related stressors. It is associated with increased medical errors and reduced quality of patient care[18]. There is also an increase in suicidal thoughts among medical trainees who experience burnout[19]. The day-to-day work in the hospital and the learning environment, which includes the training program, organization, and overall atmosphere, is a complex structure. Mentors and feedback play a crucial role in burnout prevention[18]. Positive mentor relationships and regular feedback are associated with lower burnout symptoms. A negative learning environment culture, including experiences with consultants, nurses, administrative staff, and patients, can influence burnout among male and female residents[20]. Contributing factors to high burnout levels include psychological stress, longer work hours (>100 hours/week), and working in a public institution[21]. The COVID-19 pandemic has led to increased burnout among frontline health workers due to stress, depression, and anxiety[22].

The findings of this study aim to benefit both the trainees and the medical education training core in dealing with the prevalence of burnout among trainees and improving the training culture conducive for learning as well as maintaining general well-being of the residents and fellows. Identified confounding factors are mental health disorders and the current rotation of the trainees, which may affect the prevalence of burnout. This study aims to investigate the association between the training culture and prevalence of burnout among the pediatric trainees during the COVID-19 pandemic. The specific objectives are to identify the current and preferred training culture, determine prevalence of burnout, and examine the association between training culture and burnout. The results of this study will provide insight to the impact of the training culture on burnout, highlighting the need for addressing this issue and possibly making amendments in the pediatric residency and fellowship training to reduce burnout and drop-out rate.

Materials and Methods

This cross-sectional study was conducted between October to December 2022 at the Philippine Children's Medical Center. The study included pediatric residents and fellows with more than 6 months of training during the data collection period, while subspecialty fellows not under the Philippine Pediatric Society (PPS) and outside rotators (residents and fellows) were excluded.

The study employed a total population sampling approach and was appropriate due to

the small and well-defined characteristics of the population (i.e. all pediatric trainees). To determine the association between the dominant training culture and burnout, a minimum sample size of 86 participants was utilized. This sample size provided 80% statistical power to detect an effect size of 0.40 using Spearman correlation analysis, with a significance level of 0.05.

This study was administered via pen-and-paper format. Prior to data collection, the investigator provided an orientation to the pediatric trainees either through an online platform (such as Zoom or Google Meet) or in person. The survey instruments were individually number coded for each trainee and enclosed in a brown envelope that corresponded to their year level (for residents) or subspecialty (for fellows). The envelopes were distributed by the primary investigator, and trainees who voluntarily participated, signed copies of the informed consent form. Regular reminders were sent via text message by the investigator during data collection. The completed survey instruments were personally collected by the investigator and encoded in MS Excel.

The two validated survey instruments used were the Organizational Culture Assessment Instrument (OCAI) and the Maslach Burnout Inventory (MBI) to assess the training culture and burnout, respectively. The Organizational Culture Assessment Instrument (OCAI) is a validated tool for evaluating organizational culture, which was developed by Robert Quinn and © Kim Cameron at the University of Michigan[23]. Based on their Competing Values Framework, it assesses the organization's internal versus external focus and stability versus flexibility, and categorizes organizations into Clan, Adhocracy, Hierarchy, and Market culture[24]. The OCAI consists of 24 questions divided into 6 categories: dominant characteristics, organizational leadership, management, organizational glue, strategic emphases, and criteria for success, using a 100-point scale divided among the four cultures (A – Clan, B – Adhocracy, C – Market, D – Hierarchy) in each category. The instrument has been validated in the healthcare-setting[25] and has been used extensively in hospital organizations worldwide[26-27]. Locally, it has also been used in our hospitals[28] and schools for research purposes[29-30].

The Maslach Burnout Inventory (MBI) is a widely used tool considered as the "gold standard" in measuring burnout and has been validated in countries worldwide, particularly in the healthcare setting[31]. It accurately assesses the 3 dimensions of burnout among healthcare professionals, namely, emotional exhaustion, personal accomplishment, and depersonalization[32]. The tool has been extensively used in the Philippines especially among healthcare workers, such as medical residents, nurses, and emergency room personnel[11,33-35]. It has 22 items divided into the 3 components written in the form of statements about personal feelings and

attitudes[36]. The MBI is oriented with the World Health Organization's 2019 definition of burnout as a valid occupational phenomenon[37]. The tool uses a 7-point scale for responses, which can range from 0 or "never" to 6 or "every day". Emotional exhaustion is defined as a state of emotionally worn-out and drained because of stress from a person's life or at the workplace[38]. Depersonalization or derealization disorder involves a recurring feeling of being detached from one's body or mental process[39]. The last subscale in the MBI is the personal accomplishment which is composed of 8 questions about a person's achievement, energy, and actions toward the patient[36]. A higher mean score in emotional exhaustion and depersonalization indicates an increased level of burnout, while a higher mean score in personal accomplishment reflects a low-level of burnout. Approval from Professor Robert E. Quinn and © Kim Cameron was sought and granted prior to data collection. The Maslach Burnout Inventory (MBI) was purchased online in the official publisher website, Mind Garden Incorporated.

Frequency was used to summarize the current and preferred culture of the residents and the fellows in the different subspecialties. The average of each alternative, which corresponds to the four cultures, in the OCAI survey was computed to identify the dominant culture. The mean and standard deviation were computed to determine the prevalence of the three dimensions of burnout[36]. A high degree of exhaustion is defined as more than or equal to 27 (Table 1), moderate degree for scores 19-26, and low degree for less than or equal to 18. To evaluate depersonalization, a high degree is defined as more than or equal to 10, moderate degree for scores 6-9, and low degree for less than or equal to 5. For personal accomplishment assessment, a high degree is defined as more than or equal to 40, moderate degree for scores 34-39, and low degree for less than or equal to 33.

Table 1. Levels of Burnout Domains

	HIGH	MODERATE	LOW
Emotional Exhaustion	≥27	19-26	≤18
Depersonali-zation	≥10	6-9	≤5
Personal Accomplish-ment	≤33	34-39	≥40

Spearman correlation analysis, a commonly employed non-parametric test, was used to assess the relationship between the dominant training culture and burnout, specifically measuring the prevalence of emotional exhaustion, depersonalization, and personal accomplishment. This statistical analysis method is frequently used to determine the strength of association between two variables.

Approval was sought from the Institutional Research – Ethics Committee prior to commencement of data collection. Prior to data collection, the participants were required to give informed consent as per the

National Ethical Guidelines for Health and Health-Related Research (2017), while ensuring their privacy in accordance with the Data Privacy Act of 2012 by maintaining anonymity. Instead, identification numbers were assigned to each trainee for encoding data, and only the investigator has access to the master list of all participants. Trainees who scored moderate to high in each burnout domain were provided with contact information for appropriate mental health support, while maintaining their anonymity from others.

This research paper was submitted to the Center for Research and Development (CRD) and General Pediatric Services Division (GPSD) of the Philippine Children's Medical Center. The physical copies of the survey forms were securely stored in a filing cabinet located at the PCMC General Pediatric Services Division Office. These records will be disposed through shredding after three years or earlier if deemed unnecessary. Digital copies of the data were saved on a password-protected portable digital storage device (USB) which is solely accessible to the primary investigator. The data will be permanently deleted by reformatting the storage disk along with the hard copies.

RESULTS

A total of 92 trainees participated in the study, which included 50 pediatric residents and 42 fellows from the different subspecialties: adolescent medicine (3), ambulatory pediatrics (1), pediatric infectious diseases (7), nephrology (3), hematology and oncology (4), pulmonology (3), neonatology (5), endocrinology (2), pediatric critical care (5), gastroenterology (2), neurology (1), and neurodevelopmental pediatrics (6). Eleven participants (3 residents and 8 fellows) were not included in the study because they either graduated (9), did not return the questionnaires (1), or resigned from training (1).

The results show that the current dominant training culture among the trainees (Table 2), is the market or compete culture (mean = 28.0%).

Table 2. Overall Current Dominant Culture

Culture Type	Mean (%)
Clan	26.7
Adhocracy	19.1
Market	28.0
Hierarchy	26.1

Among the 12 pediatric subspecialties, six have market or compete cultures, namely, adolescent medicine, ambulatory pediatrics, hematology-oncology, neurodevelopmental pediatrics, neurology, and pulmonology (Table 3). The sections of endocrinology, nephrology, pediatric critical care, and pediatric infectious diseases have a clan or collaborate culture. The section of neonatology has 2 current dominant cultures, the market (mean = 26.3%) and clan culture (mean = 26.3%). The gastroenterology section has a current culture of hierarchy (mean = 37.1%)

Table 3. Current Dominant Culture according to trainees

Subspecialty	Culture Type			
	Clan	Adhocracy	Market	Hierarchy
	Mean (%)			
Adolescent Medicine	23.3	18.6	29.4	28.6
Ambulatory Pediatrics	30.0	20.0	30.8	19.2
Endocrinology	34.2	13.8	21.3	30.8
Gastroenterology	20.8	12.1	29.6	37.1
Hematology and Oncology	19.2	19.6	30.8	30.0
Neurodevelopmental Pediatrics	18.1	17.5	32.8	31.7
Neonatology	26.3	24.4	26.3	23.1
Nephrology	39.7	14.7	19.2	26.4
Neurology	26.7	18.3	36.7	18.3
Pediatric Critical Care	34.5	19.2	28.8	17.7
Pediatric Infectious Diseases	35.7	18.8	18.5	27.5
Pulmonology	23.5	22.7	27.1	26.3
Residents	25.9	19.4	29.1	25.5

The preferred training culture among all trainees is the clan or collaborate culture (mean = 34.1%) (Table 4).

Table 4. Overall Preferred Culture

Culture Type	Mean (%)
Clan	34.1
Adhocracy	22.7
Market	23.1
Hierarchy	22.6

Except for one, all subspecialties including the residents prefer clan or collaborate culture. Only the section of endocrinology favors market or compete culture (Table 5).

Table 5. Preferred Culture according to trainees

Subspecialty	Clan Type			
	Clan	Adhocracy	Market	Hierarchy
	Mean (%)			
Adolescent Medicine	26.4	25.6	25.6	24.2
Ambulatory Pediatrics	27.5	21.7	25.8	22.5
Endocrinology	25.4	31.7	33.3	18.8
Gastroenterology	27.9	23.3	24.2	23.8
Hematology and Oncology	29.2	23.3	25.8	22.5
Neurodevelopmental Pediatrics	34.2	21.0	21.5	24.6
Neonatology	27.7	24.2	24.2	24.8
Nephrology	46.7	22.2	22.5	17.5
Neurology	29.2	25.0	23.3	24.2
Pediatric Critical Care	39.3	18.4	20.1	23.3
Pediatric Infectious Diseases	45.7	18.5	19.9	23.5
Pulmonology	29.8	22.3	21.7	27.3
Residents	33.7	23.3	23.2	22.0

For the prevalence of burnout among all pediatric trainees (Table 6), 66 respondents have high levels of emotional exhaustion (72%), 13 have moderate levels (14%), and 13 have low levels (14%). For depersonalization, 59 respondents have high levels (64%), 16 have moderate levels (17%), and 17 have low levels (19%). Lastly, 52 respondents have low levels of personal accomplishment (57%), 27 have moderate levels (29%), and 13 have high levels (14%).

Among the residents (Table 6), 43 of them have high levels of emotional exhaustion (86%), 6 have moderate levels (12%), and 1 have low level (2%). For depersonalization, 42 residents have high levels (84%), 6 have moderate levels (12%), and only 2 have low levels (4%). For levels of personal accomplishment, 37 respondents have low levels (74%), 10 have moderate levels (20%), and 3 have high levels (6%).

Table 6. Frequency of trainees according to burnout levels for each burnout domain

	Emotional Exhaustion			Depersonalization			Personal Accomplishment		
	Low	Mod	High	Low	Mod	High	Low	Mod	High
Adolescent Medicine	2	0	1	2	0	1	1	0	2
Ambulatory Pediatrics	1	0	0	1	0	0	1	0	0
Endocrinology	1	0	1	1	0	1	1	1	0
Gastroenterology	0	1	1	0	2	0	0	2	0
Hematology and Oncology	1	1	2	0	2	2	1	3	0
Neurodevelopmental Pediatrics	0	1	5	1	0	5	3	0	3
Neonatology	1	2	1	2	1	1	1	2	1
Nephrology	1	0	2	1	0	2	2	1	0
Neurology	0	0	1	0	0	1	0	1	0
Pediatric Critical Care	1	1	3	1	3	1	2	2	1
Pediatric Infectious Diseases	3	1	3	3	2	2	3	2	2
Pulmonology	1	0	3	3	0	1	0	3	1
Residents	1	6	43	2	6	42	37	10	3
TOTAL	13	13	66	17	16	59	52	27	13

Spearman's test of association was computed to assess the relationship between the current dominant training culture and the domains of burnout (Table 7). There was a positive association between emotional exhaustion (spearman rho = 0.437, p <0.001) and depersonalization (spearman rho = 0.347, p <0.001) with the market culture, while it is not linked with personal accomplishment (spearman rho = -0.140, p 0.183).

Table 7. Association between the market culture and domains of burnout

	Emotional Exhaustion	Depersonalization	Personal Accomplishment
Spearman rho	0.437	0.347	-0.140
p-value	<0.001	<0.001	0.183

DISCUSSION

Prior to the COVID-19 pandemic, 18% of pediatric residents at the Philippine Children's Medical Center (PCMC) reported experiencing high levels of burnout[12]. This study revealed a notable increase in all three domains of burnout during the pandemic: 72% experienced significant emotional exhaustion, 64% exhibited high levels of depersonalization, and majority (57%) had low levels of personal accomplishment. The results are comparable to the study done at the Philippine General Hospital (PGH), which also revealed high levels of burnout among pediatric residents during the pandemic[11]. The observed outcomes could be attributed to the confounding variable of the ongoing pandemic. In general, a significant majority of the medical trainees reported high levels of burnout across all three domains. This aligns with the global trend of elevated burnout rates among physicians during the pandemic, likely influenced by factors such as increased patient load, long working hours, and night-work shifts[40].

Recognizing the significance of the training culture is crucial as it can either enhance or diminish an institution's objectives and goals. A positive culture plays an important role as it attracts applicants, fosters engagement, promotes retention, and influences satisfaction, all of which impact overall performance. A study in a hospital in the UK[41] found that their current dominant culture is market culture while its preferred is clan culture, same with the results of this study. In terms of providing care to patients, the clan culture offers better quality of care and high patient satisfaction compared to market culture[42-43]. Market culture is characterized by a prominent sense of competition among individuals, with a strong focus on achieving results and prioritizing the needs of clients or patients. While it offers benefits such as increased productivity and self-improvement, an excessively competitive environment can lead to unhealthy competition and burnout[44], as supported by the findings of this study. On the other hand, the preferred clan culture fosters collaboration, commitment, participation, and loyalty, while promoting a sense of belongingness and open communication, creating a family-like atmosphere and a positive working environment.

A shift to a clan culture in an institution can increase work engagement and job satisfaction, reduce medical errors and patient complaints, and create a healthy patient safety environment[45]. It is imperative to gradually change the training culture of the trainees to address the high prevalence of burnout and their preferred clan culture. Various interventions are recommended to address burnout, which includes increasing awareness of burnout in the hospital, implementing stress-reduction programs that incorporate regular mental health and emotional awareness activities facilitated by professionals, establishing a comprehensive wellness curriculum for trainees to foster well-being, providing workshops on communication skills and managing difficult patient interactions, and ensuring a manageable workload. Additionally, encouraging regular mentor-mentee discussions and organizing team-building activities can also be effective strategies in reducing burnout[46]. In shifting to a clan culture, the organization needs to establish trust with its trainees by developing deeper connections with them. Instead of individual recognition, encouraging shared team rewards can foster a sense of teamwork, and boosting resident's morale through their inclusion in the Program on Awards and Incentives for Service Excellence (PRAISE) committee of the institution. Furthermore, promoting a feedback culture can enhance the bond among trainees, encouraging open communication between each other and with their superiors. Creating a sense of connection within the organization can lead to improved individual and team performance, ultimately resulting in overall team success.

The limitation of this study is the few respondents in some subspecialties. Furthermore, the research was done during a pandemic which may be a confounding variable in the prevalence of burnout.

A follow-up study should be carried out in the future to monitor the prevalence burnout among the trainees and if there is a change in the culture of the institution. Additionally, conducting a supplemental study (categorical analysis) may also be done to assess association between other types of culture and burnout, as well as exploring the prevalence of burnout among residents across different year levels, fellows in each subspecialty training, post-graduate interns (PGI), and medical students.

Conclusion

The high prevalence of burnout among the pediatric trainees in our institution is congruent with the experiences of most medical residents worldwide. This study revealed that the current training culture is associated with burnout, specifically on emotional exhaustion and depersonalization. Preventive measures should be implemented to

burnout of the trainees and a gradual shift to the preferred clan culture, which negatively correlates with burnout.

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ARTICLE

Short term outcomes of children with acute kidney injury treated with hemodialysis in a tertiary pediatric hospital: a six-year review

Socorro Marie V. Buensalido, Nathan C. Bumanglag

OBJECTIVE: This paper aimed to describe the clinical profile and short-term clinical outcomes of children with Acute Kidney Injury (AKI) requiring hemodialysis in a tertiary pediatric hospital.

MATERIALS AND METHODS: A retrospective cohort on in-patients who received hemodialysis treatments at our institution was performed. Medical charts of patients admitted between July 2018 and July 2023 were retrieved. Demographic data, clinical profiles and subsequent outcomes in terms of mortality and recovery or non-recovery from AKI were recorded.

RESULTS: After meeting the inclusion and exclusion criteria, 129 patients were included in the study's statistical analysis. There was an even distribution between males and females. The average age of treated patients was 10 years old (SD ± 4.3). The average weight of patients was 35kg (SD ± 16.9). The most common diagnosis of patients was severe dengue (21.7%), followed by severe sepsis (14.7%). More than half of patients (51.9%) had an existing co-morbidity, of which Systemic Lupus Erythematosus (22.4%) and solid tumors (22.4%) were most common. The most common indication for hemodialysis was uremia (52.7%). In terms of short-term outcome, majority of patients died during the same admission (56.5%), while 31 patients (24.0%) recovered.

CONCLUSION: The clinical profile of patients who underwent hemodialysis treatments for AKI were comparable to international data. The study did not differentiate deaths from AKI or underlying illness, but demonstrated a higher mortality rate compared to other existing studies. This study is the first known local paper to describe the profile and outcomes of children who received hemodialysis for AKI.

KEYWORDS: *Pediatric AKI. Hemodialysis. Outcomes. Severe sepsis. Severe dengue.*

Introduction

Acute Kidney Injury (AKI) is a well-recognized complication in hospitalized children and has been observed in patients both critically-ill and non-critically ill. Its clinical implications include a wide range of short-term to long-term complications of varying degrees of severity. It may result in immediate consequences such as death or may extend well beyond the initial inciting event, and eventually be a risk factor for the development of Chronic Kidney Disease (CKD) in adulthood. To date, there are no known published studies profiling patients who develop pediatric AKI in the country and their subsequent outcomes. Consequently, there is also a lack of robust data on the most common etiologies of pediatric AKI in the country, as well as the most common indications for Renal Support Therapy (RST), and outcomes of RST in these patients. Such information is important in guiding physicians and policy-making bodies make important and informed decisions with regards to managing these cases on the clinical and public health level.

In the latest local report of Renal Disease Registry by the Pediatric Nephrology Society of the Philippines (1), there was a total of 408 reported cases of AKI in 2022, with 10.8% requiring any form of RST. No data are available outlining the etiologies and outcomes of the cases above. A review of studies in other countries showed a predominance of infectious etiologies of AKI. Clinical outcomes of these cases varied widely depending on the etiology of the disease, existing co-morbidities, and other factors such as availability of different modalities of RST.

This study was conducted in a referral institution receiving cases from secondary and provincial hospitals around the country. The unit is manned by pediatric-trained nursing and physician staff. The aim of this study was to describe the clinical profile and outcomes of children who required hemodialysis treatments in the management of AKI in a tertiary pediatric hospital in the Philippines. Further, it aims to provide a picture of the most commonly encountered cases of pediatric AKI in the country.

Materials and Methods

The study was a single-center retrospective cohort of patients admitted at a tertiary children's hospital who underwent hemodialysis treatment for AKI between July 2018 and July 2023. All records of admitted patients who underwent hemodialysis treatments for AKI between the said study period were retrieved and reviewed for completion of data.

Following approval from the Institutional Research Ethics Committee, a list of all patients who received hemodialysis treatments for AKI was submitted to the

medical records section for chart retrieval. Records of patients who fulfilled the inclusion and exclusion criteria were included in the study. Patients who underwent treatment for reasons other than acute kidney injury (hemoperfusion only, drug intoxication, etc.) were excluded.

The diagnosis of AKI was made with the fulfillment of the KDIGO criteria and staging system for AKI based on the presence of an increase in serum creatinine and decrease in urine output. A review of charts was done to collect data on demographics, clinical impression on referral, existing co-morbidities, if present, and indications for dialysis. Short-term outcomes were defined as any one of the following outcomes upon discharge from the present admission, or death:

a) mortality

b) AKI – recovered

c) Acute Kidney Disease or

d) Chronic Kidney disease

All patients and corresponding medical records were assigned a case number during data collection. Identifying information including name and addresses were not recorded and a non-disclosure and confidentiality agreement with the Medical Records was also completed prior to data collection.

All data were encoded in Microsoft Excel. SPSS 24 was used for data processing and analysis. Patient characteristics were summarized as means with standard deviation for continuous variables and frequency with proportions for categorical variables. The rates mortality, AKI recovery, AKD and CKD were summarized using incidence rates with 95% confidence interval.

RESULTS

A total of 174 acute hemodialysis (HD) treatments were identified from the Hemodialysis Unit master list of patients. Thirty-nine patients who were treated with hemoperfusion only (no diagnosis of AKI), and six patients who had a diagnosis of AKI on top of CKD were excluded from data analysis. A total of 129 patients were analyzed.

Baseline clinical profile showed a comparable distribution between males and females. Most patients who received HD treatments belonged to the 11-15 year-old age group. The average weight of patients was 35kg and ranged between 9-78kg. Average body surface area (BSA) was 1.1.

Table 1. Demographic profile, underlying disease and comorbidities of children with AKI who underwent hemodialysis treatments between July 2018 – July 2023

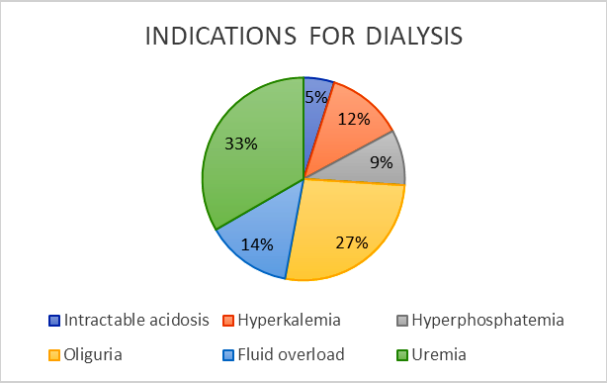
DEMOGRAPHICS		**N=129**
Age, years (mean ± SD)		*10.4±4.3*
Gender		
	Male	*62 (42.1%)*
	Female	*67 (51.9%)*
Weight, kg (mean ± SD)		*35.4±16.9*
Height, cm (mean ± SD)		*134.8±25.9*
Body surface area, m2 (mean ± SD)		*1.1±0.4*
UNDERLYING DISEASE		**N=129**
AKI/MODS sec to Severe Dengue		*28 (21.7%)*
AKI/MODS sec to Severe sepsis		*19 (14.7%)*
RPGN sec to Glomerulonephritis (excluding SLE)		*15 (11.6%)*
Tumor Lysis Syndrome		*13 (10.1%)*
AKI/MODS sec to Leptospirosis		*12 (9.3%)*
AKI/RPGN sec to Lupus nephritis		*11 (8.5%)*
Others		*10 (7.8%)*
AKI sec to obstructive uropathy		*7 (5.4%)*
AKI sec to diabetic ketoacidosis		*3 (2.3%)*
AKI sec to autoimmune vasculitis		*3 (2.3%)*
AKI sec to Vancomycin toxicity		*2 (1.6%)*
AKI sec to MIS-C		*2 (1.6%)*
AKI sec to atypical HUS		*2 (1.6%)*
AKI sec to cardiorenal syndrome		*1 (0.8%)*
AKI sec to hepatorenal syndrome		*1 (0.8%)*
CO-MORBID CONDITIONS		**N=67**
Solid tumor		*15 (22.4%)*
Systemic Lupus Erythematosus		*15 (22.4%)*
Leukemia		*7 (10.4%)*
Tuberculosis infection		*5 (7.5%)*
Cardiac condition		*3 (4.5%)*
Diabetes mellitus type 1		*3 (4.5%)*
Autoimmune vasculitis		*3 (4.5%)*
Nephrotic Syndrome		*2 (3.0%)*
Renal tubular acidosis		*2 (3.0%)*
Cerebral palsy		*2 (3.0%)*
COVID infection		*2 (3.0%)*
Portal hypertension		*1 (1.5%)*
Hereditary Spherocytosis		*1 (1.5%)*
Henoch Schonlein Purpura nephritis		*1 (1.5%)*
Neurogenic bladder		*1 (1.5%)*
Anti-NMDAR encephalitis		*1 (1.5%)*

The most common clinical impression of patients who were referred for hemodialysis treatments was severe dengue, followed by severe sepsis, with rapidly progressing glomerulonephritis (excluding those secondary to lupus nephritis).

About half of all patients (51.9%, N=67) had preexisting co-morbidities, with systemic lupus erythematosus (SLE) and solid tumors as the most common conditions.

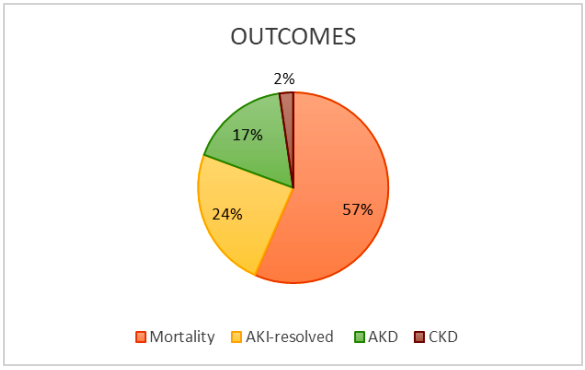
Fifty-six patients (43.4%) presented with a multiple indications for hemodialysis, with uremia as the most common indication, followed by oliguria (42.6%) and fluid overload (21.7%), and hyperkalemia (19.4%).

Figure 1. Indications for initiation of hemodialysis in 129 children with AKI



In terms of short-term outcomes, most patients who underwent hemodialysis died within their admission. Twenty-four (24%) percent had complete recovery from AKI. Twenty-two (22%) were discharged with stable, but elevated serum creatinine levels, while 3% were discharged as confirmed cases of chronic kidney disease.

Figure 2. Outcomes of 129 children with acute kidney injury treated with hemodialysis



Discussion

Acute Kidney Injury or AKI is defined as a decrease in glomerular filtration rate (GFR), as manifested by an elevated or a rise in serum creatinine from baseline, and/or a reduction in urine output (2), that may result from renal ischemia, sepsis, or toxicant-induced renal cell injury (3). In pediatrics, the most commonly adopted criteria and staging system is the KDIGO criteria which takes into account either an increase in serum creatinine levels or a decrease in urine output for a certain time period. This criteria system was used in the identification of cases of pediatric AKI for this study.

Owing to the advancements in diagnosis and early detection of the condition, AKI has been increasingly recognized as a common complication in hospitalized patients in the

recent years. It has been best described in cases of critically-ill children but has also been found to play a significant role in non-critically ill patients. Some studies report that it can occur in 5% of hospitalized children, while it may be present in 20-30% of critically-ill children (3). AKI may result from a host of risk factors and inciting events and may as well, result in various short-term and long-term outcomes.

This study included only patients who encompass AKI stage 3, who required hemodialysis during their hospitalization, and aimed to define the clinical profiles of these patients. Short-term clinical outcomes were defined as outcomes within the same admission as the initiation of hemodialysis treatments and were recorded upon discharge or occurrence of death.

Patient Anthropometrics

As in many other medical procedures, pediatric hemodialysis differs from that of the adult population in that many technical considerations are dependent on the patient's anthropometrics (weight, height and BSA). Calculated blood flow and dialysate flow rates for hemodialysis are based on a patient's weight and equivalent estimated blood volume, and are therefore much lower compared to adult prescriptions. Additionally, most of available equipment and consumables related to hemodialysis use in the country are adult-sized given that majority of hemodialysis centers cater mostly to adult patients. This may serve as a challenge for hemodialysis centers catering to small children who will need modifications to their HD prescriptions and setups in order to utilize adult blood lines, dialyzers, catheters and other supplies. Results of this study found that most patients who required hemodialysis treatments for AKI weighed an average of 35kg, translating to an estimated blood volume of 2,450mL. Dialyzer size was determined by the patient's corresponding BSA and available dialyzers in the institution ranged between BSA of 1.0 and 1.8. Subsequent extracorporeal blood volume was then determined by the dialyzer size appropriate for the patient's BSA. The rule that the volume of extracorporeal blood circuit should not exceed 10% of the patient's estimated blood volume is a generally accepted one (4). In cases where ECV exceeds 10% due to the inappropriately-large extracorporeal volumes associated with using adult lines and dialyzers, priming of dialysis circuits is employed in our center. Depending on the patient's hemodynamic stability and current hematocrit current practice in our center includes using either 5% albumin or blood products, such as packed red blood cells or reconstituted whole blood for priming, depending on the individual needs of patients. This consideration has important operational implications for pediatric hemodialysis units.

Because pediatric patients vary significantly in terms of anthropometrics, a dialysis unit catering to this population must be equipped not only with a range of differently-sized blood lines and dialyzers, but also with resources that will allow for accessible blood and other priming products to ensure that safe and efficient dialysis treatments are delivered to patients.

This becomes an important consideration in future pediatric centers in the country. In order to effectively cater to very small children, availability of pediatric blood lines and dialyzers in addition to availability of priming products such as albumin and blood are mandatory. \

Illnesses and AKI

Several factors have been known to incite kidney injury resulting in laboratory and clinical manifestations of AKI, and underlying illnesses may differ from population to population. Additionally, it has been suggested that that severity of AKI correlates with disease severity (5). Our study has found that the most common diagnosis of patients who received hemodialysis treatments for AKI was severe dengue (21.7%) followed by severe sepsis (14.7%), and then by various etiologies of glomerulonephritides (11.6%). This is similar to findings of international studies that identified infection and glomerular disease as leading causes of etiology of AKI in children, especially in lower-income countries where access to healthcare and health-seeking behavior are lacking, and where communicable diseases, including zoonotic diseases are still prevalent. This is in comparison to more developed countries where etiologies of AKI are commonly associated with complex surgical procedures as a consequence of volume depletion, prolonged ischemia from cardiac surgeries, or use of nephrotoxic medications. This highlights the fact that there remains to be much room for improvement in terms of early detection and prevention of communicable diseases that result in major health implications in the country.

This study also identified tumor lysis syndrome as one of the top etiologies of hemodialysis-requiring AKI. This may be due in part to the institution being a cancer and hematology referral center in the country, with a significant population of patients with hematologic and oncologic conditions, in whom tumor lysis syndrome may occur.

Comorbidities and AKI

Other than etiology of AKI, this study also to identified pre-existing co-comorbidities of children who underwent hemodialysis treatment for AKI. We found that 52% (N=67) of patients had pre-existing conditions prior to initiation of treatment. The most common comorbidities were found to be solid tumors and systemic lupus erythematosus, which are consistent with the most common primary diagnoses of patients mentioned above.

In these groups of patients, 86% of those with solid tumors and 46% of those with SLE were mortalities. This is consistent with a study published in 2015, where Asinobi et al. found that patients with irreversible comorbidities such as malignancies and glomerulonephritis were at higher risk of mortality compared to those who had a reversible cause of AKI (6). This information may prompt physicians to more closely monitor these patients in whom worse outcomes are associated, compared with patients who do not have pre-existing comorbidities.

Indications for Hemodialysis

Despite the numerous possible etiologies of AKI, there are only a number of indications for initiation of renal replacement therapy. Dialysis modalities are often employed when medical management is not sufficient nor effective, or when consequences of AKI have become life threatening and must be reversed immediately. In our institution two modalities of RST are available: hemodialysis and peritoneal dialysis. Each has its own advantages and disadvantages and the choice of modality ultimately depends on multiple factors determined by the patient's clinical status and availability of equipment and staff knowledgeable about each RST modality. Historically, peritoneal dialysis has performed satisfactorily in the management of pediatric AKI and has been the choice of pediatric nephrologists for RST due to its wide availability in settings of both high-income and low-income countries. In the advent of newer technologies however, such as CRRT and increasing availability of pediatric-specific supplies for conventional dialysis, there had been a decline in the choice of RRT for pediatric AKI (7). Our study showed that the most common indication for hemodialysis in patients with AKI was uremia (52.7%), which may present as uremic encephalopathies and uremic bleed, among other manifestations. This was followed by oliguria (42.6%), fluid overload (21.7%), and hyperkalemia (19.4%) which requires rapid correction to avoid potentially lethal cardiac arrhythmias. As earlier mentioned, all of these indications may be addressed effectively with peritoneal dialysis, albeit with slightly less room for modifications of prescriptions as compared to hemodialysis.

Fluid and ultrafiltration management in hemodialysis may also be slightly more advantageous as compared to peritoneal dialysis in patients presenting with severe fluid overload. This is due to the fact that hemodialysis machines can be modified to attain a more precise ultrafiltration over a specified time of treatment. Furthermore, rates of ultrafiltration may be adjusted in real time at any point during the treatment, which is particularly helpful in patients whose hemodynamics are labile.

Hyperkalemia as an indication for dialysis may correlate with one of the most common etiologies of AKI found in this study.

The institution, being a tertiary referral institution with multiple specialties including hematology and oncology, caters to a large population of children who may present with hematologic emergencies such as tumor lysis syndrome (TLS). Renal replacement modalities such as hemodialysis in particular, are an integral part of the management of these patients. Hyperkalemia remains the most dangerous component of TLS (8) due to the possibility of cardiac arrhythmias and therefore must be corrected promptly. Compared with the other available modality of RST in the institution, hemodialysis offers a much faster ability to correct hyperkalemia and other electrolyte derangements associated with TLS, addressing potentially fatal consequences in a timely manner.

Outcomes of Children with AKI who Received Hemodialysis Treatments

Compared to the adult population, studies exploring outcomes of pediatric cases of AKI requiring HD are limited. This may be due in part to the lack of a standard definition of AKI in the past, which precludes a timely and accurate diagnosis. There had also been several classification and criteria systems that are employed by different centers, resulting in some differences in statistical data of AKI in children. The recent iteration of the KDIGO criteria for diagnosis of AKI will hopefully usher in more standardized data and result in more studies exploring outcomes of HD-requiring AKI in children. Despite the relative paucity of well-documented outcomes of AKI following RST, it is now known that the diagnosis of AKI is a risk factor for the development of chronic kidney disease, hypertension, cardiovascular disease and death in adulthood (9). Short-term sequelae on the other hand include a greater risk for mortality among other complications. Existing studies vary greatly in the incidence of mortality in patients, depending on the geographical location of the centers and the population studied. We found that mortality rates in pediatric AKI ranged between 6.5 – 40% (6, 10, 11, 12). In contrast, our study revealed a higher incidence of mortality with the outcome occurring in 56.5% of patients. It is important however to note that mortalities recorded in our study were all-cause mortalities and did not discriminate between deaths attributable to AKI or deaths attributable to other causes which may have occurred after recovery from AKI but have occurred within the same admission. Further statistical analyses with this data set may help elucidate better a causal relationship between the study's exposures and outcomes.

Less than half of patients included in the study were eventually discharged, with 24% having completely recovered from AKI prior to their discharge from the institution. The remaining patients (19.4%) were discharged with non-normal serum creatinine levels. Three of whom (2.3%) were discharged as cases confirmed of chronic kidney disease while 17% were found to have elevated serum creatinine levels on discharge. The latter group of patients are those in whom serum creatinine levels remained elevated but did not yet meet

the duration of three months to be managed as chronic kidney disease. These patients represent a condition in the spectrum of kidney injury now recognized as Acute Kidney Disease (AKD), who may carry the same risk of progression to chronic kidney disease and other renal complications in adulthood as AKI does. Close monitoring for these patients is imperative as they may exhibit sustained recovery or progressive decline in serum creatinine.

Data from this study demonstrated that the institution through its hemodialysis unit is able to deliver urgent renal support therapy in various cases of acute kidney injury even in very small children despite the lack of age-specific blood lines and pediatric-specific machines. The cases of AKI treated in our dialysis unit were similar to cases documented in international studies, in terms of etiology and indications. Treatments were made possible by the resources available in the institution such as a dedicated blood bank providing essential blood products for circuit priming, which allows hemodialysis treatments for children in whom the extracorporeal blood volume exceeds 10% of estimated blood volume. Such dialysis prescription modifications require special staff knowledge and training and are difficult to carry out in primarily adult-dedicated hemodialysis centers, where experience with pediatric patients are minimal. A study published in 2017 by Raina, et al. reported that pediatric dedicated HD units and trained staff were available only in 33.3% of hemodialysis centers in developing countries (13). This underscores the need for more hemodialysis units able to cater to the pediatric population. In fact, in the 2005 revision of the Hemodialysis General Practical Guidelines from the European Pediatric Dialysis Working Group in 1999, outlined as the first guideline the need for hemodialysis treatments to be "delivered in a pediatric dialysis center with a multidisciplinary support team which supports individualized and integrated therapy" for patients (14). The institution's unit, being an exclusive pediatric hemodialysis center has its staff training focused on pediatric cases and has been integral in the efficacy of delivery of care for these patients. In addition to this, the hospital is also home to several other subspecialties able to attend to patients with differing needs and are part of the multi-disciplinary approach to the management of acute kidney injury in children.

Compared to other existing studies, outcomes of patients treated at our institution were relatively less satisfactory, with more than half of patients succumbing to death. A limitation of the study is not being able to determine which deaths were due to immediate complications of AKI or as a result of other complications of the primary disease. Additionally, the study followed up patients up until their discharge, which meant that patients who may have recovered from their AKI and who died for other reasons after recovery from

AKI were still considered as mortalities in their final outcomes.

Conclusions

Our study characterized pediatric patients who underwent acute hemodialysis treatments for AKI in a tertiary pediatric hospital, and showed similar clinical profiles including etiology of AKI, nature of comorbidity, and indications for hemodialysis, as existing studies, particularly in developing nations. In terms of outcomes, majority of our patients fell under mortalities, which, unfortunately, did not distinguish between mortalities directly due to AKI and mortalities not related to renal failure. Dialysis treatments of even very small children were made possible by the institution's pediatric-dedicated facilities such as the blood bank and other subspecialties available, as well as the hemodialysis unit's pediatric-trained nursing and physician staff. This emphasizes the urgent need for more hemodialysis units capable of catering to and effectively delivering pediatric-specific hemodialysis treatments.

To the author's best knowledge, this is the first local study to describe the clinical profiles and short-term outcomes of children who received hemodialysis treatments for AKI. Recommendations for future studies include establishing associations and correlations between etiologies of AKI and outcomes, and delineating mortalities that may directly be attributed to the initial kidney injury from mortalities that are unrelated to acute kidney injury. Thus, a prospective study on this topic is recommended. Additionally, future research may include identification of risk factors for development and incidence of long-term outcomes in patients who developed hemodialysis-requiring AKI in children including other markers of dialysis adequacy, and markers of disease severity such as hospital stay, inotropic support, mechanical ventilation, among others.

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ARTICLE

Utility of the BLUE (Bedside lung ultrasound in emergency) protocol in acute undifferentiated dyspnea among pediatric patients

Christian Anne C. Dauz, Jenina Liza Danao, Joie Aseamie Flores, Cristan Q. Cabanilla, Michael D. Cabato, Jacquelyn Olib-Velazquez

OBJECTIVE: This cross-sectional study aimed to evaluate the effectiveness of the BLUE (Bedside lung ultrasound in emergency) protocol compared to clinicoradiologic diagnosis for promptly identifying acute undifferentiated dyspnea in pediatric patients.

MATERIALS AND METHODS: Conducted at the emergency room of the Philippine Children's Medical Center from August 2022 to May 2023, the study involved performing the BLUE protocol within 2 hours of patient arrival. Chest radiography was also conducted, with images independently interpreted by a pediatric pulmonologist, emergency medicine specialist, and radiologist. The results were then compared to the clinicoradiologic findings.

RESULTS: A total of 111 participants were included, with the majority being male (55.4%) and under 1 year old (48.2%). Pneumonia was the most observed diagnosis (88.2%), followed by asthma (7.2%). Utilizing the BLUE protocol, pneumonia was identified as the most prevalent diagnosis (81%), followed by pleural effusion (12.6%) and asthma (6%). The pulmonologist, emergency medicine specialist, and radiologist exhibited high sensitivity in diagnosing pneumonia (91.01%, 89.89%, 96.77% respectively) but low specificity (26%, 21%, 57.89%). Diagnosing pleural effusion and/or congestion showed high sensitivity (89%) and low specificity (21%) based on the pulmonologist's reading, low sensitivity (37%) and high specificity (99%) based on the emergency medicine specialist's reading, and 100% specificity based on the radiologist's reading. All readers demonstrated high specificity (95%, 93%, 93%) and low sensitivity (50%, 71%, 71%) in diagnosing asthma. The ultrasound readings between the readers exhibited a high concordance rate of 98%.

CONCLUSION: The study findings show that the BLUE protocol has high sensitivity in diagnosing pneumonia and high specificity in diagnosing asthma. The high concordance rate among readers suggests consistent ultrasound findings. These results support the practical application of the BLUE protocol for promptly diagnosing acute undifferentiated dyspnea in pediatric patients within the emergency department.

KEYWORDS: *dyspnea, chest radiography, chest ultrasound*

Introduction

Breathing difficulty, or dyspnea, accounts to 5% of emergency room visits which could be explained by an array of differential diagnosis which could be determined using radiographic techniques.[1-4] A study by Shrestha et al, showed that among patients presenting with dyspnea, the most common diagnosis was involving the respiratory system in 52.3%.[5-8] In relation to this, in 2021 the emergency room consults of Philippine Children's Medical Center was 11, 727. Among these, 258 patients consulted due to difficulty of breathing and accounted for 2.2 % of emergency room visits.

A reduction in in-hospital mortality can be achieved by recognizing and responding quickly to signs of deterioration. [5-6] Resolving symptoms is best achieved by treating the underlying problem. [4] Researchers found that Point of Care Ultrasonography (POCUS) can aid in the diagnosis of respiratory and circulatory failure in critical care settings.[7] In observational studies, POCUS appears to improve the likelihood of early diagnosis and decrease the time to administration of management in both acute respiratory and circulatory failure.[7] Furthermore, POCUS use lessens diagnostic uncertainty and can detect life-threatening illnesses that would otherwise be missed.[7] The Bedside Lung Ultrasound in Emergency (BLUE) method, established by Lichtenstein et al., emphasized the use of lung ultrasonography in the evaluation of breathing difficulties in emergency room visits.[8] Respiratory failure can be accurately assessed using a short technique (less than three minutes long) which could lessen the time for a definitive diagnosis and eventually a definitive treatment.[9] On review of data, in PCMC, it takes an average of 15 minutes to 1 hour for a chest radiography to be done from the time of admission.

An easy, non-invasive approach will help identify respiratory failure early, reducing the risk of unnecessary tests and procedures. Adult studies provide examples of using lung ultrasound in determining different causes of respiratory failure.[9] Although there had been pediatric studies done at the emergency room, most studies done focused on comparing lung ultrasound and radiography with one disease entity. To date, no studies have been done to assess its applicability in the emergency room in the Philippines. The purpose of this study is to investigate the utility of the BLUE Protocol in the diagnosis of acute undifferentiated dyspnea in emergency room patients. Hence this study determined the applicability of the BLUE protocol in comparison to clinical diagnosis using clinical and radiographic findings in the immediate diagnosis of acute undifferentiated dyspnea among pediatric patients.

Materials and Methods

This is a cross-sectional study which determined the utilization of the BLUE protocol in comparison to the clinical diagnosis of the pediatric resident on duty

using clinical and radiographic findings in the immediate diagnosis of acute undifferentiated dyspnea among pediatric patients.

The study was done at the emergency room of Philippine Children's Medical Center (PCMC) from August 1, 2022, to May 31, 2023, which included service patients less than 19 years old with a chief complaint of difficulty of breathing either subjective complaint of the patient or observed by the caregiver. The population computed was adjusted to a known population size. A total of 111 participants were enrolled in this study which included an attrition of 20% to account for possible drop out.

All service patients less than 19 years old with a chief complaint of difficulty of breathing either subjective complaint of the patient or observed by the caregiver and fulfilled the inclusion criteria were eligible to be part of this study, these includes: a.) patients with tachypnea based on age using the PPS guidelines (0 to 3 months: >60bpm, 3 to 12 months: >50 bpm, 1 to 5 years old: >40bpm, more than 5 years old: >30bpm); b) patients with chest indrawing or supraclavicular or intercostal or subcostal retraction. Exclusion criteria included: a) unstable patients ongoing cardiac arrest or post cardiac arrest or impending cardiac arrest with severe bradycardia; b) patients who cannot tolerate the procedure.

Purposive sampling was done. All patients who fulfilled the criteria were considered and no patient was forced to be part of this study. Once a patient who fulfilled the criteria entered the emergency department, the resident on duty informed the primary co-investigators. The primary co-investigator explained the study to the parents or caregiver and patients and secured the consent because the primary investigator was blinded in the recruitment process. The BLUE protocol was not done until the patient was assessed by the pediatric resident on duty to ensure that the patient does not need any additional medical intervention at that moment. After the initial assessment, management or resuscitative measures were done and the patient was stabilized by the pediatric resident on duty, a consent form was obtained from the parents or caregiver and patient by the primary co-investigators. An assent form was taken once the patient was stable and capable of understanding the assent. Within the first 2 hours of the patient's arrival, both BLUE protocol and chest radiography were performed whichever was available first without causing delay on the patient's management. This was assured by the primary co-investigators. No studies were found that determined the acceptable interval between the two procedures. Chest radiography with anterior posterior projection was done as the reference study for chest imaging. Only the primary co-investigators were able to know the history, physical examination and previous diagnostics done on the patient.

The BLUE protocol was performed by the primary investigator (Pediatric Pulmonology Fellow) who underwent online theoretical

theoretical training and point-of-care ultrasound workshop. The primary investigator was blinded to the clinical history and physical examination findings of the patient as well as any previous diagnostics done. The procedure was done in a properly draped area wherein the caregiver/parent, primary investigator and patient were present. Only the part to be examined was exposed. The BLUE protocol was done within 10 minutes using a GE Venue Go ultrasound with microconvex transducer with 3.1 – 12.9 MHz while the patient was on a supine position. The transducer was applied on the chest wall across the intercostal space with the marker oriented towards the head. The study followed the BLUE Protocol. [5-7] Bilateral chest wall was examined starting with the right anterior chest. Areas of investigation followed the BLUE points and protocol. With the transducer placed perpendicularly on the intercostal space, pleural line was evaluated first on the anterior upper and lower chest. Followed by the presence or absence of lung sliding on the anterior upper and lower chest wall using the M mode. Lastly, identification of A line, B Line, Consolidation and Effusion were evaluated using the zigzag technique. R1, R3 and R5 were evaluated first followed by the R2, R4 and R6, the same procedure was done on the contralateral side.

Table 1: Areas of investigation[6]

Chest	**Sector**	**Boundaries**
Anterior	R1 or L1 (anterior upper)	Upper: Clavicle Lower: 4th rib Medial: Sternal edge Lateral: Contents of axilla or clavipectoral triangle
	R2 or L2 (anterior lower)	Upper: 4th rib Lower: variable depending on habitus, abdominal contents Medial: Sternal edge Lateral: Axillary line
Lateral	R3 or L3 (lateral axilla)	Upper: axilla Lower: Axis of 4th rib Anterior: Anterior axillary line Posterior: Posterior axillary line
	R4 or L4 (lateral lower)	Upper: Axis of 4th rib Lower: variable Anterior: Anterior axillary line Posterior: Posterior axillary line
Posterior	R5 or L5 (Posterior Upper)	Upper: defined by LUS Medial: thoracic spine Lateral: medial border of scapula Lower: Inferior angle of scapula
	R6 or L6 (Posterior lower)	Upper: Inferior angle of scapula Medial: thoracic spine Lateral: Posterior axillary line

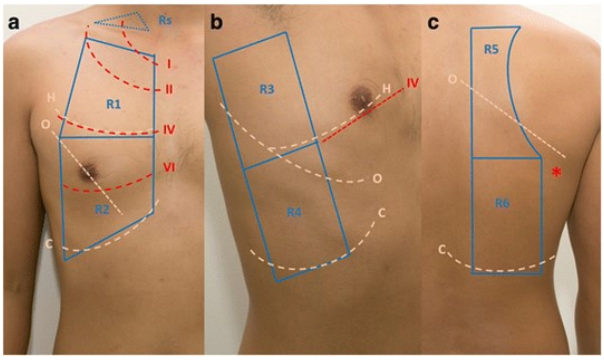

Figure 1: Areas of investigation[6]

Once BLUE Protocol was done, findings were categorized as A profile: defined as predominant bilateral anterior A lines plus lung sliding. A' profile is an A profile with abolished lung sliding. B profile defined as predominant B lines plus lung sliding. B' profile is a B profile with abolished lung sliding. A/B profile defined as massive B lines on one side and A lines on the other side. C profile designates consolidation and the PLAPS profile. There were no measurements on the findings of the BLUE Protocol. The different categories were correlated to the disease entity they likely represent and were the outcome of the BLUE protocol. The estimated time from the consent to the procedure proper lasted for approximately 30 minutes.

BLUE Protocol and Chest Radiography interpretation

The BLUE protocol images and results were recorded and saved on the ultrasound machine, copied to an external device and were given to the supervising investigators for review. All the images were interpreted by the supervising investigators: pediatric pulmonologist, emergency medicine specialist and radiologist. All the images were deleted after readings were completed. This was ensured by the primary investigator. The chest radiography was interpreted by the radiologist reader assigned to the patient. The pediatric pulmonology fellow, pulmonologist, emergency medicine specialist and radiologist were blinded with the patients' demographics, clinical history, physical examination, previous diagnostic examinations and chest radiography reading in our institution as data were kept in a secured logbook and electronic spreadsheet accessible only to the primary co-investigators at that point of the study. Interpretation was solely focused on the imaging. In the event that there was a disagreement among the readings of the pulmonologist, emergency specialist and radiologist, the BLUE protocol interpretation by the radiologist was considered the official reading. The result the BLUE protocol was compared to the immediate diagnosis of the patient using the clinical and radiologic findings.

As this was a cross-sectional study, data collection concluded upon completion of the BLUE Protocol. BLUE Protocol was not yet part of the standard of care, and the clinical decision of the pediatric resident on duty continued to be the deciding factor in the patient's care. Initial readings from the BLUE Protocol were provided to the pediatric

Throughout the duration of the trial, the researchers did not influence the clinical management of the patient.

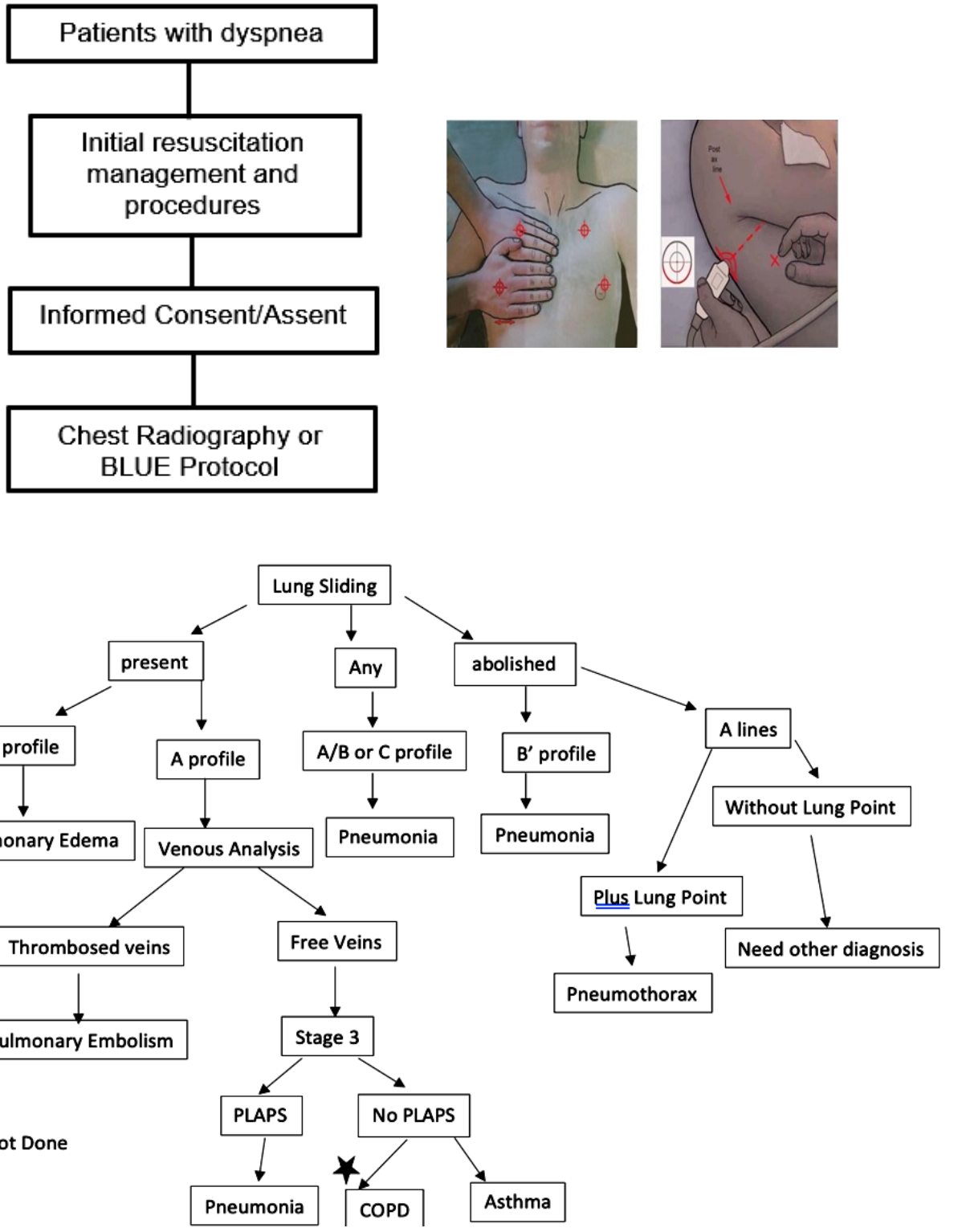

Figure 2. Study Procedure: Modified BLUE Protocol[5]

This study evaluated the applicability of the BLUE protocol in immediately diagnosing acute undifferentiated dyspnea among pediatric patients in the emergency room, compared to clinical diagnosis using clinical and radiologic findings. It also assessed the discordance between readings of emergency medicine specialists, radiologists, and pulmonologists during the BLUE protocol. Caregivers and parents were not required to withdraw during the 5 to 10-minute BLUE Protocol procedure, as patient monitoring was not conducted. Participants were given the option to withraw from the study at any point in time.

Data were logged in a laboratory logbook and encoded in Microsoft Excel worksheets coded suitable for analysis. All data were stored in a password protected laptop and will be saved for two years for reference purposes. The data yield was analyzed using the SPSS v21. Frequency, mean and percentages were the main descriptive statistical methods used. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Positive Likelihood Ratio and Negative likelihood ratio were computed between the BLUE protocol results by the radiologist and chest radiography as reference study in the diagnosis of dyspnea among those included in the study. Chi square test was used to determine the presence of significant difference between the diagnosis of each reader. A p value of ≤ 0.05 was considered statistically significant.

The study had no direct monetary compensation, but patients and caregivers received nonmaterial benefits such as health education. It posed minimal risk, and adverse events were closely monitored. If successful, the BLUE protocol could be an alternative diagnostic tool for acute undifferentiated dyspnea in the emergency room, benefiting the local community by enabling early identification of respiratory failure and reducing unnecessary procedures and costs. The protocol was reviewed and approved by the Clinical Research Division and Ethics Review Board of Philippine Children's Medical Center. Consent was obtained, and participants were assigned coded identifiers for data confidentiality. Data were securely stored with limited access and kept in a locked office and locker.

RESULTS

A total of 111 participants were included in the study with no dropout or any adverse event during the collection of data using the BLUE protocol. The majority were less than 1 year of age (48.2%) with the least number of patients coming from the adolescent age group (5.4%). Majority were male (55.4%) with Pneumonia as the predominant diagnosis (88.2%) with an average of 15.39 minutes to conduct the procedure.

Table 2: Demographic profile of patients included in the study.

Characteristic	Frequency	Percentage
Age		
<1 year old	54	48.2%
1-5 years old	40	35.7%
6 to 10 years old	12	10.7%
11 years old and above	6	5.4%
Sex		
Male	62	55.4%
Female	50	44.6%
Admitting Diagnosis		
Pneumonia	98	88.2%
Bronchial Asthma	8	7.2%
Rheumatic Heart Disease	4	3.6%
Chronic Kidney Disease	1	0.9%
Average time of POCUS in minutes (MEAN +/- SD)	15.39	(+/- 4.72)

Table 3 shows the sensitivity, specificity, positive predictive value and negative predictive value of the BLUE protocol reading in comparison to the clinicoradiologic diagnosis of each patient. Both reading from the pulmonologist (91.01%); ER specialist (89.89%) and Radiologist (96.77) have high sensitivity with low specificity at 26% (pulmonologist); 21% (ER specialist) and 57.89% (radiologist) in the diagnosis of Pneumonia. The diagnosis of pleural effusion and/or congestion showed high sensitivity (89%) and low specificity (21%) based on the pulmnologist reading; a low sensitivity (37%), high specificity (99%) on the ER specialist reading and a 100% specificity on the radiologist reading. All readers showed high specificity (95%; 93%; 93%) and lowsensitivity (50,71,71%) on the diagnosis of Asthma.

Table 3: Sensitivity and Specificity of BLUE protocol in comparison to the clinicoradiologic diagnosis of the patient. (a) Pneumonia; (b) Pleural Effusion; (c) Asthma/Normal

(a)

	Pediatric Pulmonologist Reading		ER Medicine Reading		Radiologist Reading	
PNEUMONIA	(+)	(-)	(+)	(-)	(+)	(-)
(+)	**81**	**17**	**80**	**18**	**90**	**8**
(-)	**8**	**6**	**9**	**5**	**3**	**11**
Sensitivity	**91.01% [CI 83.05%-96.04%]**		**89.89% [CI 81.67%-95.27%]**		**96.77% [CI 90.86%-99.33%]**	
Specificity	**26.09% [10.23% - 48.41%]**		**21.74% [7.46% - 43.70%]**		**57.89% [33.50% - 79.75%]**	
Positive Predicative Value	**1.23 [0.96 – 1.58]**		**1.23 [0.92 – 1.44]**		**2.30 [1.35 – 3.90]**	
Negative Predictive Value	**0.34 [0.13 -0.89]**		**0.17 [0.17 -1.25]**		**0.06 [0.02 - 0.18]**	

(b)

	Pediatric Pulmonologist Reading		ER Medicine Reading		Radiologist Reading	
PLEURAL EFFUSION	(+)	(-)	(+)	(-)	(+)	(-)
(+)	**3**	**1**	**3**	**1**	**4**	**0**
(-)	**10**	**98**	**5**	**103**	**3**	**105**
Sensitivity	**23.08% [CI 5.04%-53.81%]**		**37.50% [CI 8.52% -75.51%]**		**57.14% [CI 18.41%-90.10%]**	
Specificity	**98.99% [94.50% - 99.97%]**		**99.04% [94.76% - 99.98%]**		**100% [96.55% - 100%]**	
Positive Predicative Value	**22.85 [2.56 – 203.75]**		**39 [04.56 – 333.45]**		**-**	
Negative Predictive Value	**0.78 [0.58 -1.05]**		**0.63 [0.37 -1.08]**		**0.43 [0.18 -1.01]**	

(c)

	Pediatric Pulmonologist Reading		ER Medicine Reading		Radiologist Reading	
ASTHMA	(+)	(-)	(+)	(-)	(+)	(-)
(+)	**3**	**13**	**2**	**0**	**2**	**0**
(-)	**3**	**93**	**6**	**104**	**6**	**104**
Sensitivity	**50% [CI 11.81%-88.19%]**		**71% [CI 41.90%-91.61%]**		**71% [CI 41.90%-91.61%]**	
Specificity	**95.28% [79.94% - 93.31%]**		**93.88% [87.15% - 97.72%]**		**93.88% [87.15% - 97.72%]**	
Positive Predicative Value	**4.08 [1.58 – 10.53]**		**11.67 [5.02 – 27.11]**		**11.67 [5.02 – 27.11]**	
Negative Predictive Value	**0.57 [0.26 -1.27]**		**0.30 [0.13 -0.70]**		**0.30 [0.13 -0.70]**	

Concordance rate was also determined among the three BLUE protocol readers (Pulmonologist, Emergency medicine specialist and Radiologist) as shown in Table 4 which showed a high concordance rate at 98% and a p value >0.05 indicating no significant difference among groups.

Table 4: Concordance rate among ultrasound findings between readers.

	Pediatric Pulmonologist	P value	Emergency Medicine specialist	P value	Initial Impression	P Value
Ultrasound Reading	98.09%	0.506	98.24%	0.483	98.01%	0.621

DISCUSSION

The study aimed to investigate the frequency of using the BLUE protocol in pediatric patients with dyspnea and evaluate its effectiveness in diagnosing different conditions. The findings indicated that the BLUE protocol had high sensitivity in detecting pneumonia and a high specificity in diagnosing asthma. Additionally, an important finding is that all readers consistently demonstrated a high concordance rate at 98% or more.

The BLUE Protocol, a point-of-care ultrasound technique, has been extensively studied in various clinical scenarios. Bekcoz et al[6] conducted a study to assess the diagnostic accuracy of the BLUE Protocol in identifying causes of acute dyspnea which revealed a high sensitivity (95%) and specificity (98%). These results highlighted the potential of the BLUE Protocol as a valuable tool in the evaluation and management of patients with acute dyspnea, aiding in the prompt identification of the underlying pathology.

Bedside lung ultrasound in emergency utilizes the immediate availability of ultrasound in the emergency room setting. If readily available, lung ultrasonography or BLUE protocol may reduce the need for unnecessary interventions or even exposure to radiation, as concluded in the study by Zieleskiewicz et al.[7] Furthermore, Potter et al emphasized that, unlike other imaging procedures, lung ultrasound does not involve ionizing radiation, provides rapid and serial bedside evaluation with real-time feedback, lessens the potential risks of transportation and importantly promotes time at the bedside of the critically unwell child.[12] While it may be accurate to highlight the positive aspects of the BLUE protocol, the reality remains that ultrasound machines are not easily accessible in every emergency room, especially in low to middle income countries like the Philippines. Therefore, this study could underscore the significance of acquiring this device due to its good diagnostic capabilities. In another study by Lichtenstein et al, the findings of the BLUE protocol showed a specificity of 90% in determining the diagnosis of acute respiratory failure.[5] This is consistent with the findings of this paper. Additionally, they reported that over 25% of patients assessed using conventional methods had an undetermined diagnosis within the first 2 hours of admission leading to incorrect management.[5] Lung ultrasound, on the other had, is nearly as effective as CT scan in identifying most disorders and is highly feasible.[5]

In a study by Potter et al, lung ultrasound demonstrated high diagnostic accuracy and increased sensitivity and specificity in comparison to chest radiography in identifying consolidation, pleural effusion and interstitial syndrome.[12] Similarly, this paper also observed similar trend, wherein the BLUE protocol diagnosed 14 cases of pleural effusion compared to the 6 cases identified by

radiography. In another study by Ayuningtyas et al, lung ultrasound showed a sensitivity of 14.3% and specificity of 73% in diagnosing pleural effusion.[14] Our study showed similar results although results vary depending on the reader: pulmonologist (sensitivity 89%, specificity 21%), ER specialist (sensitivity 37%, specificity 99%), radiologist (sensitivity 57%, specificity 100%). In a study by Bourcier et al, lung ultrasound showed a sensitivity of 95% in diagnosing pneumonia.[8] Comparably, the study also showed high sensitivity in diagnosing pneumonia, although the specificity was low. It's worth noting that this could be related to the sample used, as all patients in the study had dyspnea. In another study by Attansi et al, lung ultrasound showed a specifity of 90% and sensitivity of 83% in diagnosing asthma exacerbation.[15] This is also observed in the current study wherein all readers showed high specificity (95%; 93%; 93%) although with low sensitivity (50,71,71%) on the diagnosis of Asthma. On the other hand, Asmara et al investigated the utility of the BLUE Protocol in patients with suspected acute respiratory distress syndrome (ARDS) thru meta analysis.[22] The study demonstrated that the BLUE Protocol had a high sensitivity of 97% and specificity of 94% in diagnosing ARDS. These results show that the BLUE Protocol can serve as an effective means in early identification and management of ARDS in critically ill patients, enabling timely intervention and improved patient outcomes. In a study by Scialanga et al on the accuracy of lung ultrasound in detecting pneumothorax among pediatric patients presenting with chest pain, results showed 100% sensitivity and specificity of 92%. This finding further implicates the important of POCUS as a noninvasive diagnostic tool in the Emergency department.[30]

In a meta analysis conducted by Pereda et al, studies that involved lung ultrasound performed by emergency department physicians, general practitioners, residents, or health care professionals, had a pooled sensitivity of 95% (95% CI: 91%–97%) and a specificity of 91% (87%–95%).[23-26] This is consistent with our findings which showed a low discordance among readers. Evidently, findings from studies done by highly skilled physicians had a higher specificity to diagnose pneumonia with ultrasound, nonexpert trained physicians' studies still showed a high sensitivity and specificity.[23,28] Interestingly, in the present study, despite the trainings received by the readers, results showed high concordance rate on their readings.

Taken together, these studies provide substantial evidence supporting the utility of the BLUE Protocol in different clinical scenarios. However, it is essential to consider factors such as patient population, operator expertise, and other diagnostic modalities when interpreting and applying the findings of the BLUE Protocol in clinical practice. The BLUE Protocol offers promise as a valuable tool in the assessment and management of various

respiratory conditions, aiding clinicians in making timely and accurate diagnoses, ultimately improving patient care outcomes.

Conclusion

The findings of this study show that the BLUE protocol displays high sensitivity in diagnosing pneumonia and high specificity in diagnosing asthma. The high concordance rate between readers indicates consistent ultrasound findings. The results support the practical application of the BLUE protocol in diagnosing acute undifferentiated dyspnea in pediatric patients within the emergency department.

The study was limited to patients presenting with dyspnea at the emergency room of the Philippine Children's Medical Center and may not represent the whole population. BLUE protocol images reviewed by the supervising investigators were recorded and not done real time. The operator dependence of the ultrasound was another limitation. Cut off values were not determined because all participants in the study or analysis are known to be pathological. Furthermore, the absence of a healthy or non-pathological group in the dataset makes it imposible to create 2 distinct categorical datasets to separate. In statistical analysis, the determination of a cut-off value typically relies on the presence of two or more distinct groups with different characteristics or outcomes.

A prospective design which focuses not only on patients presenting with dyspnea and includes healthy patients is recommended to further asses the applicability and accuracy of the BLUE protocol furthermore a multicentered study is also recommend to determine its applicability in the low to middle income countries.

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ARTICLE

Factors associated with central line-associated bloodstream infection (CLABSI) among children in a tertiary government hospital: a case-control study

Joeraine Kristine L. Labapis, Mary Antonette Cuady-Madrid

OBJECTIVE: The study aims to determine the factors associated with central line-associated bloodstream infection (CLABSI) among children admitted in a tertiary government hospital.

MATERIALS AND METHODS: This was a retrospective case-control study which utilized records review of pediatric patients admitted from January 2018 to December 2022. Random sampling was employed to include confirmed cases of patients with CLABSI and controls who did not develop CLABSI. Patients were matched in terms of unit of admission. Data were collected through chart review and odds ratio was used to determine the factors associated with CLABSI using univariate and multivariate regression analysis.

RESULTS: A total of 92 cases and 184 controls were included in the study. Results of multivariate regression analysis revealed that the age group of 6 to 12 years old (OR=18.91, 95% CI 2.32 to 153.9) had the highest odds of acquiring CLABSI. Blood transfusion as indication for central line insertion increased the risk of CLABSI (OR=5.24, 95% CI 1.67 to 16.48). Those more likely to acquire CLABSI were patients with duration of CVC use of more than 14 days (OR=25.68, 95% CI 2.77 to 238.4), those who received total parenteral nutrition (OR=13.44, 95% CI 2.67 to 67.56) and chemotherapeutic or immunosuppressive drugs (OR=3.07, 95% CI 1.2 to 7.85).

CONCLUSION: This study revealed that age, blood transfusion as indication for central line use, receipt of total parenteral nutrition, receipt of chemotherapeutic and immunosuppressive drugs, and duration of CVC utilization of more than 14 days were found to increase the risk of CLABSI. Careful consideration of these factors in patients with CVCs should be observed to prevent the occurrence of CLABSI.

KEYWORDS: *Central line-associated bloodstream infection, CLABSI, associated factors, children*

INTRODUCTION

Central venous catheterization is an indispensable procedure in treating children with life-threatening conditions. The process involves inserting a central venous catheter (CVC) at a peripheral location, advancing and coursing through a major vein, such as the internal jugular, subclavian, brachiocephalic, or femoral vein,[1] until the distal tip of the catheter reaches the superior vena cava, inferior vena cava or the junction with the right atrium. Vascular access in hospitalized, critically ill neonates and children are often needed for monitoring hemodynamics, antibiotic therapy, parenteral nutrition, fluid administration and other indications.[2,3] However, the usefulness of central lines for these patients suffers significant drawbacks as microbial contamination can lead to central line-associated bloodstream infection (CLABSI).[4]

CLABSI is a common hospital-acquired infection that may lead to severe sepsis, increased risk for intensive care unit (ICU) admission, prolonged hospitalization, increased mortality and morbidity, and overinflated healthcare costs.[5] Previous studies have found varying CLABSI rates in tertiary care settings across regions, ranging from 0.28 to 24.73 per 1000 catheter days.[6–8] Most studies, however, involved pediatric patients admitted in ICUs. Factors found to be linked to CLABSI development have been explored, such as duration of catheterization, catheter replacement, multiple catheterizations, and total parenteral nutrition.[9,10] Younger age, birth weight, type of CVC, dwell time, and number of central lines were found to be insignificant.[11,12] In a retrospective cohort study among neonatal ICU patients with percutaneously inserted CVCs at the Philippine Children's Medical Center (PCMC), See Tsai[13] found that patients with CLABSI had a significantly longer median duration of catheterization than those who did not develop CLABSI. The most frequent organisms isolated among ICU-admitted children and neonates were coagulase-negative *Staphylococcus* (CONS), *Candida spp.,* and *Staphylococcus aureus,*[14,15] while for non-ICU patients, coagulase-negative *Staphylococcus* (CONS) was also the most common organism identified.[15]

Despite the advances in the prevention and management of CLABSI, its incidence in critically ill neonates and children remains unchanged.[16] On the other hand, CLABSI is also a preventable hospital-acquired infection. Revealing the characteristics of patients at risk for developing CLABSI can aid physicians in making suitable clinical decisions in managing and recommending preventive approaches applicable in the local study setting. This study aims to determine the associated risk factors of CLABSI among hospitalized children below 18 years old admitted at PCMC from January

2018 to December 2022. Specifically, it aims to describe the demographic and clinical characteristics of children who developed and did not develop CLABSI; determine the factors associated with CLABSI in children who developed CLABSI; and lastly, describe the microbiologic profile and antibiotic susceptibility of CLABSI in children who developed CLABSI.

Materials and Methods

Research Design. This study utilized a case-control design, approved by the Institutional Review-Ethics Committee of PCMC. All patients with central venous catheters under 18 years old admitted at PCMC between January 2018 and December 2022 were included.

Inclusion Criteria. To be included as a subject, the study required patients to meet these requirements: (1) admitted in-patients at PCMC between January 2018 to December 2022; (2) all genders below 18 years old; (3) admitted to the ward or ICU (neonatal, pediatric, septic); (4) with at least one central venous catheter; (5) any place of CVC insertion (ward, ICU, operating room, emergency room); (6) with or without peripheral intravenous line. For cases: (7) CLABSI should have occurred 48 hours after admission and CLABSI diagnosis was confirmed by blood culture according to the Centers for Disease Control and Prevention (CDC) criteria. For controls: (8) presence of CVC for at least 48 hours and did not develop CLABSI or had negative blood culture results for CLABSI suspicion.

Exclusion Criteria. The following patients were excluded from the study: (1) with incomplete data on medical records (2) with laboratory confirmed sepsis before inserting the CVC based on medical records; (3) referred from another hospital with CVC already inserted; (4) transferred to another hospital or went home against medical advice.

Finding Potential Cases and Controls. Children with CVCs inserted during their hospitalization within the retrospective period of this study were identified by reviewing the Neonatology and Surgery services logbooks. The records of the Microbiology section and Section of Pediatric Infectious Diseases were also reviewed to determine patients who have had growths on their central line blood cultures during their hospitalization. Meanwhile, patients with CVCs who did not have blood culture testing for CLABSI or had negative results during their hospitalization were also recorded in a logbook.

Patients diagnosed with CLABSI were cross validated to confirm that they met the study's criteria for the case definition per the CDC guidelines and for the inclusion of the patient as a case in the present study. Neonates with growth of a common commensal pathogen with only a single blood

culture obtained were included as potential cases since obtaining paired samples in neonates is not commonly practiced in PCMC, provided that the patient had at least one of the following signs or symptoms: fever (>38.0°C), hypothermia (<36.0°C), apnea, or bradycardia and the organism identified in blood is not related to an infection at another site. To focus on hospital-acquired CLABSIs, we only considered CLABSI which occurred after 48 hours from admission. For multiple CLABSIs of a single CVC, only the first episode was included in the analysis. Likewise, for patients with multiple CVCs, only the first documented CLABSI was included in the analysis. A patient with more than one CLABSI incidence was used as a case subject only once and only the first admission was included. The same was done for patients who did not develop CLABSI or had negative results to ensure they met the inclusion criteria for controls. Patients who satisfied the criteria after the cross-validation proceedings were categorized into two groups according to their CLABSI diagnosis.

Sample Size Calculation and Sampling. The study required a sample size of at least 62 cases and 124 controls (ratio of 1:2) at a 95% confidence interval and 80% power of the test. The computation was based on the findings of the study of Wylie, et al.,[17] where three factors were shown, including duration of ICU central venous catheterization, use of parenteral nutrition, and blood product transfusion.

Based on the hospital admission date, the cases were sorted sequentially from one to the last. Case units were chosen by drawing random numbers from the patients who developed CLABSI. Potential controls were sorted by the unit of admission and admission date. The two controls who were admitted to the same unit of admission and closest to the admission date of the case (within three months) were selected purposively. This was done to control confounding factors that may be related to the unit of admission, such as the severity of illness, and to account for potential temporal trends in the exposure and outcome among cases and controls. The process was repeated until the minimum sample size required was reached. We did not limit the sample size to 62 cases and 124 controls so as to accommodate more entries from the records, as well as to increase the statistical power of the study.

Data Collection Procedure. A standardized data collection form and coding manual was used during the data collection proceedings. The following were the independent variables collected and analyzed as potential risk factors for CLABSI: age (0-29 days, 1-12 months, 2-5 years, 6-12 years, 13-18 years), sex, nutritional status based on height/length and weight (normal, wasted/ severely wasted, overweight/obese), underlying diagnosis (cardiovascular, respiratory, gastrointestinal, renal, hematologic/oncologic, neurologic, surgical, infectious, other neonatal pathology),

indication for central line placement (fluid resuscitation, blood transfusion, drug infusion, nutrition, hemodialysis), type of central line inserted (non-tunneled, tunneled, totally implanted, umbilical, peripherally inserted central catheter), place of CVC insertion (general ward, ICU, operating room, emergency room), site of central line placement (internal jugular vein, subclavian vein, femoral vein, umbilical vein, arm or leg), receipt of blood products, receipt of total parenteral nutrition (TPN), receipt of chemotherapeutic or immunosuppressive drugs, duration of central line use (number of days from the date of CVC insertion to the date of CVC removal). The following data were also collected: the onset of CLABSI (number of days from the date of CVC insertion to the date of symptom onset), length of hospital stay (number of days from the date of patient's admission to the date of discharge or demise, whichever comes first), outcome if with CLABSI (died or recovered) and the microbiologic profile of CLABSI cases. A unique alphanumeric identification code was assigned to each study subject to maintain their anonymity and protect their information.

Statistical analysis. Data collected using the standardized data collection form were encoded into the study's data sheet in Microsoft Excel. Descriptive statistics, such as mean standard deviation, median and interquartile range were used to describe continuous variables. On the other hand, frequency and percentage were used to present categorical data. Odds ratio was obtained to determine the factors associated with CLABSI using univariate and multivariate regression analysis (among variables with p <0.20). Moreover, for variables that resulted in 0 cells, Fisher's exact test was then utilized. The level of significance was at 5%. Medcalc statistical software was used to carry out statistical calculation.

RESULT

A total of 92 CLABSI cases and 184 controls were included in the study. Table 1 shows the characteristics of CLABSI patients at PCMC from January 2018 to December 2022. The majority (82.6%) of patients only had a single episode of CLABSI. CLABSI recurrence was noted in 18.5% of cases, most of which occurred in a different CVC site. The prevalence of mortality is 10.9%.

TABLE 1. CHARACTERISTICS OF CLABSI PATIENTS AT THE PHILIPPINE CHILDREN'S

MEDICAL CENTER FROM JANUARY 2018 TO DECEMBER 2022

Variables	**CASE (n = 92)**	
	n	**%**
Unit of admission		
Neonatal ICU	21	22.8
Pediatric ICU	20	21.7
Septic ICU	7	7.6
General ward	44	47.8
Number of CLABSI experienced		
One	76	82.6
Multiple (2-3)	16	17.4
CLABSI re-occurrence		
None	75	81.5
Yes, same CVC site	1	1.1
Yes, different CVC site	16	17.4
Outcome		
Recovered	82	89.1
Died	10	10.9
Onset of CLABSI (days), median	17 (13 to 20.0)	

Table 2 presents the demographic and clinical characteristics of patients with and without CLABSI during the study period. Cases and controls were matched in terms of unit of admission. The proportion of CLABSI cases was significantly higher among those aged 1-12 months old, in contrast to the control group (34.8% vs 14.1%, p<0.0012). Male to female split, nutritional status, and median number of central lines placed were not significantly different between the two groups. The underlying diagnosis differed substantially, as a higher proportion of cases had underlying neurologic conditions than controls (31.5% vs 14.7, p=0.0161). In terms of indication for central line use, among the cases, the following had significantly higher proportion of CLABSI compared to controls: fluid resuscitation (85.9% vs 69.6%, p<0.0032), drug infusion (85.9% vs 72.3%, p<0.0001), blood transfusion (44.6% vs 22%, p<0.0001), nutrition (29.3% vs 8.7%, p<0.0001), other indication (13% vs 5.4%, p<0.0281). A significantly higher proportion of CLABSI cases than controls had non-tunneled catheters (92.4% vs 78.8%, p<0.0042) and had central lines inserted in the internal jugular vein (85.9% vs. 82.1%, p=0.0077) or the femoral vein (7.6% vs. 2.7%, p=0.0077). Majority of CVC insertion were done in the operating room for both groups. Receipt of blood products, TPN and chemotherapeutic or immunosuppressives were significantly higher in those with CLABSI than controls. The median duration of CVC utilization was significantly longer among those with CLABSI than controls (19 days vs 10.5 days, p<0.0001). Median duration of hospital stay was also significantly longer among those with CLABSI than controls (49 days vs 21 days, p<0.0001).

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CHILDREN WITH CLABSI AND WITHOUT CLABSI AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER FROM JANUARY 2018 TO DECEMBER 2022

Variables	CASE (n = 92) With CLABSI		CONTROL (n = 184) Without CLABSI		p-value
	n	%	n	%	
Age (years)					
0 – 29 days	9	9.8	39	21.2	
1 – 12 months	32	34.8	26	14.1	0.0012*
2 – 5 years	13	14.1	33	17.9	
6 – 12 years	18	19.6	42	22.8	
13 – <18 years	20	21.7	44	23.9	
Sex					
Male	44	47.8	93	50.5	0.6709
Female	48	52.2	91	49.5	

Underlying primary diagnosis					
Cardiovascular	1	1.1	9	4.9	
Respiratory	10	10.9	14	7.6	
Gastrointestinal	12	13.0	16	8.7	
Renal	18	19.6	52	28.3	
Hematologic/Oncologic	8	8.7	32	17.4	
Neurologic	29	31.5	27	14.7	0.0161*
Surgical	2	2.2	6	3.3	
Infectious	11	12.0	27	14.7	
Other Neonatal Pathology	1	1.1	1	0.5	
Others	0	0.0	0	0.0	
Weight, median (IQR)	12.75 (3.75 to 32)		15 (4 to 34)		0.3108
Nutritional status					
Normal	45	48.9	100	55.6	
Wasted/Severely wasted	38	41.3	68	37.8	0.7305
Overweight/Obese	9	9.8	16	8.9	
Indication for central line					
Fluid resuscitation	79	85.9	128	69.6	0.0032*
Blood transfusion	41	44.6	22	12.0	0.0001*
Drug infusion	79	85.9	133	72.3	0.0118*
Nutrition	27	29.3	16	8.7	0.0001*
Hemodialysis	22	23.9	61	33.2	0.1153
Others	12	13.0	10	5.4	0.0281*
Type of central line inserted					
Non-tunneled catheter	85	92.4	145	78.8	0.0042*
Tunneled catheter	0	0.0	2	1.1	
Totally implanted (port-a-cath)	1	1.1	14	7.6	
Umbilical catheter	0	0.0	15	8.2	
Peripherally inserted central catheter	6	6.5	8	4.3	
Place of CVC insertion					
NICU	12	13.0	23	12.5	0.5654
PICU	0	0.0	0	0.0	
Septic ICU	0	0.0	0	0.0	
General Ward	1	1.1	0	0.0	
Operating Room	76	82.6	155	84.2	
Emergency Room	3	3.3	6	3.3	
Number of central lines placed, median (IQR)	1.0 (1.0 to 1.0)		1.0 (1.0 to 1.0)		0.4771
Site/s of central lines insertion					
Internal jugular vein	79	85.9	154	83.7	0.0077*
Subclavian vein	0	0.0	2	1.1	
Femoral vein	7	7.6	5	2.7	
Umbilical vein	0	0.0	15	8.2	
Arm (PICC line)	3	3.3	1	0.5	
Leg (PICC line)	3	3.3	7	3.8	
Duration of CVC utilization, median (IQR)	19.0 (15 to 23)		10.5 (7.0 to 14.0)		0.0001*
Duration of CVC utilization					
<7 days	1	1.1	42	22.8	
7 to 14 days	21	22.8	97	52.7	0.0001*
>14 days	70	76.1	45	24.5	
Receipt of blood products	60	65.2	49	26.6	0.0001*
Receipt of total parenteral nutrition	47	51.1	19	10.3	0.0001*
Receipt of chemotherapeutic or immunosuppressive drugs	51	55.4	66	35.9	0.0112*
Length of hospital stay (days), median (IQR)	49 (37.5 to 71.5)		21 (13 to 36)		0.0001*

Significant @ p-value ≤ 0.05; IQR – interquartile range

Table 3 presents the univariate logistic regression analysis of factors associated with CLABSI. Results showed that 10 factors were significantly associated with CLABSI. Children aged 1 to 12 months were 5 times more likely to acquire CLABSI than those 0-29 days old (OR=5.33, 95% CI 2.19 to 13.23). Those with underlying neurologic diagnosis were also 9 times more likely to acquire CLABSI (OR=9.67, 95% CI 1.15 to 81.46). Indication for central line was also significantly associated with CLABSI, specifically, fluid resuscitation (OR=2.66, 95% CI 1.37 to 5.17), blood transfusion (OR=5.92, 95% CI 3.23 to 10.85), drug infusion (OR=2.33, 95% CI 1.19 to 4.55), nutrition (OR=4.36, 95% CI 2.21 to 8.62), as well as other indications (OR=2.61, 95% CI 1.08 to 6.29). Moreover, those with non-tunnel type of CVC were 3 times more likely to acquire CLABSI as compared to other types of central line (OR=3.27, 95% CI 1.40 to 7.63). Site of CVC insertion was also significant, as those with femoral vein insertion were 8 times more likely to acquire CLABSI (OR=8.4, 95% CI 1.57 to 44.92). Those with duration of CVC use of more than 14 days and 7 to 14 days were 65 times (OR=65.33, 95% CI 8.68 to 491) and 9 times (OR=9.09, 95% CI 1.18 to 69.83) more likely to acquire CLABSI than those with less than 7 days of use, respectively. Receipt of TPN (OR=9.07, 95% CI 4.85 to 16.97), receipt of blood products (OR=5.17, 95% CI 3.01 to 8.86) and chemotherapeutic or immunosuppressive drugs (OR=1.94, 95% CI 1.16 to 3.25) were all significantly associated with higher odds of acquiring CLABSI. Furthermore, patients with a median duration of hospital stay exceeding 49 days are at higher risk of CLABSI (OR=1.03, 95% CI 1.02 to 1.04).

TABLE 3. Univariate Logistic Regression Analysis of Factors Associated With CLABSI At The Philippine Children's Medical Center from January 2018 to December 2022

Variables	COR	95% CI		p-value
		Lower	Upper	
Age (years)				
0 – 29 days		*Reference*		
1 – 12 months	5.33	2.19	13.23	0.0002*
2 – 5 years	1.71	0.65	4.39	0.279
6 – 12 years	1.86	0.75	4.62	0.183
13 – <18 years	1.97	0.8	4.83	0.1386
Sex				
Male	1.11	0.68	1.84	0.6704
Female		*Reference*		

Cardiovascular		*Reference*		
Respiratory	6.43	0.7	59.17	0.1004
Gastrointestinal	6.75	0.75	60.76	0.0885
Renal	3.12	0.37	26.33	0.2967
Hematologic/Oncologic	2.25	0.25	20.44	0.4713
Neurologic	9.67	1.15	81.46	0.0370*
Surgical	3	0.22	40.93	0.4100
Infectious	3.67	0.41	32.49	0.2431
Other Neonatal Pathology	9	0.28	285.5	0.2129
Nutritional status				
Normal		*Reference*		
Wasted/Severely wasted	1.24	0.73	2.11	0.4235
Overweight/Obese	1.25	0.51	3.04	0.6228
Indication for central line				
Fluid resuscitation	2.66	1.37	5.17	0.0040*
Blood transfusion	5.92	3.23	10.85	0.0001*
Drug infusion	2.33	1.19	4.55	0.0133*
Nutrition	4,36	2.21	8.62	0.0001*
Hemodialysis	0.63	0.36	1.12	0.1161
Others	2.61	1.08	6.29	0.0326*
Type of central line inserted				
Others		*Reference*		
Non-tunneled catheter	3.27	1.40	7.63	0.0062*
Place of CVC insertion				
Others (ER/General ward)		*Reference*		
Operating Room	0.74	0.2	2.68	0.6418
NICU	0.78	0.18	3.32	0.7395
Number of central lines placed	2.02	0.28	14.59	0.4849
Site/s of central lines insertion				
Others		*Reference*		
Internal jugular vein	3.14	0.9	10.98	0.0734
Femoral vein	8.4	1.57	44.92	0.0128*
Arm (PICC line)	1.8	0.3	10.64	0.5168
Duration of CVC utilization				
<7 days		*Reference*		
7 to 14 days	9.09	1.18	69.83	0.0338*
>14 days	65.33	8.68	491	0.0001*
Receipt of blood products	5.17	3.01	8.86	0.0001*
Receipt of total parenteral nutrition	9.07	4.85	16.97	0.0001*
Receipt of chemotherapeutic or immuno-suppressive drugs	1.94	1.16	3.25	0.0115*
Length of hospital stay	1.03	1.02	1.04	0.0001*

***Significant @ p-value ≤ 0.05*; COR – Crude odds ratio

Table 4 summarizes the results of multivariate logistic regression analysis where the following factors were analyzed: age, underlying diagnosis, indication for central line insertion, type of central line inserted, site of central line insertion, duration of CVC utilization, receipt of blood products, receipt of TPN, receipt of chemotherapeutics or immunosuppressive and length of hospital stay. Five factors were found to be significantly associated with CLABSI. Results revealed that age groups of 1 to 12 months (OR=11.58, 95% CI 2.16 to 62.04), 1 to 5 years (OR=9.3, 95% CI 1.13 to 76.4), 6 to 12 years (OR=18.91 95% CI 2.32 to 153.9) and 13 to 18 years old (OR=15.45, 95% CI 1.83 to 130.6) were associated with higher odds of acquiring CLABSI as compared to children aged 0 to 1 month old. Indication for central line, specifically blood transfusion, was also associated with higher odds of CLABSI (OR=5.24, 95% CI 1.67 to 16.48). Those with duration of CVC use of more than 14 days were 25 times (OR=25.68, 95% CI 2.77 to 238.4) more likely to acquire CLABSI than those with less than 7 days of use. Receipt of total parenteral nutrition (OR=13.44, 95% CI 2.67 to 67.56) and receipt of chemotherapeutic or immunosuppressive drugs (OR=3.07, 95% CI 1.2 to 7.85) were also significantly associated with CLABSI.

TABLE 4. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF FACTORS ASSOCIATED WITH CLABSI AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER FROM JANUARY 2018 TO DECEMBER 2022

Variables	AOR	95% CI		p-value
		Lower	Upper	
Age (years)				
0 – 29 days		*Reference*		
1 – 12 months	11.58	2.16	62.04	0.0041*
2 – 5 years	9.30	1.13	76.40	0.0378*
6 – 12 years	18.91	2.32	153.9	0.0060*
13 – <18 years	15.45	1.83	130.6	0.0119*
Indication for central line				
Fluid resuscitation	-	-	-	-
Blood transfusion	5.24	1.67	16.48	0.0046*
Drug infusion	-	-	-	-
Nutrition	1.87	0.26	13.63	0.5362
Hemodialysis	1.19	0.36	4.01	0.7737
Others	1.72	0.38	7.79	0.4827
Duration of CVC utilization				
<7 days		*Reference*		
7 to 14 days	7.66	0.83	71	0.0733
>14 days	25.68	2.77	238.4	0.0043*
Receipt of total parenteral nutrition	13.44	2.67	67.56	0.0016*
Receipt of chemotherapeutic or immunosuppressive drugs	3.07	1.2	7.85	0.0193*

Significant @ p-value ≤ 0.05; AOR – Adjusted odds ratio

Table 5.1. summarizes the microorganisms isolated among patients with CLABSI. There was a total of 92 organisms isolated (56 were grown from both the central line and a peripheral venipuncture site, 17 were grown from two peripheral venipuncture sites, 19 were grown from a single peripheral venipuncture site). About 48.9% of isolates were gram-negative organisms followed by gram-positive organisms with 44.6%, and fungal organisms with 6.5%. Among the four gram-positive species isolated, around 63.4% were coagulase-negative staphylococci (CONS), followed by 17.1% methicillin-sensitive *Staphylococcus aureus* (MSSA). Among the 13 gram-negative species isolated, *Klebsiella pneumoniae (K. pneumoniae)* accounted for 31.1%, followed by *Acinetobacter baumannii (A. baumannii),* with 24.4%. On the other hand, *Candida spp.* was the most common fungal organism in the study (83.3%).

TABLE 5.1. CLABSI MICROBIAL ISOLATES AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER FROM JANUARY 2018 TO DECEMBER 2022

Microorganisms	n (%)
Gram-positive	41 (44.6)
Coagulase-negative Staphylococci	26 (63.4)
Methicilin-sensitive *Staphylococcus aureus*	7 (17.1)
Methicilin-resistant *Staphylococcus aureus*	6 (14.6)
Enterococcus faecalis	2 (4.9)
Gram-negative	45 (48.9)
Klebsiella pneumoniae	14 (31.1)
Acinetobacter baumannii	11 (24.4)
Enterobacter cloacae	3 (6.7)
Pseudomonas aeruginosa	3 (6.7)
Serratia marcescens	3 (6.7)
Achromobacter xylosoxidans	2 (4.4)
Sphingomonas paucimobilis	2 (4.4)
Stenotrophomonas maltophilia	2 (4.4)
Burkholderia cepacia	1 (2.2)
Escherichia coli, ESBL	1 (2.2)
Pantoea spp.	1 (2.2)
Pseudomonas putida	1 (2.2)
Pseudomonas stutzeri	1 (2.2)
Fungi	6 (6.5)
Candida spp.	5 (83.3)
C. albicans	1 (16.7)

ESBL – extended spectrum beta-lactamase

Table 5.2 presents the antibiotic susceptibility of gram-positive organisms. Results revealed that CONS were mostly resistant to the different antibiotics, except for vancomycin to which 100% of the isolates were sensitive. All isolates of MRSA were 100% sensitive to vancomycin and linezolid. Among two patients with *Enterococcus faecalis (E. faecalis),* both were still sensitive to the drug of choice, penicillin, while no resistance to vancomycin was documented.

TABLE 5.2. ANTIBIOTIC SUSCEPTIBILITY OF CLABSI-CAUSING GRAM-POSITIVE ORGANISMS AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER FROM JANUARY 2018 TO DECEMBER 2022

Variables	**CONS n=26 (63.4%)**		**MSSA n=7 (17.1%)**		**MRSA n=6 (14.6%)**		***E. faecalis* n=2 (4.9%)**	
	S	**R**	**S**	**R**	**S**	**R**	**S**	**R**
Cefazolin	0(0.0)	26 (100)	7 (100)	0 (0.0)	0 (0.0)	6 (100)	-	-
Oxacillin	0 (0.0)	26 (100)	7 (100)	0 (0.0)	0 (0.0)	6 (100)	-	-
Clindamycin	0 (0.0)	26 (100)	7 (100)	0 (0.0)	6 (100)	0 (0.0)	-	-
Erythromycin	0 (0.0)	26 (100)	6 (85.7)	1 (14.3)	6 (100)	0 (0.0)	-	-
Gentamicin	0 (0.0)	26 (100)	7 (100)	0 (0.0)	6 (100)	0 (0.0)	-	-
Linezolid	0 (0.0)	26 (100)	7 (100)	0 (0.0)	6 (100)	0 (0.0)	-	-
Trimethoprim sulfamethoxa-zole	1 (3.8)	25 (96.2)	7 (100)	0 (0.0)	1 (16.7)	5 (83.3)	-	-
Vancomycin	26 (100)	0 (0.0)	7 (100)	0 (0.0)	6 (100)	0 (0.0)	-	-
Ciprofloxacin	0 (0.0)	26 (100)	7 (100)	0 (0.0)	6 (100)	0 (0.0)	2 (100)	0 (0.0)
Levofloxacin	0 (0.0)	26 (100)	7 (100)	0 (0.0)	6 (100)	0 (0.0)	2 (100)	0 (0.0)
Ampicillin	-	-	-	-	-	-	2 (100)	0 (0.0)
Penicillin	-	-	-	-	-	-	2 (100)	0 (0.0)

Gram-Positive Microorganisms: CONS - Coagulase-negative staphylococci, *E. faecalis* - *Enterococcus faecalis*, MRSA – Methicillin-resistant *Staphylococcus aureus*, MSSA - Methicillin-sensitive *Staphylococcus aureus*; ***Susceptibility:*** S – Sensitive, R – Resistant, (-) – Not tested

Table 5.3 shows the antibiotic susceptibility of the top five gram-negative organisms. Fourteen patients with *K. pneumoniae* were 100% sensitive to colistin, 92.9% to amikacin, and 71.4% to carbapenems (ertapenem, imipenem, meropenem). Of the 14 isolates of *K. pneumoniae,* 13 were multidrug-resistant (nonsusceptible to at least one antibiotic in three or more drug classes) while 1 was extremely drug-resistant (nonsusceptible to at least one agent in all but two or fewer drug classes). Among 11 patients with *A. baumannii,* 90.9% were sensitive to amikacin, followed by 81.8% to gentamicin and trimethoprim sulfamethoxazole. Of the 11 isolates of *A. baumannii*, 10 were multidrug-resistant while 1 was extremely drug-resistant.

TABLE 5.3. ANTIBIOTIC SUSCEPTIBILITY OF TOP FIVE CLABSI-CAUSING GRAM-NEGATIVE ORGANISMS AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER FROM JANUARY 2018 TO DECEMBER 2022

Variables	***K. pneumoniae*** **n=14 (31.1 %)**		***A. baumannii*** **n=11 (24.4%)**		***E. cloacae*** **n=3 (6.7%)**		***P. aeruginosa*** **n=3 (6.7%)**		***S. marcescens*** **n=3 (6.7%)**	
	S	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**	**R**
Cefepime	1 (7.1)	13 (92.9)	3 (26.3)	8 (72.7)	3 (100)	0 (0.0)	1 (33.3)	2 (66.7)	0 (0.0)	3 (100)
Cefotaxime	0 (0.0)	14 (100)	2 (18.2)	9 (81.8)	2 (66.7)	1 (33.3)	-	-	0 (0.0)	3 (100)
Ceftazidime	0 (0.0)	14 (100)	3 (27.3)	8 (72.7)	2 (66.7)	1 (33.3)	1 (33.3)	2 (66.7)	0 (0.0)	3 (100)
Ceftriaxone	0 (0.0)	14 (100)	1 (9.1)	10 (90.9)	2 (66.7)	1 (33.3)	-	-	0 (0.0)	3 (100)
Cefuroxime	0 (0.0)	14 (100)	-	-	2 (66.7)	1 (50)	-	-	0 (0.0)	3 (100)
Gentamicin	2 (14.2)	12 (85.7)	9 81.8)	2 (18.2)	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)	0 (0.0)	3 (100)
Piperacillin tazobactam	5 (35.7)	9 (64.3)	3 (27.3)	8 (72.7)	3 (100)	0 (0.0)	1 (33.3)	2 (66.7)	2 (66.7)	1 (33.3)
Trimethoprim-Sulfamethoxa-zole	2 (14.2)	12 (85.7)	9 (81.8)	2 (18.2)	3 (100)	0 (0.0)	-	-	0 (0.0)	3 (100)
Ciprofloxacin	7 (50.0)	7 (50.0)	3 (27.3)	8 (72.7)	3 (100)	0 (0.0)	2 (66.7)	1 (33.3)	0 (0.0)	3 (100)
Levofloxacin	6 (42.8)	8 (57.2)	-	-	-	-	1 (50)	1 (50)	0 (0.0)	3 (100)
Ampicillin	0	14 (100)	-	-	0 (0.0)	3 (100)	-	-	-	-
Amoxicillin clavulanic acid	0	14 (100)	-	-	0 (0.0)	3 (100)	-	-	-	-
Ertapenem	10 (71.4)	4 (28.6)	-	-	3 (100)	0 (0.0)	-	-	3 (100)	0 (0.0)
Imipenem	10 (71.4)	4 (28.6)	2 (18.2)	9 (81.8)	3 (100)	0 (0.0)	2 (66.7)	1 (33.3)	3 (100)	0 (0.0)
Meropenem	10 (71.4)	4 (28.6)	3 (27.3)	8 (72.7)	3 (100)	0 (0.0)	2 (66.7)	1 (33.3)	3 (100)	0 (0.0)
Amikacin	13 (92.9)	1 (7.1)	10 (90.9)	1 (9.1)	3 (100)	0 (0.0)	2 (66.7)	1 (33.3)	3 (100)	0 (0.0)
Colistin	14 (100)	0 (0.0)	-	-	-	-	3 (100)	0 (0.0)	-	-

Gram-Negative Microorganisms: *K. pneumoniae - Klebsiella pneumoniae, A. baumannii - Acinetobacter baumannii, E. cloacae – Entero-bactercloacae, P. aeruginosa - Pseudomonas aeruginosa, S. marcescens - Serratia marcescens* ***Susceptibility:*** S – Sensitive, R – Resistant, (-) – Not tested

Table 5.4 shows the antifungal susceptibility patterns of fungal organisms. All six patients with Candida were 100% sensitive to fluconazole, flucytosine, and voriconazole, while one was resistant to amphotericin B.

TABLE 5.4. ANTIBIOTIC SUSCEPTIBILITY OF CLABSI-CAUSING FUNGAL ORGANISMS AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER FROM JANUARY 2018 TO DECEMBER 2022

Anti-Fungal	*Candida spp.* n=5 (83.3%)		*C. albicans* n=1 (16.7%)	
	S	R	S	R
Amphotericin B	4 (80.0)	1 (20.0)	1 (100)	0 (0.0)
Fluconazole	5 (100)	0 (0.0)	1 (100)	0 (0.0)
Flucytosine	5 (100)	0 (0.0)	1 (100)	0 (0.0)
Voriconazole	5 (100)	0 (0.0)	1 (100)	0 (0.0)

DISCUSSION

Although the use of CVCs has been widely recognized as an essential part of medical care in critically-ill neonates and children, they carry the risk of CLABSI which may lead to increased morbidity, mortality, length of hospital stay and healthcare cost.[17] As there is limited data regarding CLABSI in children in the local setting, this study aimed to identify factors associated with the development of CLABSI involving children admitted in a tertiary government hospital. The risk factors for CLABSI encompass a wide range of variables. In this study, age, blood transfusion as indication for central line use, receipt of TPN and chemotherapeutics/ immunosuppressives, and duration of CVC use of more than 14 days were found to be significant risk factors for CLABSI.

CLABSI can occur in individuals of all ages, but certain age groups may have specific risk factors that contribute to their vulnerability. This study showed that children belonging to the 6–12-year-old age group had the highest odds of acquiring CLABSI (OR=18.91 95% CI 2.32 to 153.9) when compared to children less than 1 month old. This contrasts with a study done by Broudic, et al.,[18] where neonates were identified to be at highest risk of CVC related infection due to their underdeveloped skin barrier and immune system, which make them more susceptible to infections. In another study by Advani, et al., younger age (<1 year) has also been identified as a risk factor for CLABSI.[15] Due to the poor skin integrity of this age group, their skin can be easily damaged during repeated catheter manipulation leading to increased risk of infection. Maintenance of CVCs in this age group can also be more challenging due to their small veins which may increase the risk of complications such as dislodgement or leakage which can provide opportunities for

opportunities for infection.[15] The unanticipated result in this study, however, may be explained by other factors, including the possible predominance of complex medical conditions in older children that may require longer treatment duration and longer duration of central line use, which is also a known risk factor for CLABSI.

The study highlighted underlying medical conditions as a contributing risk factor for CLABSI development. Although no significant association was identified on multivariate analysis, the majority (31.5%) of CLABSI cases occurred in those with underlying neurologic diagnosis. This may be attributed to the possibility that neurological conditions are chronic in nature. Neurologic patients commonly have comorbid medical conditions that compromise their immune system and make them more susceptible to infections. Prolonged hospitalization due to brain injury is also common in these patients which subsequently increases the utilization of external devices such as CVCs, ventricular drains, and ventilators, among others, thus, increasing the risk of bacteremia and catheter infections.[19]

Several medical interventions and patient-level characteristics were significantly associated with the emergence of CLABSI. In the current study, blood transfusion as an indication for CVC insertion, receipt of total parenteral nutrition, receipt of chemotherapeutic or immunosuppressive therapies, and duration of catheter use. These factors are also similar to the results of a previous study done by Wylie, et al.[17]

Previous prospective and retrospective studies have recognized transfusion of blood products as a risk factor for CLABSI.[20,21] Immune suppression, increased frequency of line access, and pathogen multiplication with transfusion are some potential mechanisms to explain the risk associated with blood transfusion. These mechanisms may also explain as to how administration of parenteral nutrition increases CLABSI rate. Other studies suggest that the risk of CLABSI may also be influenced by lipid contamination, glycemic alterations, and gastrointestinal mucosal breakdown brought about by inadequate enteral nutrition which poses more risk of infection.[15,22,23] Moreover, TPN solutions contain high concentrations of glucose that promote bacterial growth when central lines are contaminated.[23] With this, early switch to enteral feeding is suggested to probably decrease the risk of CLABSI.[17] Immediate replacement of tubings used to administer these products should be observed within 24 hours of initiating the infusion to avoid contamination.[24]

Receipt of chemotherapeutic or immunosuppressive medications was also seen as a significant risk factor for CLABSI development in this study. This association may be related to the increased susceptibility to infection brought about by cytostatic

drug-induced neutropenia.[25,26]

Infection prevention efforts on the prompt removal of CVCs have been emphasized in many guidelines since the length of central line access has been identified as a consistent risk factor for bloodstream infection. This study identified the duration of CVC use of more than 14 days as an independent risk factor for CLABSI. This confirms the findings of previous studies that prolonged catheter dwell times increase the risk of CLABSI. [15,17] The development of CLABSI in patients with prolonged CVC use may be attributed to the degradation and dysfunctionality that CVCs acquire over time from repeated manipulations.[27] Long-term central venous access, however, is frequently unavoidable particularly in critically ill children admitted in government hospitals. In addition, immediate replacement of the central line is not always possible due to their high cost. Nonetheless, periodic assessment of CVCs should be done to determine if these can be removed or if an alternative and less invasive access line can be used.

In contrast to other studies, this study found no significant association between the types of central line inserted and the development of CLABSI, as well as the site of central line insertion and the odds of acquiring CLABSI. The non-significant findings could be attributed to the limitations of a relatively small sample size, as well as the potential influence of other confounding factors, such as variations in catheter insertion techniques and patient characteristics. However, it is worth noting that majority of the central lines inserted in PCMC were non-tunneled catheters. These catheters are associated with an increased risk of CLABSI due to several reasons. Direct insertion of non-tunneled CVCs provides a direct pathway for bacteria to enter the bloodstream, increasing the risk of contamination during the insertion process.[15,24] Moreover, non-tunneled CVCs often are less securely anchored in place as compared to tunneled or totally implanted catheters which can lead to instability and increased risk of contamination at the insertion site.[24] Considering these factors, it is still advisable to limit the use of non-tunneled CVCs for short-term purposes when possible.

As in other studies,[11,28,29] the most frequent microorganism isolated in CLABSI cases were gram-positive cocci, specifically, CONS. This may be attributed to the colonization of the patient's skin flora or a result of several healthcare providers manipulating the device.[27] Increasing rates of gram-negative organisms are also being reported globally. Of note, this study showed a higher proportion of gram-negative (n=45, 48.9%) compared to gram-positive organisms (n=41, 44.6%), particularly *K. pneumoniae* and *A. baumannii.* This can be a cause for concern as gram-negative organisms are associated with higher morbidity and

mortality rates and are prone to antibiotic resistance, making them more difficult to treat.[30] Thus, empiric use of antibiotics based on the antibiotic susceptibility of these organisms should be considered to ensure that effective treatment is given to patients at the onset.

For the clinical outcome of CLABSI cases, 10.9% of those who developed CLABSI died. However, it was not possible to determine whether death was a direct consequence of CLABSI in those patients.

This study also revealed that in PCMC, the majority of CLABSI cases occurred in patients admitted at the general wards. Hence, efforts to prevent infection of CVCs, not only in the ICUs but also in general wards should be strictly implemented. Care bundles to prevent CLABSI beginning from insertion to site care should be made available to healthcare workers in all areas and should be reviewed on a regular basis. Knowledge of the different risk factors associated with CLABSI can help healthcare providers in identifying patients who are at higher risk of developing CLABSI. Enhanced infection control measures should be practiced in patients who are likely to need blood transfusion, parenteral nutrition and chemotherapeutics to prevent or reduce CLABSI occurrence. Adjunctive interventions to prevent CLABSI in these patients such as antiseptic dressings and antibiotic lock therapy may also be considered.[31] More importantly, frequent hand hygiene, personnel training, use of skin antiseptics, provision of barrier methods, daily evaluation of catheters and removal of the CVCs when no longer needed are practices that should always be implemented.[24] Continued surveillance of CLABSI is also important to document changes in the epidemiological features and antibacterial resistance.

Discussion

This study has some limitations. First, the study only involved patients with hospital-acquired CLABSIs which limited the study sample size and limited the generalizability to only hospitalized cases. As this is a single-center study, the results may not be representative of the entire pediatric population. A wide confidence interval was also observed in some of the risk factors identified, hence, it is difficult to make precise predictions or draw definitive conclusions based on the results of this study. Therefore, the researcher recommends that a prospective study with a larger sample size be conducted in the future to validate these risk factors. Research focused on evaluating and comparing different prevention strategies aimed at reducing CLABSI rates may also be explored.

Conclusion

This study showed that age, blood transfusion as indication for central line use, receipt of total parenteral nutrition, receipt of chemotherapeutic and immunosuppressive drugs, and duration of CVC utilization of

more than 14 days were found to be independent risk factors for CLABSI among children admitted in PCMC during the study period. The diagnosis of CLABSI should be considered in symptomatic patients with central lines who have the abovementioned risk factors. Coagulase-negative *Staphylococcus* (CONS), *K. pneumoniae* and *A. baumannii* were the most commonly isolated organisms in patients with CLABSI. Hence when considering CLABSI empiric antibiotic coverage in our institution should include coverage for both gram-negative and gram-positive organisms.

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ARTICLE

Ocular manifestations of infants with Congenital Rubella Syndrome (CRS) at Philippine Children's Medical Center from 2015-2021

Joanne Paula B. Manalo, Mary Ann C. Bunyi, Norman Eric F. Fajardo

OBJECTIVE: The study determined the ocular manifestations as well as the clinico-demographic, maternal profile, and management of infants with Congenital Rubella Syndrome (CRS) seen at the Philippine Children's Medical Center from 2015 to 2021.

MATERIALS AND METHODS: A retrospective chart review was conducted among children less than 1 year of age, born between January 1, 2015, to December 31, 2021, who met the clinical case definition of CRS.

RESULTS: Among the 398 reviewed charts, 312 were suspected cases of CRS, 79 were probable, and 7 were laboratory-confirmed. Ocular conditions were found in 54 suspect cases, 14 probable cases, and 2 confirmed cases. Congenital cataract was the most common ocular manifestation in infants with CRS, and associated clinical manifestations were mainly congenital heart disease followed by microcephaly and hearing loss.

CONCLUSION: This study highlighted the challenge of CRS diagnosis in the country, with most cases diagnosed based on clinical manifestations and a limited number of laboratory-confirmed cases due to the expense and availability of confirmatory tests. These findings emphasize the importance of recognizing ocular manifestations as an early indicator of CRS and the need for improved surveillance and awareness of the disease to facilitate early recognition and management.

KEYWORDS: *Congenital Rubella Syndrome, congenital cataract, rubella infection in pregnancy*

Introduction

Congenital Rubella Syndrome (CRS) is a severe condition resulting from rubella virus infection in non-immune pregnant women, with the greatest risk of congenital infection and defects occurring during the first trimester of pregnancy. CRS can lead to various birth defects, including heart disease, hearing, vision, neurological, endocrinologic, and other disorders [1]. Due to its teratogenic effects, CRS is of significant public health concern. Cases of rubella are underreported in the Philippines, and there is no specific surveillance system for CRS in place. A local retrospective study done by Lopez et al. in 2017 [2] used hospital-based data from four tertiary hospitals, including PCMC, and estimated a national burden of 20 to 31 CRS cases per 100,000 annually, underlining the need for improved monitoring and management.

CRS can cause various ocular manifestations, affecting structures like the lens, retina, ciliary body, and cornea, leading to conditions such as cataracts, microphthalmia, retinopathy, strabismus, and glaucoma [3]. In the Philippines, childhood blindness is a concern, with cataracts being a primary cause [4]. Notably, congenital rubella is identified as a common cause of secondary cataract cases in the country [5], similar to findings in India [6].

This study's objective is to provide data on the ocular conditions of patients suspected or confirmed to have CRS, with a focus on infants seen at the Philippine Children's Medical Center from 2015 to 2021. It also details the clinico-demographic and maternal characteristics as well as the management for the ocular conditions. This is a separate sub-study under the larger multi-center research conducted by Gonzales [7], and the data collected were permitted to be used for analysis in this paper.

Materials and Methods

This descriptive study was conducted with ethics approval from the PCMC Institutional Research - Ethics Committee and employed a retrospective chart review of patients with ocular manifestations associated with CRS.

Patients who were less than 1 year of age and were born between January 1, 2015 to December 31, 2021 were included in the records review. Charts with the following discharge diagnoses were used to identify suspected CRS cases for full review:

Table 1. *Discharge diagnosis with ICD-10 codes for retrieval of charts for review*

Discharge Diagnosis	ICD-10
Congenital rubella syndrome (CRS)	P35
Cataracts (unilateral or bilateral)	Q12.0,
Congenital glaucoma	Q15.0, Q15.9, H40
Pigmentary retinopathy	H35.5
Deafness and hearing impairment	H90

Congenital heart disease	**Q20-Q26**
Patent ductus arteriosus (PDA)	Q25.0
Peripheral pulmonary artery stenosis (PS)	Q25.6
Dermal erythropoiesis	P83.8
Congenital and hereditary thrombocytopenic purpura	D69.42
Microcephaly	Q02
Meningoencephalitis (unspecified)	G04.90
Meningoencephalitis (rubella-associated)	B06.01

The following patients were excluded from review:

Infants <2,500 grams with isolated PDA or isolated microcephaly and no other signs of CRS

Documented negative rubella-specific IgG test for the child

Documented positive laboratory test for other possible etiology of CRS manifestation, such as positive cytomegalovirus or toxoplasmosis test, in the absence of a positive rubella laboratory test

Not a resident of the Philippines

Case Definitions of CRS

Clinical Criteria: an illness, usually manifesting in infancy, resulting from rubella infection in utero and characterized by signs and symptoms from the following:

Category A: congenital cataract/glaucoma, pigmentary retinopathy, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary stenosis), or hearing loss

Category B: purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease

Laboratory Criteria

Isolation of rubella virus,

Demonstration of rubella IgM antibody or infant rubella IgG antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month), or

Polymerase Chain Reaction (PCR) positive for rubella virus

Suspect case: A case that has some compatible clinical findings but does not meet the criteria for a probable case.

Probable case: A case that is not laboratory confirmed but has any two conditions listed in category A or one condition from category A and one condition from category B, and lacks evidence of any other etiology.

Confirmed case: A case that has any one condition from category A or one condition from category A and one from category B and meets the laboratory criteria.

Total enumeration of all CRS cases based on the inclusion and exclusion criteria was done. A standardized data abstraction form adapted from the study of Gonzales (2022) [7]

was used for data collection with additional questions on ocular manifestations and interventions done formulated by the primary investigator. Questions on additional ocular conditions, specific surgical interventions, and timing of management were added to the form for this study. The form was converted to an electronic version using the Kobo toolbox platform. Data were collected using the Kobo Collect application using an electronic device either online or offline. Access to the application as well as the encoded data was limited to the investigators and research assistants through standard encryption and password protection. Data collection was done by the primary investigator along with two research assistants.

An initial screening of records was done based on the inclusion and exclusion criteria among infants born between January 1, 2015, to December 31, 2021, with discharge diagnoses as detailed in Table 1. A full chart review was done, and each case was classified based on the case definitions of CRS provided. Those that fulfilled the case definition were classified into suspect, probable, or confirmed cases. Ocular manifestations were recorded, and the clinico-demographic profile, maternal risk factors, and management for the specific ocular conditions were recorded through the Kobo Collect application. Descriptive data analysis was done using Microsoft Excel. Categorical data were expressed as frequency and percentages.

RESULT

In this study, a total of 546 medical records were reviewed, focusing on patients with discharge diagnoses related to Congenital Rubella Syndrome (CRS). After excluding 105 cases and consolidating multiple consults and admissions for the same patient, 398 unique CRS cases were identified. Among these, 312 were suspect cases, 79 were probable cases, and 7 were laboratory-confirmed CRS cases. The analysis showed 54 (13.5%) CRS cases presented with ocular manifestations, highlighting the prevalence of eye-related conditions in infants with CRS. Of the 54, 38 (48.1%) were suspect cases, 14 (17.7%) were probable cases, and 2 (2.9%) were confirmed cases.

Table 2 shows the clinico-demographic profile of CRS cases exhibiting ocular manifestations. The mean age of diagnosis was earlier in laboratory-confirmed cases at 1.2 months (range: 10 days to 2 months) compared to probable cases at an average age of detection at 4.4 months (range: 6 days to 9 months) and suspect cases at 4.7 months. There were more cases among males. Around a third of patients weighed more than 2,000 grams. Due to limitations in chart documentation, more than half of the cases had unknown birthweight. Both confirmed cases tested positive for Rubella IgM, and one was positive for Rubella IgG. Rubella PCR was not requested for any case in this study. All probable and suspect cases were diagnosed based on signs and symptoms and were not serologically tested.

Table 2. *Clinico-demographic profile of CRS cases with ocular manifestations (PCMC, 2015-2021)*

	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Birthweight				
1,000 to 1,999 grams	1 (50%)	3 (21%)	1 (3%)	5 (9%)
2,000 to 2,999 grams	0	5 (36%)	7 (18%)	12 (22%)
3,000 to 3,999 grams	0	0	6 (16%)	6 (11%)
Birthweight not documented	1 (50%)	6 (43%)	24 (63%)	31 (58%)
Sex				
Male	1 (50%)	8 (57%)	24 (63%)	33 (61%)
Female	1 (50%)	6 (43%)	14 (37%)	21 (39%)
Mean age at CRS diagnosis (mean ± std dev)	1.2 ± 1.2	4.4 ± 3.2	4.7 ± 3.1	4.5 ± 3.1
Age at CRS diagnosis				
1 month and below	1 (50%)	4 (28%)	4 (11%)	9 (17%)
Between 1 to 6 months	1 (50%)	5 (36%)	21 (55%)	27 (50%)
6 months and above	0	5 (36%)	13 (34%)	18 (33%)
Rubella IgM				
Positive	2 (100%)	0	0	2 (4%)
Negative	0	0	0	0
Not done	0	14 (100%)	38 (100%)	52 (96%)
Rubella IgG				
Positive	1 (50%)	0	0	1 (2%)
Negative	0	0	0	0
Not done	1 (50%)	14 (100%)	38 (100%)	53 (98%)

Table 3 illustrates the maternal profile of CRS cases with ocular manifestations. Among confirmed, probable, and suspect cases, the mean maternal age was 27.6 years (range: 18 to 41 years). Around half of the mothers attained at least a high school degree. Majority had prenatal check-ups and delivered in a healthcare facility attended by a healthcare worker. Both confirmed cases had a prenatal history of rubella-like illness while only less than a third of probable cases had a maternal history of fever and rash by recall. Majority of documented maternal rubella-like illness occurred during the first 12 weeks of pregnancy. Half of the suspect cases had unknown history of rubella-like illness. History of exposure to rubella was unknown in most cases (68%).

Table 3. *Maternal profile of CRS cases with ocular manifestations (PCMC, 2015-2021)*

	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Mean maternal age (in years, mean ± std dev)	23 ± 0	27.4 ± 6.2	27.9 ± 5.2	27.6 ± 5.4
Maternal age				
<17 years old	0	0	0	0
18-29 years old	2 (100%)	9 (63%)	21 (55%)	32 (59%)
30-39 years old	0	2 (14%)	13 (34%)	15 (27%)
>40 years old	0	1 (7%)	1 (3%)	2 (3%)
Unknown	0	2 (14%)	3 (8%)	6 (11%)
Educational attainment				
Elementary graduate	0	1 (7%)	1 (3%)	2 (3%)
High school graduate	1 (50%)	3 (21%)	14 (37%)	18 (34%)
College graduate	1 (50%)	6 (43%)	8 (21%)	15 (27%)
Unknown	0	4 (29%)	15 (39%)	19 (36%)
Prenatal check-ups				
Yes	2 (100)	12 (86%)	32 (84%)	46 (85%)
No	0	0	0	0
Unknown	0	2 (14%)	6 (16%)	8 (15%)
Delivered in a healthcare facility attended by a healthcare worker				
Yes	2 (100%)	11 (79%)	33 (87%)	46 (85%)
No	0	2 (14%)	1 (3%)	3 (6%)
Unknown	0	1 (7%)	4 (10%)	5 (9%)
History of rubella-like illness during pregnancy				
Yes	2 (100%)	4 (29%)	3 (8%)	9 (17%)
No	0	7 (50%)	16 (42%)	23 (43%)
Unknown	0	3 (21%)	19 (50%)	22 (40%)
Age of gestation of rubella-like illness				
12 weeks and below	2 (100%)	4 (29%)	1 (3%)	7 (13%)
13 to 27 weeks	0	0	2 (5%)	2 (4%)
28 to 40 weeks	0	0	0	0
Unknown	0	10 (71%)	35 (92%)	45 (83%)
History of exposure to rubella				
Yes	0	0	1 (3%)	1 (2%)
No	0	5 (36%)	11 (29%)	16 (30%)
Unknown	2 (100%)	9 (64%)	26 (68%)	37 (68%)

Table 4 describes the distribution of ocular manifestations seen in infants with CRS. Some suspect cases presented with more than one ocular finding. Cataract was the most common ocular manifestation in infants with CRS, followed by strabismus and nystagmus.

Table 4. *Ocular manifestations of infants with CRS (PCMC, 2015-2021)*

Ocular manifestations	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Cataract	0	10	30	40
Strabismus	1	0	5	6
Nystagmus	0	1	4	5
Pigmentary retinopathy	1	2	2	5
Microphthalmia	0	1	1	2
Glaucoma	0	0	1	1
Aniridia	0	0	1	1

In Table 5, the presence of associated systemic conditions in CRS infants with ocular manifestations is illustrated. It was observed that most probable and both confirmed cases exhibited one or more systemic findings, whereas certain suspect cases did not display any associated systemic manifestations. For confirmed cases, microcephaly was the prevailing associated clinical manifestation. On the other hand, among probable and suspect cases, the most observed associated conditions were congenital heart disease, followed by microcephaly and hearing impairment.

Table 5. *Systemic manifestations of CRS cases with ocular conditions (PCMC, 2015-2021)*

Clinical manifestations	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Congenital heart disease	0	15	8	23
Microcephaly	2	7	2	11
Hearing loss	1	5	0	6
Developmental delay	1	1	2	4
Purpura	0	2	1	3
Neonatal jaundice	1	0	0	2

Table 6 outlines the interventions performed for ocular conditions in infants with CRS. Multiple interventions were done in some cases. In the two confirmed cases, no interventions were carried out for pigmentary retinopathy and strabismus; instead, these conditions were closely monitored through follow-up consultations with ophthalmologists. Nine probable cases and 26 suspect cases had interventions done for their ocular conditions. Among probable and suspect cases with cataracts, lensectomy was the predominant intervention. Remarkably, five of these cases underwent anterior vitrectomy during the same procedure. Additionally, two of these cases also underwent posterior capsulotomy at the same timing as lensectomy and anterior vitrectomy.

Table 6. *Interventions for ocular manifestations of CRS (PCMC, 2015-2021)*

Interventions	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Lensectomy	0	8	24	32
Medical management	0	1	3	4
Anterior vitrectomy	0	1	5	6
Posterior capsulotomy	0	1	3	4
None	2	5	12	19

Table 7 provides insights into the timing of interventions for ocular conditions in infants with CRS, revealing that approximately one-third of these interventions were initiated when the infants were six months old or younger. However, due to limitations in chart documentation, one-third of cases lacked information regarding the timing of their management.

Table 7. *Timing of interventions performed for ocular conditions in infants with CRS (PCMC, 2015-2021)*

Timing of interventions	Confirmed (n=0)	Probable (n=9)	Suspect (n=26)	Total (n=35)
1 month and below	0	1	2	3
Between 1 to 6 months	0	3	7	10
6 months and above	0	2	7	9
Not documented	0	3	10	13

DISCUSSION

Congenital Rubella Syndrome is an underrecognized public health concern in the country with far-reaching implications. CRS results from maternal rubella virus infection during pregnancy, leading to a wide array of congenital abnormalities and developmental disorders in affected infants. One of the most common manifestations of CRS are distinct ocular findings which may or may not be seen in association with other systemic conditions. The ocular consequences of CRS warrant a focused discussion as they may serve as crucial diagnostic indicators, offering an opportunity to early recognition and intervention.

In the country, cases of rubella remain to be underreported since surveillance is only based on the testing of measles-negative cases. Based on the latest surveillance report by the Department of Health (DOH) Epidemiology Bureau, there was a recorded 541% increase in measles and rubella cases combined from January to February 2023 compared to the same period of 2022 [8]. Similarly, there is also no CRS surveillance in place in the Philippines.

This study identified 38 suspect, 14 probable, and 2 laboratory-confirmed CRS cases with ocular manifestations. Cataract was the most common ocular finding, similar to findings of several local and foreign studies. A retrospective study by Lopez et al. in 2017 showed 52 cataract cases among probable and confirmed CRS cases [2]. A similar study by Vijayalakshmi et al. in 2002 also revealed cataract as the most common ocular finding (93%) with nuclear morphology being the most predominant type [9]. The presence of a nuclear type cataract in a child under 1 year old was revealed to have a 75% positive predictive value for CRS [6] Hence, there should be high suspicion for CRS in any ill infant with congenital cataract.

Another study by Vijayalakshmi et al. in 2007 further exploring the eye signs of congenital rubella showed that the presence of cataract may hold the strongest association with CRS among other eye findings [10]. National congenital cataract data has been used by the several studies as a case finding strategy for Congenital Rubella Syndrome and for extrapolating incidence rates of CRS [2], [11]. Cataract data were well-archived and included the pre-operative assessments, including echocardiograms, which improve documentation of other associated defects.

Pigmentary retinopathy is another common ocular finding in CRS as seen in local [12] and in older foreign studies [13], [14]. Nystagmus and strabismus may also be observed and have been identified in one study as predictors of poor visual outcome [12].

Congenital heart disease was the predominant associated systemic manifestation, which was also observed in

due to difficulty securing clearances from comorbid conditions such as congenital heart disease and acquiring intensive care unit accommodation.

Conclusion and Recommendation

This retrospective study concludes that early recognition of systemic manifestations can facilitate prompt management and improve quality of life. Ocular manifestations may be a useful primary indicator as many of them may be detected at an earlier age compared to other manifestations. The status of CRS in the country is a huge reflection of the effectiveness of existing programs directed at rubella prevention, which is still largely integrated with measles programs. The lack of an established surveillance system needs to be addressed to obtain the true national burden of CRS. New guidelines on CRS surveillance may serve as a good foundation and may be integrated with current rubella programs [20]. This would also promote awareness of the disease and promote early recognition and management.

This study conducted a review of cases of CRS up to 1 year of age presenting with ocular conditions. Future research may explore children beyond 1 year of age to include CRS cases who were diagnosed or sought health consult at a later age, investigate other systemic manifestations of CRS, and examine reasons for delays in management of individual conditions.

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ARTICLE

Clinical profile and outcome of Childhood Interstitial Lung Disease (chILD) Syndrome in a tertiary pediatric hospital: a 10-year review (2013-2022)

Juan Carlos D. Moreno, Jenni Rose D. Dimacali

OBJECTIVE: This study described childhood interstitial lung disease profiles at the Philippine Children's Medical Center (2013-2022).

MATERIALS AND METHODS: A retrospective chart review at PCMC analyzed pediatric interstitial lung disease cases (Jan 2013-Dec 2022). Included were patients aged 0-18 with childhood interstitial lung disease. Excluded were those with specific conditions. Data included clinical course, tests, therapeutic management, and short-term outcomes based on a previous study.

RESULTS: Twenty-three patients were included in this study. Most (52.17%) were diagnosed between 2013-2017, and were within the ages of 0-2 years. Majority of patients had normal nutritional status (52.17%). Common clinical presentation on admission included breathing difficulties, with chest retractions, crackles, and hypoxemia. Few had a family history of chronic lung disease. Comorbidities included pulmonary hypertension (30.43%) and pulmonary tuberculosis (21.74%). Chest radiography revealed infiltrates in all cases, and HRCT scans showed ground glass opacities in 82.61%. Prednisone was the primary treatment (86.96%). Lung biopsy results (43.48%) were mostly unclassified or nondiagnostic, with lymphoid interstitial pneumonia as the predominant diagnosis (20%). Improvement of signs and symptoms was seen in 39.13% of cases, whereas death occurred in 21.74%. Furthermore, the outcome remained undetermined in as much as 34.78% of cases due to inadequate follow-up.

CONCLUSION: This retrospective study emphasizes chILD's prevalence in infants under 2 years, with male predominance. Nutritional variations underscore the need for supplementation. Various common signs include crackles, retractions, and hypoxemia, with breathing difficulty as a frequent symptom. The diagnostic process involves imaging and ancillary tests, advocating a systematic approach with noninvasive methods like CXR and HRCT, reserving lung biopsy for inconclusive cases. Corticosteroids, whether used alone or in combination, prove beneficial in managing chILD by suppressing inflammation.

KEYWORDS: *Childhood interstitial lung disease, clinical profiles, treatment outcome*

INTRODUCTION

Childhood interstitial lung disease (chILD) is a heterogeneous group of rare pulmonary disorders, comprising approximately more than 200 immune- and nonimmune-mediated respiratory conditions presenting with impaired gas exchange and diffuse radiologic infiltrates on plain radiographs [1,2,5]. chILD is associated with high morbidity and mortality, and it depends on the specific type of chILD disorder [1,3]. Reports on its mortality rates, incidence and prevalence vary and are relatively underrepresented in pulmonary research as compared to adult data [1]. A study done at the Philippine Children's Medical Center (PCMC) last 2019 assessed the association of chest high resolution CT scan, histopathology findings and severity illness score to the survival rate of patients with chILD in our institution [6]. Although this study included demographic data and survival rates of chILD patients, it underestimated the total population of chILD in our institution by excluding patients who did not undergo biopsy. Biopsy is just one of the ways in which a diagnosis can be made. Biopsy is routinely requested for all patients labeled as chILD, but due to the invasiveness of the procedure, securing consent is difficult. The global thrust now is to utilize other non-invasive modalities before resorting to biopsy. According to the American Thoracic Society, fulfilling three out of the four criteria of chILD makes physicians diagnose patients as having chILD Syndrome already. These include respiratory symptoms, such as cough, rapid and/or difficult breathing, or exercise intolerance; respiratory signs like tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure; hypoxemia; and diffuse abnormalities on a chest radiograph (CXR) or computed tomography (CT) scan [4]. Clinical profiles and outcomes of chILD vary by age at presentation [1]. Despite the heterogeneity of these disorders, such as age of presentation, genetic mutations, disease course, international studies have posited overlapping clinical manifestations [2]. This review explored these issues to better elucidate the different clinical presentations of chILD in Filipino children, and their outcomes for recommendations for future research and treatment advancement. This study included patients who have and have not undergone pulmonary biopsy for histopathologic confirmation. Apart from these, this study can potentially increase international relations and partnerships with companies or pharmaceutical industries for possible funding of resources such as medications for patients with chILD.

Childhood interstitial lung disease is a rare group of pulmonary diseases, characterized by a disordered exchange of gases attributable to different pathological mechanisms [1,5]. The exact incidence of chILD is unknown, and different studies have reported varying statistics which may be due

to differences in the population included in these studies. Ferraro and associates have reported an estimate of 0.13 to 16.2 cases of chILD per 100,000 children per year [2]. In the Philippines alone, studies regarding its incidence or prevalence are lacking. Etiologies of chILD were broadly grouped in studies into those occurring in patients less than 2 years old (or ILD specific to infancy), those occurring in ages 2-18, which may be related to a primary systemic disease or follow a harmful exposure to irritable antigens [2,3]. According to a Japanese study by Kitazawa and Kure, chILD occurring in infancy are a result of congenital malformations, genetic mutations, or chronic damage of the lung due to premature birth or other congenital anomalies [2]. Diagnosis of chILD was consistent with all studies which used different clinical parameters including history and physical examination, chest radiography, high resolution chest CT, pulmonary function testing, bronchoscopy with BAL, echocardiography, genetic testing, and/or lung biopsy, which remains to be the gold standard. But according to the American Thoracic Society Clinical Practice Guidelines, the diagnosis of chILD requires that all neonates and infants below 2 years old presenting with diffuse lung disease known to have been caused by common diseases in this age group are excluded. These include cystic fibrosis, congenital or acquired immunodeficiency, congenital heart disease, bronchopulmonary dysplasia, pulmonary infection, primary ciliary dyskinesia presenting with newborn respiratory distress, and recurrent aspiration. Once these common diseases that can cause DLD have been eliminated, a neonate or infant with DLD is regarded as having "chILD syndrome" if at least three of the following four criteria are present: (a) Respiratory symptoms (cough, rapid and/or difficult breathing, or exercise intolerance); (b) respiratory signs (tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure); (c) hypoxemia; and (d) diffuse abnormalities on a chest radiograph (CXR) or computed tomography (CT) scan [4]. There is a highly variable severity of chILD at initial presentation. Some present with mild nonspecific symptoms, while others present with a very severe clinical picture at the onset [2]. Sankar and associates included an assessment of disease severity by assigning an illness score based on data gathered from the patient records at the time of their initial evaluation [5]. Ferraro, et.al. identified the common clinical manifestations of chILD depending on the age of presentation. According to this study, chILD may present shortly after birth with unexplained respiratory distress in term neonates, who can rapidly require intubation and ventilation. Preterm infants may present with an acute respiratory distress which is more severe than would be expected because of prematurity [2]. During the first two years of life, the clinical symptomatology vary from having no

Two studies from Italy and India have reported the older children present with various nonspecific respiratory manifestations, such as dyspnea, polypnea, dry cough, wheezing, recurrent respiratory infections and exercise intolerance, including other more severe signs and symptoms like hemoptysis, pallor, clubbing, crepitation, and murmur [2,5]. In the study of Sankar et.al., the outcomes assessed included death and symptomatic improvement in dyspnea, hypoxemia and/or lung function tests. It also evaluated the determinants of poor outcomes other than the abnormalities on plain radiographs and chest CT scan, which include the effect of severe hematological investigations at presentation such as total leucocyte count, and liver function tests at presentation such as serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and alkaline phosphatase (ALP) [5]. In this study, the investigators found out that apart from having a disease severity of graded 3 or higher at initial presentation, lower median serum ALP levels correlated to poorer outcomes.

This study aims to provide a comprehensive description of the clinical profiles and outcomes of pediatric patients with interstitial lung disease admitted to the Philippine Children's Medical Center (PCMC) from 2013 to 2022. Furthermore, it will likewise include determining the age and gender distribution of chILD patients admitted to PCMC, identifying common sym toms, and evaluating the diagnostics and therapeutics used in their management. Additionally, the study aims to assess the clinical outcomes of chILD patients admitted to PCMC during the specified period from 2013 to 2022.

Materials and Methods

The investigator employed a retrospective chart review of children admitted in PCMC who were discharged with a final diagnosis of interstitial lung disease between January 2013 until December 2022. This study was approved by the Philippine Children's Medical Center Institutional Review Board.

Included in the study are patients who met the following criteria: 1) patients ages 0 to 18 admitted from January 2013 until December 2022 with childhood interstitial lung disease syndrome**;** 2) patients without lung biopsy diagnosed with childhood interstitial lung disease on the basis of clinical signs and symptoms, presence of hypoxemia and characteristic findings on chest x-ray or high-resolution CT scan; 3) patients who underwent lung biopsy with findings suggestive of childhood interstitial lung disease. Children with bronchopulmonary dysplasia (BPD), cystic fibrosis, malignancy, primary or acquired immunodeficiency, coagulation disorders, vasculitis, celiac disease and vascular malformations were excluded from the study.

Case records of children diagnosed with chILD were obtained from the Medical Records Section of our institution for patients who were admitted for collection of data regarding the clinical course, ancillary tests used such as plain chest radiographs, chest high resolution CT scan, bronchospcopy and bronchoalveolar lavage (BAL) analysis. Data regarding the therapeutic management received and follow-up after hospital discharge of these children were also retrieved from patient records. Demographic data and symptomatology of each patients were collected, including laboratory findings and results of all diagnostic imaging used. Identifying the short-term outcomes was patterned from the study of Sankar, et.al. The variables which were assessed included death and improvement of symptoms—improvement in dyspnea, hypoxemia and/or lung function tests—at follow up from after 3 months of starting therapy until the time of last follow up record available [4]. Outpatient records from the Section of Pediatric Pulmonology were obtained to gather data on these immediate outcomes. In our study, the collected data were presented as frequency (f) or percentage (%) as appropriate.

RESULTS

A total of 23 patients were included in the study. Out of the 23 patients, 65.22% (n = 15) cases were diagnosed between 2013 to 2017, and 34.78% (n = 8) cases between 2018 to 2022. Table 1 shows the clinical characteristics of these patients.

Table 1. Clinical Profile of patients diagnosed with chILD admitted from January 2013 to December 2022

	Demographic Parameters	Frequency (n)	Percent (%)
Age at symptom onset	0 – < 2 years	15	65.22
	2 – 5 years	7	30.43
	6 – 10 years	-	-
	>10 years	1	4.35
Age upon diagnosis	0 – < 2 years	12	52.17
	2 – 5 years	8	34.78
	6 – 10 years	2	8.70
	>10 years	1	4.35
Neonatal Maturity	Term	-	-
	Preterm	2	8.70
Gender	Male	13	56.52
	Female	10	43.48
Weight-for-length/height	Normal for age	12	52.17
	Z score below – 2	3	13.04
	Z score below – 3	8	34.78
Signs	Hypoxemia	20	86.96
	Retractions	22	95.65
	Crackles	21	91.30
	Wheezes	13	56.52
	Tachypnea	17	73.91
	Cyanosis	6	26.09
	Hemoptysis	-	-
	Clubbing	3	13.04

Symptoms	Cough	19	82.61
	Difficulty of Breathing	23	100
	Gurgly chest	1	4.35
	Limitation of activity	-	-
Family History of Respiratory Disease	None	17	73.91
	With family history of chronic lung disease	6	26.09
Other co-morbidities	Congenital heart disease (VSD, PFO)	3	13.04
	Rheumatic heart disease	1	4.35
	Pulmonary tuberculosis	5	21.74
	Bronchial Asthma	1	4.35
	Pulmonary Hypertension	7	30.43
	Cor Pulmonale	1	4.35

Majority of patients had onset of symptoms and were diagnosed between the age of 0-2 years, comprising 65.22% and 52.17% of cases, respectively. Notably, only two cases manifested during the neonatal period, and both were premature births (8.70%). There was also note of slight male predominance.

Around 52.17% of patients had a normal weight-for-length/height. Following this, 34.78% (8 out of 23) of cases are categorized under the nutritional assessment of $z < -3$, indicating severely wasted when plotted on the World Health Organization Growth Charts.

The most common presenting symptom is difficulty of breathing which was seen in all patients with chILD. On admission, the most common signs collectively noted were chest retractions, crackles, and hypoxemia. None of these cases presented with limitation in activity and hemoptysis.

Only 26.09% (n = 6) of the cases reviewed had a family history of chronic lung disease. Family members of these patients were noted to have bronchial asthma. Majority of the patient had no co-morbidities, while 11 were noted to have other medical conditions upon diagnosis. Pulmonary hypertension and pulmonary tuberculosis were the most common co-morbidities noted, presenting at 30.43% and 21.74%, respectively. Seven patients with pulmonary hypertension were classified based on echocardiographic findings as mild pulmonary hypertension (pulmonary arterial pressure = 35-50 mmHg), while 1 was classified as moderate pulmonary hypertension (pulmonary arterial pressure = 50-70 mmHg). Of these patients with pulmonary hypertension, majority had a concomitant pulmonary tuberculosis while the others had congenital heart diseases (i.e. ventricular septal defect and patent foramen ovale)

Table 2 shows the various modalities employed in the diagnosis of these patients.

Table 2. Diagnostic procedures employed in patients diagnosed with chILD admitted from January 2013 to December 2022

	Parameters	Frequency (n)	Percent (%)
Chest X-ray Findings	Normal	-	-
	Infiltrates	23	100
	Hyperaeration	8	34.78
	Consolidation	6	26.09
	Cardiomegaly	1	4.35
High Resolution CT Scan Findings	Ground Glass Opacities	19	82.61
	Consolidation	4	17.39
	Bronchiectasis	6	26.09
	Hyperinflation	-	-
	Reticular Opacities	10	43.48
	Nodules/Cysts	4	17.39
	Fibrosis	6	26.09
Other tests done	Echocardiography	11	47.83
	Bronchoscopy	4	17.39
	Bronchoalveolar Lavage	2	8.70
	Spirometry	-	-
	Immunodeficiency Panel	2	8.70
Biopsy	Desquamative Interstitial Pneumonia	1	10
	Hypersensitivity pneumonitis	1	10
	Idiopathic Pulmonary Hemosiderosis	1	10
	Lymphoid Interstitial Pneumonia	2	20
	Post-infectious (tuberculosis)	1	10
	Focal interstitial pneumonitis	1	10
	Unclassified	3	30

All patients underwent chest radiography, which all showed presence of pulmonary infiltrates. Chest HRCT scan was done in 21 cases. Out of these the presence of ground glass opacities was the most common anomaly seen at 82.61% (n = 19).

Other ancillary tests done in these patients include echocardiography in 47.83% (n = 11) to determine the presence of pulmonary hypertension and assess its severity, as well as the presence of congenital heart diseases. Only 2 of these patients had normal echocardiographic findings. There was a 17.39% (n = 4) of patients who underwent bronchoscopy. Half of which revealed unremarkable results, while the rest showed findings of nonspecific endobronchitis, tracheomalacia, and distal segment thickening of aryepiglottic folds probably

secondary to chronic laryngopharyngeal reflux.

Only two cases (8.70%) had bronchoalveolar lavage. One of which showed nonspecific findings such as inflammatory infiltrates composed of few mononuclear cells, neutrophils, eosinophils, with no atypical or malignant cells noted. There were also 2 patients (8.70%) who had immunodeficiency panel done to determine the presence of a primary or acquired immunodeficiency. Both cases showed normal immunologic profiles.

Out of the cases examined, only 43.48% (n = 10) underwent a lung biopsy, primarily because obtaining parental consent for the procedure was challenging due to its invasive nature. Majority of the histopathologic findings were unclassified—nondiagnostic and with insufficient information. Of those which features are consistent with the classification of chILD, lymphoid interstitial pneumonia was the most common at 20% (n = 2). Other histopathologic features seen in patients who underwent lung biopsy which are consistent with chILD.

All patients received treatment, with steroids being the most common drug given, singly or in combination with hydroxychloroquine and macrolides, as shown in Table 3.

Table 3. Therapeutics used in patients diagnosed with chILD admitted from January 2013 to December 2022

	Parameters	Frequency (n)	Percent (%)
Therapeutics Received	Corticosteroids only	7	30.43
	Hydroxychloroquine only	-	-
	Anti-immunomodulatory Drugs only	-	-
	Macrolides only	3	13.04
	Corticosteroids + HCQ	3	13.04
	Corticosteroids + Macrolides	4	17.39
	Corticosteroids + HCQ + Macrolides	6	26.09

Outcomes of the patients were identified from outpatient records within 3 months from hospital discharge (Table 4). Improvement was seen in 39.13% of cases, whereas death occurred in 21.74%, due to either infection or respiratory failure. In addition, outcome could not be determined in up to 34.78% of cases due to poor follow up.

Table 4. Clinical outcomes of patients diagnosed with chILD admitted from January 2013 to December 2022

	Parameters	Frequency (n)	Percent (%)
Outcomes of patients	Died	5	21.74
	Improved activity by 3 months	9	39.13
	No improvement by 3 months	1	4.35
	Lost to follow up	8	34.78

Discussion and Conclusion

Childhood interstitial lung disease can occur at any age group ranging from infancy to adolescence. It encompasses a wider range of disorders than in adults but is more commonly seen in infancy and young children. Our study showed a similar trend, with 34.78% of patients diagnosed before 2 years old.

Clement et al. linked this to lung growth during alveolar development stages [7]. Fan et al. (2010) supported this, reporting 187 infants under 2 years with diffuse lung disease, half of whom had age-specific disorders.

Although our study showed no significant difference between the genders, it is still notable that there was a slight male predominance in terms of gender distribution, similar to other reports (57-58.1%) [9, 10].

Alsharkawy et al. (2021) linked weight loss in chILD patients to systemic inflammation, increased metabolic rate, which promotes a negative nutritional balance, and anorexia, which reduce caloric intake. Deterding et al. reported poor nutritional status in many chILD patients requiring supplementation. In our study, while most had normal weight-for-length/height, 34.78% showed severe wasting, emphasizing the importance of maintaining proper nutrition and aggressive supplementation.

Our study showed that patients with chILD present with various signs and symptoms including, cough, difficulty of breathing, tachypnea, chest retractions, crackles with wheezing on auscultation, and hypoxemia, which were comparable to previous studies [2, 3, 10]. As reported by the American Thoracic Society, tachypnea is the most common sign of chILD, which was noted in 75–93% of patients. Hypoxemia, crackles, and cough were also reported to be common.

Diffuse abnormalities on chest radiographs (CXR) or CT scans are part of chILD diagnostic criteria. CXRs are favored for their low radiation dose, cost, ease, and availability, but their low-contrast resolution often results in nonspecific findings [13]. Guillerman noted hyperinflation as a common CXR abnormality, though in our study, only 34.78% of patients had hyperaerated lungs, with all cases showing nonspecific pulmonary infiltrates. These infiltrates, visible as increased density or "whitening," are common in interstitial lung disease due to pulmonary inflammation and may indicate conditions ranging from infections to malignancies [17]. Patients with interstitial lung disease often show pulmonary inflammation, making lung infiltrates a common finding in chest radiographs, as observed in our study.

High-resolution computed tomography (HRCT) is the preferred imaging for chILD due to its high sensitivity and precision in assessing disease extent. While HRCT findings can be nonspecific, widespread ground-glass opacities (GGO), indicating active disease, were the most common feature in our study (82.61%). A 2019 institutional study linked HRCT findings to survival, with hyperinflation showing the longest mean survival time and mosaic attenuation the shortest (10.3 months) [18]. GGO was prevalent in cases of nonspecific interstitial pneumonia (73.3%), desquamative interstitial pneumonia, and bronchiolitis obliterans

organizing pneumonia, often accompanied by bronchiectasis or hyperinflation.

Hypersensitivity pneumonia (HP) andlymphocytic interstitial pneumonia (LIP) showed GGO on HRCT, while pulmonary interstitial glycogenosis (PIG) presented with consolidation. In our study, GGO with bronchiectasis was observed in DIP, HP, and post-tuberculosis cases, while LIP and idiopathic pulmonary hemosiderosis (IPH) showed GGO with fibrosis and consolidation.

While tissue biopsy is the gold standard for chILD diagnosis, it is challenging in advanced stages due to risks and may yield inconclusive results, especially in areas with honeycombing. Blanco et al. recommended targeting regions with GGO for better results [19], aligning with our findings of predominant GGO. Diagnostic approaches now favor noninvasive tests and therapeutic trials over routine biopsies. Qureshi et al. suggested steroid therapy for suspected conditions like interstitial pneumonias and fibrosing alveolitis, even without definitive biopsy confirmation [20]. Sankar et al. advised reserving biopsies for cases unresolvable through noninvasive methods or unresponsive to treatment [5].

Bronchioalveolar lavage (BAL) is valuable for cytologic, microbiologic, and molecular analysis [13], while fiberoptic bronchoscopy (FOB) allows airway inspection and biopsies but rarely provides diagnostic insights for chILD [15]. Respiratory involvement, including chILD, poses significant morbidity and mortality risks in primary immunodeficiency [16], though immunologic profiles were normal in two recurrent pneumonia cases from our study. Pulmonary hypertension, linked to chronic hypoxia or connective tissue disorders, was identified in 30.43% of cases (mild) and 4.35% (moderate). Gupta et al. reported cardiovascular involvement in 68% of chILD patients, with pulmonary hypertension being the most common at 50%.

Supportive care for children with chronic lung disease includes oxygen therapy for hypoxemia, proper nutrition, aggressive infection management, and bronchodilators. Most children with ILD also receive immunosuppressive, anti-inflammatory, or antifibrotic drugs for extended periods [7]. Corticosteroids remain the most commonly used drugs, as they may help suppress inflammation in idiopathic ILD. In our institution corticosteroids were the primary treatment, often combined with other therapies.

For steroid-resistant cases, alternative agents like hydroxychloroquine, preferred over chloroquine due to fewer side effects, are used [7]. If symptoms persist, other immunosuppressive drugs such as azathioprine, cyclophosphamide, cyclosporine, or methotrexate may be considered [7], though these were not used in our study. Macrolides like azithromycin and clarithromycin, with immunomodulatory properties [3], were also part of treatment options.

with GGO accompanied by fibrosis and consolidation.

Obtaining a tissue biopsy is considered as gold standard for diagnosis of chILD, however, the process in performing this in children is difficult especially when they present in advanced clinical stages and are considered high risk for general anesthesia. Additionally, biopsy may not always render conclusive results. According to the study of Blanco et al., several factors were associated with obtaining inconclusive histology. Biopsies performed in advanced stages of the disease were less informative. Furthermore, specimens obtained from regions exhibiting substantial honeycombing on HRCT produced unsatisfactory results, possibly attributed to the presence of reduced tissue and an abundance of enlarged air spaces with thick fibrotic walls. Consequently, regions displaying ground glass opacities were preferred as the biopsy site [19]. This could be a sensible approach, given that the majority of HRCT findings in our study indicated the presence of GGO. The trend nowadays is moving towards a systematic approach to the diagnosis, which includes noninvasive tests and response to therapy, rather than subjecting every patient to biopsy. The study of Qureshi et. al looked into the usefulness of lung biopsy in the management of ILD. According to this study, conditions like interstitial pneumonia, diffuse interstitial pneumonia, interstitial pulmonary fibrosis, fibrosing alveolitis, bronchiolitis obliterans, organizing pneumonia, sarcoidosis, hypersensitivity pneumonitis, or eosinophilic pneumonia may necessitate steroid treatment when patients exhibit symptoms. In cases where one of these conditions is suspected clinically without a definitive tissue diagnosis, it may be prudent to consider a therapeutic trial. This recommendation is grounded in the observation that even after lung biopsy procedures were conducted, the administration of steroids remained the most prevalent form of therapy in their series [20]. According to Sankar et. al, lung biopsy could be reserved for those children in whom the diagnosis is inconclusive after exhausting noninvasive diagnostic modalities and having poor response to treatment [5].

Bronchioalveolar lavage (BAL) is useful if providing specimens for cytologic, microbiologic, and molecular examinations [13].

Fiberoptic bronchoscopy (FOB) allows physicians to inspect and perform biopsy of the airways, BAL and transbronchial biopsy. However, it rarely gives diagnostic information on chILD [15]. Respiratory involvement, especially chILD, causes a significant risk of morbidity and mortality among patients with primary immunodeficiency [16]. Two patients included in our study who presented with recurrent pneumonia underwent immunologic studies. Both cases showed normal immunologic profiles.

This retrospective study concludes that chILD occurs most commonly in infants less than 2 years old. Although there is no statistically significant gender difference in its prevalence, this study still noted a slight male predominance. Majority of cases had normal nutritional status; however a number of cases were severely wasted. This emphasizes the importance of nutritional supplement as an integral part of the management of chILD. Signs and symptoms of chILD are nonspecific as any other chronic lung disease, hence, there must be a high index of suspicion when considering such diagnosis. As with previous studies, findings on chest xray and HRCT can give clues to the diagnosis, such as ground glass infiltrates. Additional ancillary tests like echocardiography, BAL, bronchoscopy, and immunodeficiency panel may be used to assess complications and risk factors. Several studies have shown improvement of symptoms with use of corticosteroids. Our study noted similar findings.

Limitations of the Study and Recommendations

This study examined a limited cohort of 23 cases over a 10-year period. For future research, we suggest expanding the review period to encompass a larger study population. In this investigation, we explored the correlation between patients' gender, signs and symptoms, chest radiograph and HRCT findings, as well as the medications they received, with their outcomes three months post-discharge. We propose that future research should also consider examining the association between 2D echocardiography findings and biopsy results with patient outcomes. It is important to note that this study exclusively focused on patients with chILD who were admitted to our institution and subsequently discharged, with follow-up in the outpatient department. Patients referred to and seen in the outpatient department without admission were not included. To enhance the comprehensiveness of demographic data within our institution, we recommend incorporating these patients into future studies.

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ARTICLE

Covid-19 hesitancy among adolescents: a systematic review

Mary Roseanne Munoz, Alicia Tamesis

OBJECTIVE: Vaccine hesitancy has been a public health issue for some time now, but gained more attention during COVID-19 pandemic. This systematic review aimed to estimate the prevalence of COVID-19 vaccination hesitancy and identify factors affecting it among adolescents.

MATERIALS AND METHODS: The preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2020) was used. A search was performed in PubMed/ MEDLINE, EMBASE, Google Scholar, Herdin, and Cochrane databases on September 2023 using the key words: (COVID-19 OR SARS-COV OR corona virus) AND (Vaccination OR immunization) AND (adolescence OR teenagers OR youth) AND (hesitancy OR acceptance). Observational studies which determined the prevalence or risk factors for COVID-19 vaccine hesitancy among adolescents aged 10-19 years old were included.

RESULTS: There were 5 good quality cross-sectional studies included. The prevalence of adolescents who did not want to be vaccinated ranged between 8.4% and 61.0%; while the prevalence of being unsure if they want to be vaccinated was between 31.6% and 88.0%. Factors associated with vaccine hesitancy included being economically disadvantaged, not having influenza vaccination, worrying about its effectiveness and safety, and low perceived necessity.

CONCLUSION: There is good quality evidence that COVID-19 vaccine hesitancy exists among adolescents. It is recommended that health workers should conduct information and education campaigns to iterate the effectiveness, safety, and misconceptions about of COVID-19 vaccination. Vaccination programs should also reach out to economically disadvantaged adolescents, and tapping parents and social media may be an effective strategy to improve vaccination acceptance among adolescents.

KEYWORDS: *COVID-19, SARS-COV, Corona virus, Vaccination, Immunization, Adolescence, Teenagers, Youth, Hesitance, Acceptance.*

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a devastating global disease impact, with over 760 million confirmed cases and 6.9 million fatalities by the end of July 2023.[1,2] In the Philippines, around 4.1 million confirmed cases and 66,000 deaths were reported.[3] Around 72% of people worldwide received at least one dose of the COVID-19 vaccine, but only 67% are fully immunized.[4] Vaccine hesitancy, a reluctance to receive vaccination, is a serious public health concern that inhibits herd immunity.[5-7] Age was identified as one of the reliable predictors of vaccine hesitancy.[8-11] Given that between 9 and 10% of Filipinos are between the ages of 10 and 19,[12] it is crucial to vaccinate this age group in order to increase population immunity. This study's findings could guide decisions on COVID-19 vaccinations, particularly in adolescents, and serve as a foundation for future research and emergency preparedness. Also, this study may serve as a basis of knowledge for future research and emergency preparedness.

Vaccination is the most important mitigation plan, cost-efficient and effective in preventing spread of COVID-19. As vaccines become more available, widespread immunization of adolescents is needed to reduce the illness burden and the likelihood of novel variant creation.[13,14] Vaccine hesitancy is a significant obstacle to vaccine uptake, influenced by factors such as complacency, convenience, and confidence.[5,15] Adolescents are more likely to be overconfident and relaxed, leading them to underestimate the dangers of the disease.[16-18] They may also experience psychological distress due to the outbreak, which could lead to less confidence in the safety and effectiveness of the vaccine.[19,20] Statistics show that only 52% of unvaccinated adolescents aged 13 to 17 years would definitely or probably receive a COVID-19 vaccine.[21] Reasons for hesitation include concerns about effectiveness, safety, side effects, lack of trust in medical professionals, conspiracies, and the perception that natural immunity is a better option. To develop specialized approaches for promoting immunization among adolescents and lowering vaccine hesitancy, these factors should be considered.[13]

The general objective of this study is to determine the prevalence of COVID-19 vaccine hesitancy and identify factors affecting it among adolescents by synthesizing available published evidence. Specific objectives are to determine the prevalence of COVID-19 vaccine hesitancy among adolescents globally and in Asian countries and to determine if demographic factors, clinical factors, parental factors, or socio-cultural influence COVID-19 vaccine hesitancy among adolescents.

METHODOLOGY

The preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2020) declaration was used to create this study.

A. Eligibility criteria:

Observational studies (Cohort, cross-sectional, case-control, previous systematic reviews) which determined the prevalence or risk factors for COVID-19 vaccine hesitancy among adolescents aged 10 -19 years old. case series, case reports, posters, and conference abstracts will be excluded. Only studies written in the English language were used. Studies with no clearly reported outcomes were excluded as well.

The study population included adolescents (10-19 years old). To be excluded were patients with a history of allergy or adverse reaction to any type of COVID-19 vaccination. Outcome of interest is vaccine hesitancy defined as delay in acceptance, or refusal, of vaccines despite the availability of vaccine services

B. Information sources and search strategy

A search was performed in PubMed/ MEDLINE, EMBASE, Google Scholar, Herdin, and Cochrane databases in September 2023. Hand-searching of printed journals was not conducted.

The search terms used included: (COVID -19 OR SARS-COV OR corona virus) AND (Vaccination OR immunization) AND (adolescence OR teenagers OR youth) AND (hesitancy OR acceptance). Duplicate articles were removed and additional relevant articles were identified by scanning the reference lists of articles found from the original search.

C. Definition of procedures

Full-text articles for potential inclusion were saved in a Google drive. Extracted data were managed using Microsoft Word. Investigator independently scanned the titles and abstracts found using the search approach described above. Papers by the same author were compared to reduce data duplication caused by duplicate reporting. The full-text articles were obtained for reports that were considered to be eligible based on the title or abstract. Full-text copies of potentially relevant papers selected were retrieved and reviewed. Articles that met the inclusion requirements were evaluated. Following the PRISMA 2020 criteria, a flow diagram for the search and selection process was created (Figure 1).

Study name (along with first author's name and year of publication), country where the study was conducted, source from which patients or study participants were selected, study design, outcomes, study strengths, and limitations were all extracted using a standardized extraction form. To ensure the correctness and consistency of the extracted data, the data extraction forms were cross-checked.

D. Data Synthesis/Analysis

Information from the studies were consolidated through a narrative review by detailing individual study characteristics and conclusions, as well as analyzing possible hypotheses to explain the factors affecting vaccine hesitancy among adolescents.

RESULT

A total of 506 articles were identified during the database search. Non- duplicate titles and abstracts were screened, and 7 articles were identified for potential inclusion. After full-text selection, 2 were further excluded because they were conducted among parents of adolescents. A total of 5 studies were finally included in this meta-analysis.

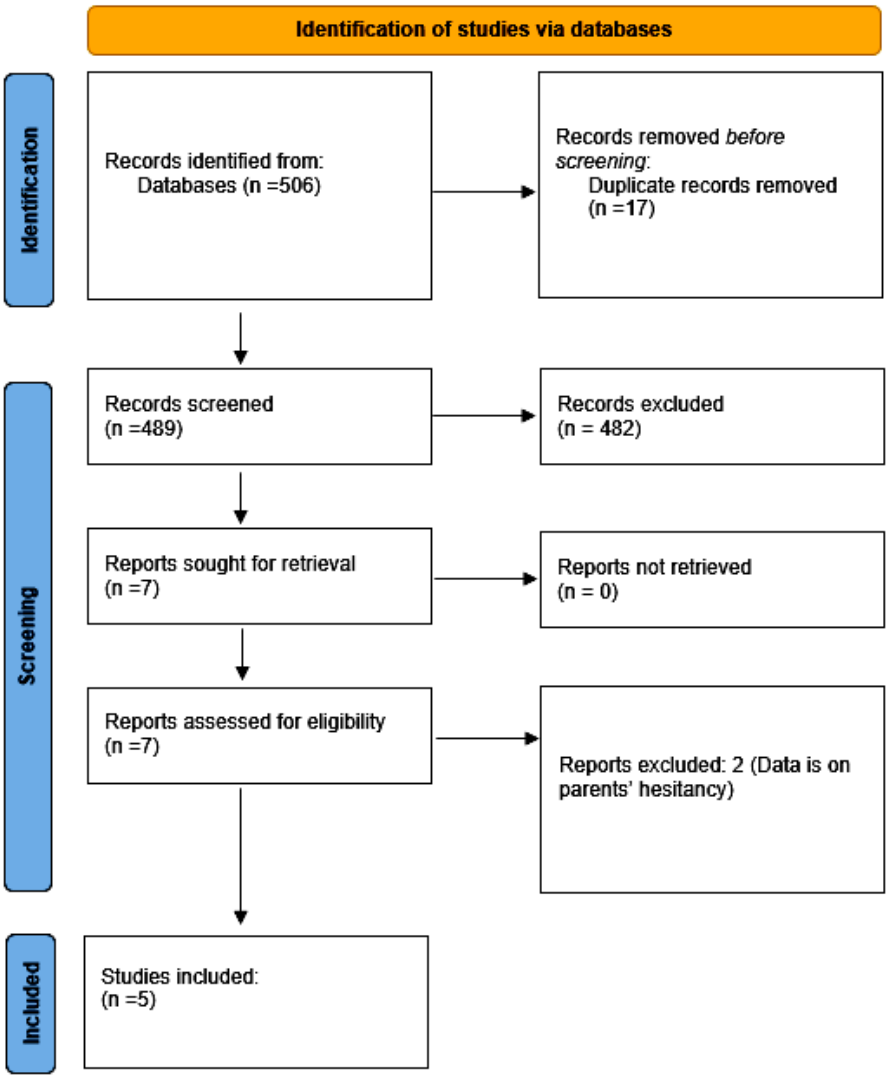

Figure 1. PRISMA Flow Diagram of the Research Study

Table 1. Characteristics of studies included in the study

Author, year	Country	Study Design	Sample size	Sex ratio and age range	Prevalence of vaccine hesitancy	Factors associated with hesitancy
Fazel, 2021[22]	United Kingdom	Cross-sectional	27,910	M:F=43:52, 10 to 18 years	37% were undecided while 13% did not want to get vaccinated	Factors related to hesitancy: Economically disadvantaged Smokers Spends more time on social media
Rehati, 2022[23]	China	Cross-sectional	9153	M:F=50:50, 12 to 17.5 years	765 (8.4%) were not willing to get vaccinated while 2891 (31.6%) were not sure about the vaccination	Factors related to hesitancy: Female sex Concerns on price No prior influenza vaccine Factors that promote willingness: Fear of transmission Perceived effectiveness Perceived convenience
Wang, 2022[24]	Africa	Cross-sectional	2662	M:F=47:53, 10 to 19 years	Vaccine hesitancy was 14% in rural Kersa, 23% in rural Ibadan, 31% in rural Nouna, 32% in urban Ouagadougou, 37% in urban Addis Ababa, 48% in rural Kintampo, 65% in urban Lagos, 76% in urban Dar es Salaam, and 88% in rural	Factors related to hesitancy: Perceived low necessity Concerns on safety Concerns on effectiveness Factors that promote willingness: Health workers, parents, teachers' recommendation

Wong, 2022[25]	Hong Kong	Cross-sectional	2609	M:F=55:45, 12 to 18 years	61.4% do not plan to receive vaccination	Factors related to hesitancy: Concerns on safety Concerns on effectiveness Factors that promote willingness: Having at least one parent vaccinated Knowing somebody diagnosed with COVID-19 Receiving the influenza vaccine Fear of transmission
Zhang, 2022[26]	China	Cross-sectional	1009	M:F=40:60, 17 to 19 years	Vaccine hesitancy is as much as 16.5%	Factors related to hesitancy: History of physical disease Maladaptive health behavior Concerns on safety Perceived low risk for transmission Factors that promote willingness: Perceived effectiveness Perceived safety

As seen in Table 1, three studies were from Asia and one each from UK and Africa. All studies were cross-sectional surveys with large sample size. The age range was 10-19 years old. Table 2 shows that all studies were of good quality with minimal risk for bias.

Table 2. Study Quality

Author, Year	Selection	Sample size	Validity of survey tool	Outcome	Overall
Fazel, 2021[22]	Truly repre-sentative	Large (≥400)	Validated tool	Self report, multi-variate analysis	4/5 (Good)
Rehati, 2022[23]	Truly repre-sentative	Large (≥400)	Large (≥400)	Self report, multi-variate analysis	4/5 (Good)
Wang, 2022[24]	Truly repre-sentative	Large (≥400)	Large (≥400)	Self report, multi-variate analysis	4/5 (Good)
Wong, 2022[25]	Truly repre-sentative	Large (≥400)	Large (≥400)	Self report, multi-variate analysis	4/5 (Good)
Zhang, 2022[26]	Truly repre-sentative	Large (≥400)	Large (≥400)	Self report, multi-variate analysis	4/5 (Good)

Prevalence of hesitancy

There were 5 cross-sectional surveys, 4 published in 2022 and 1 published in 2021, included in this systematic review. A school-based survey was done across the 4 counties of England from 14 May to 21 July 2021 to determine the willingness to receive the COVID-19 immunization in the study of Fazel et al. (2021).[22] The survey was self-reported by 27,910 students (ranging in age from 9 to 18) from 180 different schools. According to the results, 13984 (50.1%) students would choose to receive a vaccination, 10322 (37.0%) were unsure, and 3604 (12.9%) would choose not to. [22]

In the study by Rehati et al. (2022),[23] 9153 students (mean age 14.2 years) in four Chinese cities responded to a survey from 8 to 30 December 2020 to provide information regarding their concerns about receiving the COVID-19 vaccination. The findings revealed that 765 (8.4%) people were opposed to vaccination while 2891 (31.6%) were hesitant.[23]

Wang et al. (2022)[24] conducted a survey using computer-assisted telephone interviewing among adolescents in five sub-Saharan African nations (Burkina Faso, Ethiopia, Ghana, Nigeria, and Tanzania), wherein a rural area and an urban area were included in each country (except Ghana, which only had a rural area) with roughly 300 adolescents (age 10-19 years) in each area and 2662 in total, between July and December 2021. The percentage of vaccine hesitancy against COVID-19 was in rural Kersa, it was 14%; in rural Ibadan, 23%; in rural Nouna, 31%; in urban Ouagadougou, 32%; in urban Addis Abeba, 37%; in rural Kintampo, 48%; in urban Lagos, 65%; in urban Dar es Salaam, 76%; and in rural Dodoma, 88%. [24]

The attitudes of adolescents in Hong Kong concerning the COVID-19 immunization are examined in survey study conducted by Wong et al. (2022).[25] Online surveys on vaccination intentions and reasons were completed by 2609 adolescents (aged 12–18 years) from all throughout Hong Kong before 31 June 2021. A total of 61% (n=1602) of adolescents did not plan to get the COVID-19 immunization.[25]

Likewise, Zhang et al. (2022)[26] conducted an online survey between 14 March 14 and 15 April 2021 among older adolescents (16–17 years old) and young adults (18–21 years old), for a total of 2,414 respondents. The findings revealed that older adolescents had greater prevalence rates of COVID-19 vaccine hesitancy than young adults (16.5 vs. 7.9%, p<0.001). [26]

Factors associated with vaccine hesitancy

In the study of Fazel et al. (2021), students who were 'opt-out' or 'undecided' were more likely to originate from disadvantaged socioeconomic situations with higher percentages of house renting than home ownership (opt-out: OR=1.84, 95% CI 1.61-2.11, p<0.001; undecided: OR=1.53, 95%CI 1.39-1.69, p<0.001), and their school locations were more likely to be in areas of greater deprivation (opt-out: OR=2.06, 95% CI 1.77-2.4, p=<0.001; undecided: OR=1.60, 95%CI 1.44-1.77, p<0.001). They also reported lower levels of anxiety and depression (opt=out: OR=0.81, 95% CI 0.74-0.88, p<0.001; undecided: OR=0.85, 95% CI 0.8-0.9, p<0.001), were more likely to smoke or vape (opt-out: OR=1.71, 95% CI 1.34-2.17, p<0.001; undecided: OR=1.56, 95%CI 1.3-1.87, p<0.001), spend more time on social media (opt=out: OR=1.51, 95% CI 1.33-1.72, p<0.001; undecided: OR=1.49, 95% CI 1.36-1.63, p<0.001), and feel like outsiders in their educational environment (opt-out: OR=1.16, 95%CI 1.11-1.2, p<0.001; undecided: OR=1.10, 95% 1.07-1.14, p<0.001).[22]

In the study by Rehati et al. (2022), the following were associated to vaccine resistance and vaccine hesitancy: not having received an influenza vaccination before (OR=1.33, 95% CI 1.14-1.55; OR=1.57, 95% CI 1.25-1.98), no perceived susceptibility (OR=1.72, 95% CI 1.50-1.97; OR=3.57, 95% CI 2.86-4.46), and perceived no cues to action (OR=3.24, 95% CI 2.56–4.11; OR=27.68, 95% CI 21.81–35.13). Girls (OR= 1.21, 95% CI 1.09-1.36) had higher risk, while students who boarded at school (OR=0.79, 95% CI 0.68-0.92), had easy access to vaccines (OR=0.84, 95% CI 0.73-0.96), and had doctors' recommendations (OR=0.86, 95% CI 0.76-0.98) had lower risk of vaccine hesitancy. The study's findings concluded that a lack of health literacy and a lack of risk awareness were associate with students' hesitation to be immunized in China.[23]

Wang et al. (2022) reported that the three main causes of hesitation were perceived low necessity (46.70%),

safety worries (45.00%), and vaccine effectiveness worries (11.20%). The three groups with the highest effects on vaccine acceptance were healthcare professionals, parents or other family members, and instructors. Greater vaccine reluctance was associated with perceived lack of safety (aPR: 3.52; 95% CI: 3.00, 4.13) and lack of effectiveness (aPR: 3.46; 95% CI: 2.97, 4.03).[24]

In the study by Wong et al. (2022), having at least one immunized parent (OR=5.02. 95%CI 4.2–5.99) knowing someone who had the disease (OR=2.098, 95% CI 1.20–3.66), and getting the flu shot (OR=1.64, 95% CI 1.36–1.99) were all significant ($p<0.001$) factors in their decision to receive vaccination. The safety (79%) and effectiveness (52%) of the vaccine or the risk of infection were the main worries of adolescents.[25]

Likewise, Zhang et al. (2022) revealed that a history of physical disorders (OR=2.58, 95%CI 1.30-5.15, p=0.007) and atypical sickness behavior (OR=1.17, 95% CI 1.07-1.28, p=0.001) were risk factors for hesitancy in older adolescents. The most common justifications for vaccine hesitancy were worries about the side effects of the COVID-19 vaccine (67.1%) and the notion that one is immune to infection risk (41.9%). The best arguments for vaccination promotion included evidence that the vaccine reduces the risk of contracting COVID-19 (67.5%), assurances of vaccine safety (56.7%), and the low likelihood of adverse reactions (52.7%).

Discussion

The COVID-19 vaccination is an essential strategy to continuously reduce the spread of the disease and the cost it places on society. It also serves to lessen the possibility of the formation of new variants that may cause another health scare to people. However, vaccine hesitancy has gained more global attention because of COVID-19 vaccination and has put the COVID-19 vaccination efforts under pressure. The WHO has identified vaccine hesitancy as one of the top 10 concerns for 2019.[6,27] During adolescence, boys and girls start to make important decisions regarding their health wherein they also form attitudes and behaviors that they will carry into adulthood. To design specialized interventions to encourage immunization against COVID-19, it is important to thoroughly understand and take into account their issues and concerns with regard to vaccination against COVID-19.

Only one study[23] showed that the female sex was more associated with higher vaccine hesitancy, which was consistent with earlier studies.[28-30] This may be partially attributed to the false information spreading on social media regarding the COVID-19 vaccine impairing fertility, but more research is required to validate this. This may also be related females having a lower willingness to

to take risks than boys do (viewing getting the COVID-19 vaccine as a risky behavior).[31]

One study[22] indicated that adolescents who were hesitant to receive COVID-19 vaccination were more likely to engage in unhealthy behaviors, such as more smoking and vaping, and spend more time on social media, and they were also less socially connected and less inclined to identify with their school. Also, those who had disadvantaged socioeconomic status were associated with higher hesitancy. With 1.2 billion adolescents aged 10 to 19 in the world today, adolescents represent a significant demographic group.[32] The majority of adolescents live in environments with less access to resources. Given the distribution and acceptance of vaccination in contexts with limited resources, addressing teenage COVID -19 immunization must take into account resource implications as well as questions of equity, justice, and prioritization of certain demographic groups.[33] Furthermore, given how much time adolescents spend on social media, this platform appears essential for attempting to raise vaccine awareness and understanding.[22]

Adolescents having a parent who had received an influenza vaccination were more receptive to receiving the COVID-19 vaccine, as seen in 2 studies.[23,25] Knowing the advantages of getting vaccinated against influenza will help one understand how COVID-19 and other respiratory viral illnesses can be prevented.[34] Prior influenza vaccination experience is related to increased COVID-19 vaccine uptake.[10] The promotion of the influenza vaccine may improve the likelihood that adolescents will take the COVID-19 vaccination,[35] implying that influenza vaccine initiatives may also increase adolescent's willingness to receive the COVID-19 vaccination.

Another favorable predictor of future immunization is the self-perception of a high risk of contracting a serious COVID-19 infection.[36] Adolescents who do not perceive necessity to get the vaccine because of its nonsignificant connection to their health were more likely to exhibit vaccine resistance or hesitancy.[23,24,26] The main causes of vaccine hesitancy were a lack of information and awareness of vaccination as well as a lack of understanding of its relevance, according to a WHO/UNICEF joint report utilizing 2015-2017 data.[37] Additionally, compared to those who are eager to obtain a vaccine, vaccine-resistant individuals have been exposed to much less information about COVID-19 from the public media.[38] According to Health Belief Model, signals that can affect behavior and aid in the prevention of COVID-19 through a rise in vaccination uptake include early content education, addressing previous symptoms or concerns, and obtaining accurate information from the media.[23]

On the other hand, one study[26] showed that history of physical illnesses and atypical sickness behavior were associated with higher

vaccination hesitancy. When patients with a history of physical illnesses consider getting the COVID-19 vaccine, one of their main worries is whether the vaccine may make their pre-existing illnesses worse or cause them to repeat. On the other hand, people who exhibit abnormal disease behaviors show improper reactions in their capacity to assess and respond to their symptoms. When seeking professional assistance, these people frequently display excessive physical worry and hypochondriacal beliefs, which could hinder the development of a trusting connection.[38-40]

Greater vaccination hesitation is highly predicted with perceived inefficacy and lack of safety. These results are consistent with earlier research among adults in high- and low- and middle-income contexts.[41-43] Therefore, to increase the number of adolescents who receive the COVID-19 vaccine, public health campaigns should emphasize that the shots are both safe for adolescents and offer protection from COVID -19 infections.[44]

No single strategy can fully address the problem of vaccine hesitancy due to the diversity of causes causing COVID-19 vaccination resistance.[45-47] The significance of having reliable sources deliver this information in a widely accepted and approachable style is emphasized. It is worthwhile to increase knowledge of the value, safety, and effectiveness of COVID-19 vaccinations among adolescents. Additionally, schools should think about include the function, evolution, and impacts of vaccinations as a subject to be covered in both primary and secondary school curricula.[15] Health professionals were identified as the most reliable providers of information regarding the COVID-19 vaccine,[16,17] which is consistent with previous global surveys of the general public.[50] Wang et al. (2022) also identified parents, instructors as important people who can influence vaccine acceptance or hesitancy among adolescents.[24] Therefore, efforts are required to promote vaccine acceptance among healthcare personnel and adult community members. Increased social support from family, friends, professionals in the medical field, and public health authorities would also help to reduce vaccine reluctance and encourage vaccine acceptance[46,47]. Healthcare workers, parents, schoolteachers, and peers should be used as advocates for COVID-19 vaccines.

There is good quality evidence that COVID-19 vaccine hesitancy exists among adolescents. Health workers should conduct information and education campaigns to iterate the effectiveness and safety of vaccination against COVID-19 and correct misconceptions that it is not necessary. Vaccination programs should also reach out to economically disadvantaged adolescents to ensure their participation. Tapping parents and social media may also be a strategy to improve vaccination acceptance among adolescents.

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ARTICLE

Effectiveness of Premature Infant Oral Motor Intervention (PIOMI) as pre-feeding oral motor stimulation among preterm infants at the neonatal intensive care unit: a meta-analysis

Elaine Joy O. Viernes-Bergado, Margaret Q. Saquing, Belen E. Velasco

OBJECTIVE: The increasing survival rate of preterm infants has led to long-term complications associated with prematurity, such as oral feeding difficulties. The review aims to determine the effectiveness of early and easily administered premature infant oral motor intervention (PIOMI) among preterm infants 32 weeks and less admitted to the Neonatal Intensive Care Unit, through a meta-analysis.

MATERIALS AND METHODS: Eligible studies were retrieved from six databases (PubMed, MEDLINE, Cochrane Library, Google Scholar, Physiotherapy Evidence Database, and International Clinical Registry Platform) and PIOMI website. These were screened based on established selection criteria. The statistical analysis was conducted using the STATA

RESULTS: A total of eight randomized-clinical trials, with 290 participants between 26 to 32 weeks gestational age, were included in the meta-analysis. The study suggested that PIOMI may reduce the transition from gavage to independent oral feeding by 2 days (SMD = –1.97, z = 4.33, p = 0.001, 95% CI = –2.86 to –1.08), increase weight gain by 810 g (SMD=0.81, z=3.45, p=0.001, 95% CI = 0.35 to 1.27), and shorten hospital stay, compared to the control group.

CONCLUSION: Preterm infant oral motor intervention (PIOMI) can be considered in NICUs to improve clinical outcomes of preterm infants 32 weeks gestational age or less.

KEYWORDS: *premature infant oral motor intervention, prematurity, infant, oral motor stimulation*

INTRODUCTION

Prematurity is one of the global healthcare burdens to date. The estimated preterm birth is 15 million infants annually, with rates ranging from 5% to 18% across countries. (1) The Philippines ranked 8th with the most significant number of preterm births, with a rate of 13.3 per 100 live births. (2) The increasing survival rate of preterm infants has led to long-term complications associated with prematurity, compelling the need for supportive healthcare services. One of the crucial concerns is establishing safe and independent oral feeding, as it is one of the three physiologic competencies of preterm newborns for hospital discharge. (3) Oral feeding is a complex skill that involves an interplay between the central nervous, respiratory, and neuromuscular systems. A delay or disruption in any of these leads to oral feeding difficulties (4). The suck-swallow-breath coordination is developed at 32 to 34 weeks, predisposing preterm infants to oral feeding difficulties. Studies on earlier initiation of oral feeding among extremely and very preterm infants found it beneficial in achieving earlier postmenstrual age at full independent oral feeding and discharge.(5,6) A retrospective study by Jadcherla et al. showed that preterm infants on tube feedings had significantly lower cognitive, communication, and motor composite scores than those discharged on partial or full oral feeding at 18-24 months. (7) Preterm infants, therefore, have short and long-term benefits when oral feeding difficulties are addressed earlier. Studies on oral motor stimulation vary on the age of initiation of intervention, ranging from 29 to 36 weeks post menstrual age (PMA), and the time at which it was initiated. Despite these variations, oral motor therapy significantly shortened hospital days, duration of parenteral nutrition and transition from gavage to oral feeding, and increased feeding efficiency and milk intake. (8-10)

One of the oral motor interventions being studied is the Premature Infant Oral Motor Intervention (PIOMI). It is a standardized 5-minute oral motor therapy explicitly developed for preterm infants. It is adapted from the 15-minute Beckman Oral Motor Intervention (BOMI) designed for infants and children with developmental delays and feeding difficulties. Studies on PIOMI administered between 29 to 36 weeks postmenstrual age (PMA) significantly reduced the transition time to full oral feeding and hospital stay, increased breastfeeding rates at 1 and 3 months after discharge at the NICU, and improved Neonatal Oro Motor Assessment Scale (NOMAS). (11-14) While many studies support the benefits of administering oral motor stimulation, its implementation in the Philippines remains challenging due to the need for more trained therapists. A study by Majoli et al. comparing parent and professional-administered PIOMI did not establish a significant difference in the transition time to full oral feeding, weight gain, or the length of hospital stay. (11) This suggests that PIOMI, as an oral motor

intervention, can be administered even by non-professionals following appropriate training.

Studies on oral motor interventions have shown benefits, such as decreasing the transition time to full oral feeding and hospital stay among preterm infants. However, they are not commonly practiced in the NICU due to a lack of well-designed research and trained therapists. This study aims to determine the effectiveness of early and easily administered oral motor stimulation in oral feeding among extremely and very preterm infants. Findings in this study may help the NICU implement an oral feeding protocol among preterm infants at risk for oral feeding difficulties.

The World Health Organization defines preterm as babies born alive before 37 weeks of pregnancy. It is categorized based on the gestational age at birth, extremely preterm (less than 28 weeks), very preterm (between 28 to 32 weeks), and moderate to late preterm (32 to 37 weeks). It can also be categorized based on birthweight, low birth weight (< 2500g), very low birth weight (< 1500g), and extremely low birth weight (<1000g). An estimated 15 million infants, equivalent to 1 in 10, are born preterm annually. The rates range between 5% and 18% across 184 countries. (1) The Philippines ranked 8th with the most significant number of preterm births with a rate of 13.3 per 100 live births [1, 2].

Prematurity is a significant healthcare burden and is among the leading cause of infant mortality and long-term morbidity. UNICEF reported that prematurity is the leading cause and accounts for 32.7% of neonatal mortality in the Philippines. (12) Fortunately, the improvements in perinatal care and advancing technology have increased the survival of preterm infants. However, these also led to an increasing population of infants with morbidities associated with prematurity, particularly growth and development. In this regard, studies on preventing morbidities should also be a central health priority.

Oral feeding is one of the common concerns in the latter days of hospitalization. It is a complex skill that involves an interplay between the central nervous, respiratory, and neuromuscular systems. A delay or disruption in any of these functions leads to prolonged oral feeding maturation (4). The development of oral feeding skills begins in utero, evidenced by swallowing amniotic fluid at 11 to 12 weeks, oral gag-reflex at 12 to 16 weeks, sucking and swallowing reflex by 28 weeks.(17,18) Prematurity and medical conditions such as respiratory diseases, brain injury, and necrotizing enterocolitis, deprive preterm infants of sensory and motor experiences during critical brain development when oral feeding skills are established. These factors increase the risk of preterm infants for substantial delays in achieving full independent feedings. Consequently, delayed

delayed oral feeding results in prolonged hospitalization, increased hospital cost, growth and developmental delays, and a high rehospitalization rate. The retrospective cohort study of Jadcherla et al. demonstrated that among 194 preterm infants, 40% were discharged on tube feedings due to feeding difficulties. Neurodevelopment follow-up at 18 to 24 revealed that those on full tube feedings had significantly lower cognitive ($p<0.01$), communication ($p=0.03$), and motor composite scores ($p<0.01$). It further concluded that full oral feeding achieved at first NICU discharge was associated with superior feeding milestones and less long-term neurodevelopment impairment (NDI) compared with full or partial tube feeding.(7) Rinat and colleagues observed that early feeding difficulties among extremely preterm infants are at risk for poor motor outcomes at 4 to 5 years corrected age. Thus, early diagnosis and intervention are warranted.(15)

Literature on oral feeding difficulties and their impact and complications are relatively lacking and new compared to the other morbidities associated with prematurity. Studies on the timing of initiation of oral feeding showed beneficial results when started earlier. Gentle et al. compared oral feeding initiation at < 33 weeks postmenstrual age (PMA), cue-based feeding, and practitioner-driven feeding in infants unable to achieve independent oral feedings by 36 weeks on PMA at independent oral feeding and discharge. They found that earlier oral feeding initiation among very preterm infants was associated with decreased PMA at independent oral feeding and discharge as opposed to cue-based feeding with insignificant reduction of the outcomes.(5) Similarly, Simpson et al. reported that earlier initiation of oral feeding 48 hours after achieving full gavage feeding of 120ml/kg/day accelerated the transition time to independent oral feeding compared to practitioner-driven feeding.(6)

The Preterm Infant Oral Motor Intervention (PIOMI) is a standardized oral stimulation program developed by Brenda Knoll. It was based on the principles of Beckman Oral Motor Intervention (BOMI), an oral motor intervention designed for term infants, children, and adults with developmental delays with feeding difficulties. It consists of 11 oral motor steps and is usually performed in 15 minutes. The PIOMI, on the other hand, is a 5-minute oral motor stimulation designed explicitly for preterm infants. It comprises 8 steps to activate muscle contraction and movement against resistance to build strength as shown in Appendix 1. The techniques were modified to accommodate the oral cavity's small size and ensure the preterm infant's correct positioning. It can be started before oral feeding hemodynamically stable preterm infants. (11)

Like other methods of oral motor intervention, studies on PIOMI differ in the

timing of initiation of intervention (29 to 34 weeks gestational age), frequency, and duration (7 to 10 days). Regardless of these differences, studies showed a significant reduction in the number of days from gavage to oral feeding and a decrease in the number of hospital days (11-14, 24). Contrary to other studies, Thakkar et al. found that it improved weight gain. (20) Arora et al. showed that it improved the Neonatal Oro Motor Assessment Scale, a reliable tool for the evaluation of neonatal sucking patterns in both preterm and term infants.(10)

Regarding the easiness of administration, Majoli et al. found no significant difference between parent-administered versus professional-administered premature infant oral motor intervention in terms of transition time to full oral feeding, weight gain, or the length of hospital stay among infants between 31 to 32 weeks PMA. It also increased the parents' satisfaction and enhanced their perception of their capability to care for their infant in the parent-administered group.(11)

Despite substantial evidence of the benefits of early oral motor intervention, it is not commonly practiced in most NICUs because of a lack of trained professionals. Also, not all preterm infants follow the expected normal oral feeding development. Initiation of oral feeding often leaves clinicians with the question of how long to wait before initiating alternative means to facilitate sustained oral feeding before discharge. In this regard, studies on oral feeding intervention for infants in the NICU are essential to facilitate an earlier transition to full oral feeding and hospital discharge.

Objectives of the study

General Objective:

To determine the effectiveness of Preterm Oral Motor Intervention as a pre-feeding oral motor stimulation among preterm infants less than or equal to 32 weeks gestational age.

Specific Objectives:

To determine if Preterm Infant Oral Motor Intervention among preterm infants less than or equal to 32 weeks gestational age

Reduces the transition from tube to oral feeding.

Increases weight gain.

Decreases the duration of hospital stay.

METHODOLOGY

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines and was conducted between July and September 2023.

We conducted a thorough electronic search through PubMed, MEDLINE, the Cochrane Library, Google Scholar, Physiotherapy Evidence Database (PEDro), non-English databases, and unpublished clinical trials through the International

Clinical Registry Platform (iCRTP) from 2011 to August 2023. The developer of PIOMI was also asked for possible references and unpublished articles. The citation or reference lists of eligible studies were also reviewed for relevant articles. The MeSH terms and free text words used were Preterm Infant, OR Premature Infant OR Prematurity OR Neonatal Prematurity, AND Pre-feeding OR before feeding, AND Premature Infant Oral Stimulation OR PIOMI, AND Randomized-controlled trials OR controlled clinical trial OR clinical trial. The studies were excluded based on the inclusion and exclusion criteria, and the full-text articles of the remaining studies were retrieved and screened.

The included studies were prospective randomized clinical trials evaluating the effects of the Preterm Infant Oral Motor Intervention (PIOMI) in transition to independent oral feeding, weight gain, and length of hospital stay.

The inclusion criteria were: (a) Population: Preterm infants born on or before 32 weeks age of gestation and admitted to NICU, (b) Design: Randomized clinical trials, (c) Language: English, (d) Intervention: Premature Infant Oral Motor Intervention administered on or before 32 weeks age of gestation.

The exclusion criteria were: (a) Population: Preterm infants more than 32 weeks age of gestation and not admitted to the NICU, (b) Intervention: Other oral motor intervention/stimulation, (c) Design: Non-randomized clinical trials, (d) Language: Studies not written in English and also unavailable full-text articles. Preterm infants over 32 weeks were excluded from this study to minimize bias from the expected oral feeding development skills. The primary investigator and co-investigator performed an independent and thorough screening of abstracts generated by the search strategy and reviewed the full-text articles of eligible studies. There were no discrepancies between the two reviewers.

The risk of bias of the included studies were appraised and classified as low, moderate or unclear, and high risk using the Cochrane Collaboration's GRADE (2011). This critical appraisal tool evaluates a trial in the following areas: 1. sequence generation, 2. blinding, 3. allocation concealment, 4. incomplete outcome data, 5. selective outcome reporting, and 6. other sources of bias. The answers to all domains of bias based on an algorithm generates a proposed judgement on the risk of bias. A low risk of bias indicates low risk assessment in all domains; unclear risk means unclear risk assessment for all domains; and, high risk denotes a high-risk assessment in one or more key domains.

The primary outcome in this analysis is the transition to full independent oral feeding for the control and intervention groups. The secondary outcomes are length of hospital stay and weight gain.

The co-investigator and a research assistant conducted the data extraction, including the study design, facility location, patient population, control/comparator, intervention, and all outcomes, and were tabulated in Table 1. For the missing data, the authors were contacted to provide the data or were computed based on appropriate statistics.

The statistical analyses were conducted using STATA MP Parallel Edition Statistical Software, Version 18, College Station, TX: StataCorp LP. The outcomes were continuous variables and are presented as standardized mean difference, alongside their corresponding 95% confidence intervals. A p-value ≤ 0.05 was considered statistically significant. Heterogeneity or between-study variations in the included studies was evaluated using Q statistics test, I^2 statistics, and tau squared (τ^2) statistics. I^2 values more than 50% denote substantial heterogeneity, while a significant Q-statistic implies a statistically significant heterogeneity. For an outcome with substantial heterogeneity ($I^2 \geq 50\%$) random-effects model was used to calculate the mean effect size and the source of heterogeneity was examined using a subgroup analysis. In contrast, a fix-effects model was used in studies with homogenous outcomes ($I^2 < 50\%$) .

RESULT

Study Selection

Figure 1 shows the summarized flowchart of the study selection process. Ninety-seven (97) articles were retrieved based on the search strategy. Articles were excluded at each stage for the reasons. Twenty-seven studies were excluded from the initial screening because of ongoing studies and other study designs. Eight articles were reviewed and included in the meta-analyses.

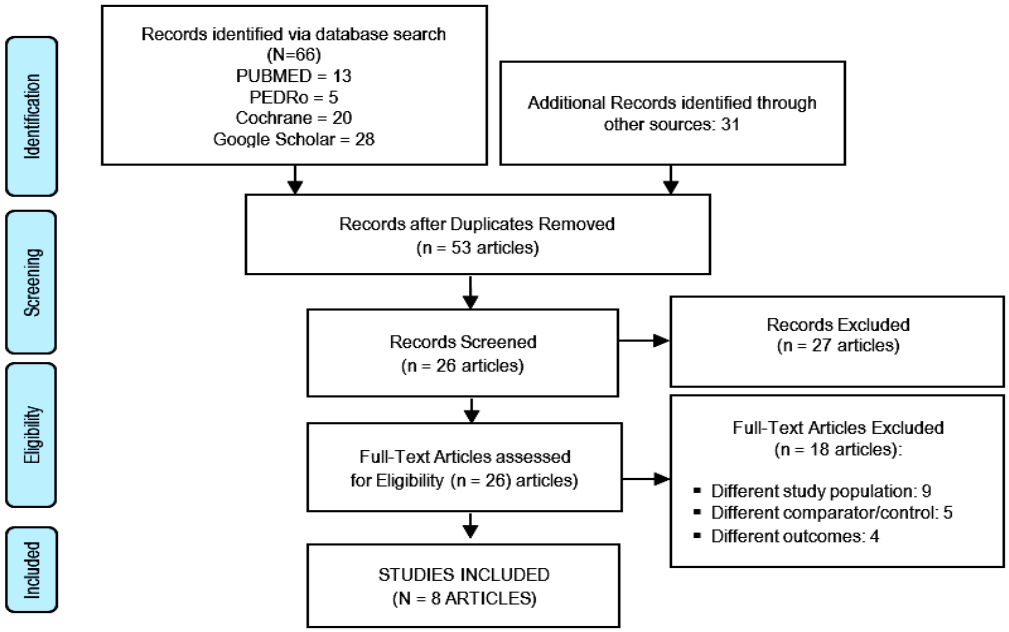


Figure 1. PRISMA Flow Diagram of Study Selection

Study Characteristics of Individual Studies

All eight included studies were prospective randomized controlled trials comparing the effect of PIOMI with standard care or sham intervention among preterm infants born less than or equal to 32 weeks gestational age. The cumulative sample was 290 participants: 147 in the PIOMI group and 143 in the control group.

One study was done in 2 NICU centers in Turkey, while the rest were single-centered studies from India (4), Iran (1), Egypt (1), and the USA (1). Six studies were included for the transition from gavage to full oral feeding, two studies for weight gain, and all studies for the length of hospital stay. The duration and frequency of the PIOMI in the intervention group varied from 7 to 14 days and once a day to three times a day.

Randomization, either by block or computer generation, was mentioned in all studies. Blinding of the participants and assessors was also reported in all studies. Table 1 presents a summary of the characteristics of the clinical trials included in the study.

Table 1. Characteristics of Included Research Studies (N=8)

Study (Year) And Country	Population Sample (N) Groups (n)	Method/ Design	Comparator	Intervention	Outcomes
Arora et al. (2014), India[10]	N: 30 Control: 14 PIOMI: 16 Inclusion: Born 28 – 32 weeks GA, no respiratory support for 48 hours, on full gavage feeding (150ml/kg/day), Exclusion: Preterm infants with RDS, and chronic medical complications (BPD, IVH, PVL, NEC, Chromosomal anomalies, or craniofacial malformation)	Randomized clinical trial	Sham Intervention (Unstructured oral intervention)	PIOMI TID for 7 days	1. Neonatal Oro Motor Assessment Scale (NOMAS) 2. Transition time to reach full independent wait spoon feeds 3. Duration of hospital stay, 4. Weight gain after the intervention

Bandyo-padhyay et al. (2023,) India[21]	N: 32 Control: 16 PIOMI: 16 Inclusion: Born 28 – 32 weeks GA, physiologically stable at the time of intervention, on full gavage feedings (150ml/kg) and in transition from gavage to spoon feeds, receiving Non-nutritive sucking (NNS) and Kangaroo Mother Care (KMC) as part of routine care. Exclusion: Preterm infants with IVH ≥ grade 2, NEC stage ≥ 2, PVL, BPD, and chromosomal anomalies or congenital malformations, history of perinatal asphyxia, and neonatal jaundice for exchange transfusion	Randomized clinical trial	Standard care including non-nutritive sucking and Kangaroo mother care	PIOMI BID until full feeding (lasted for 9 days)	1. Transition to full spoon feeding 2. Episodes of bradycardia, or desaturation during or immediately after spoon feeding, blood culture positive sepsis 3. Duration of hospital stay
Ghomi et al. (2019) Iran [22]	N: 30 Control: 15 PIOMI: 15 Inclusion: Born 26- 29 weeks GA, physiologically stable at the time of intervention, AS of ≥ 6 at 5 mins of birth, parental consent Exclusion: Congenital disorders or chromosomal abnormalities, chronic medical conditions (BPD< IVH gr 3 & 4, NEC, asphyxia, seizures, neonatal jaundice for exchange transfusion	Randomized clinical trial	Standard care	PIOMI OD x 10 days	1. Transition to full oral feeding 2. Weight gain 3. Length of hospital stay
Guler et al. (2018) India [23]	N: 60 Control: 30 PIOMI: 30 Inclusion: Born 26 to 29 weeks GA, Stable vital signs for at least 24 hours, Respiratory support of oxygen cannula, oxygen hood, and CPAP, APGAR score ≥ 4 at 1 and 5 minutes of life, IVH limited to grade 1 and 2	Randomized controlled design	Sham intervention	PIOMI OD for 14 days	1. Sucking capacity: sucking power, sucking time, and sucking amount 2. Feeding transition - Tube feeding to first bottle feeding - Tube feeding to initiation of breast feeding 3. Anthropometrics 4. Length of hospital stay (Enrollment to day of discharge)

Lessen (2011) USA [9]	N: 19 Control: 9 PIOMI: 10 Inclusion: Born between 26-29 weeks GA, AGA, clinically stable but could be receiving oxygen per high flow cannula Exclusion: Congenital anomalies, NEC, brain injury including IVH > grade 1, history of prenatal illicit drug exposure, on assistive ventilation more than high flow nasal cannula,	Randomized clinical trial	Standard of care	PIOMI OD X 7 days	1. Feeding progression (first to full oral feeding) 2. Length of hospital stay (Enrollment to discharge)
Mahmoodi et al (2019) Turkey [24]	N: 40 Control: 20 PIOMI: 20 Inclusion: Born 28 to 32 weeks GA, Fed at least 10 cc/kg gavage feeding, lack of any disorders such as cleft lip and palate, and congenital disorder Exclusion: Preterm infants with sepsis, congenital heart disease, NEC, severe	Randomized clinical trial	Routine care	PIOMI OD for 7 days	1. Premature Oral Feeding Readiness Scale (POFRAS) 2. Tube feeding to initiation of first oral feeding 3. Length of hospital stay
Osman et al. (2016) Egypt [25]	N: 75 Control: 25 Group 1: PIOMI low dose Group 2: PIOMI high dose Inclusion: Born 30 to 32 weeks GA, AGA Exclusion: Preterm infants with congenital anomalies, NEC, brain injury including IVH, receiving assisted ventilation or high flow nasal cannula ≥ 4L/min, clinically unstable	Randomized clinical trial	Sham intervention (no unstructured oral motor intervention)	Group 1: OD for 7 days Group 2: OD until full feeding	1. Transition to full oral feeding (first to full oral feeding) 2. Length of hospital stay (Admission to discharge) 3. Weight gain
Sasmal et al. (2023) India [26]	N: 29 Control: 14 PIOMI: 15 Inclusion: Born 26 to 32 weeks GA, birthweight < 1500, APGAR score ≥ 6 at 5th min after birth, without - or with respiratory support via nasal cannula ≤ 2 L/min or nasal prong 0.1 – 0.2 L/min Exclusion: history of prenatal illicit drug exposure, congenital and chromosomal anomalies, medical conditions such as BPD, severe asphyxia, NEC, neonatal jaundice for exchange transfusion, seizures, IVH grade 3 & 4, PVL, on assistive ventilation other than high flow nasal cannula, sepsis, on NPO, and SGA, and transferred to other hospital	Randomized controlled trial	Routine care	PIOMI BID x 7 days	1. Premature Oral Feeding Readiness Scale (POFRAS) 2. Early Feeding Skill (EFS) 3. Preterm Infant Breastfeeding Behavior Scale (PIBBS) 4. Transition to full oral feeding (First to full oral feeding) 5. Duration of hospital stay (from admission to discharge) 6. Weight gain 7. Feeding mode at discharge

Risk of Bias (ROB) and Quality of Evidence Assessment using the Cochrane GRADE Tool

The Cochrane GRADE Tool, illustrated in Figures 2a and 2b, was used for the risk of bias and the quality of evidence assessment. Figure 2a shows a low risk of selection bias due to random sequence generation and allocation concealment, detection bias due to blinding of outcome assessors, attrition bias due to incomplete outcome data, and other biases. However, there is approximately 40% high risk for performance bias due to the lack of blinding of participants and personnel. There is about 60% unclear risk of bias for reporting bias due to selective reporting of results and data.

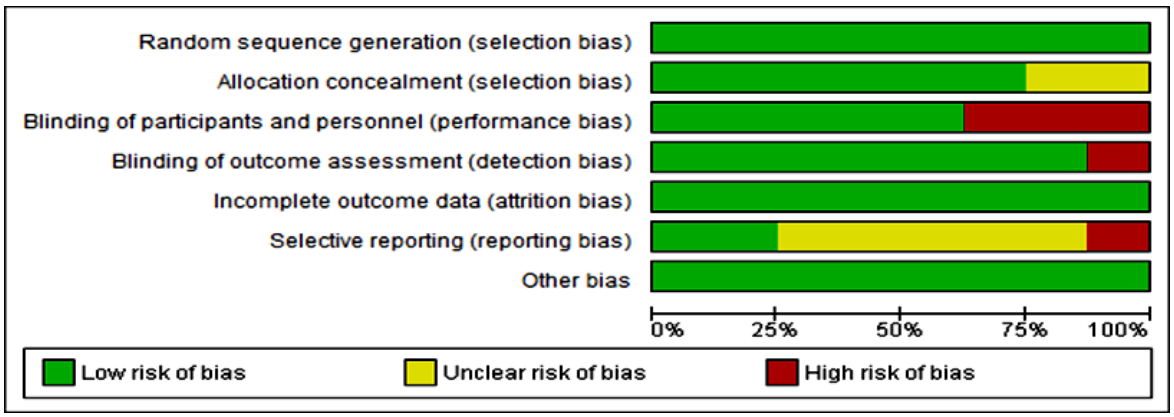


Figure 2a. Risk of Bias Assessment Graph of the Included Studies using the Cochrane GRADE Tool

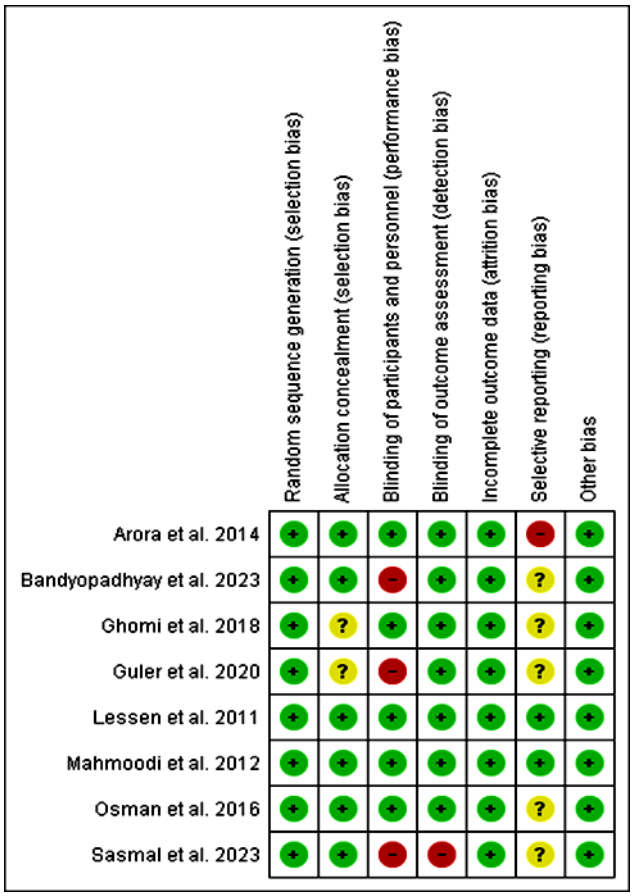
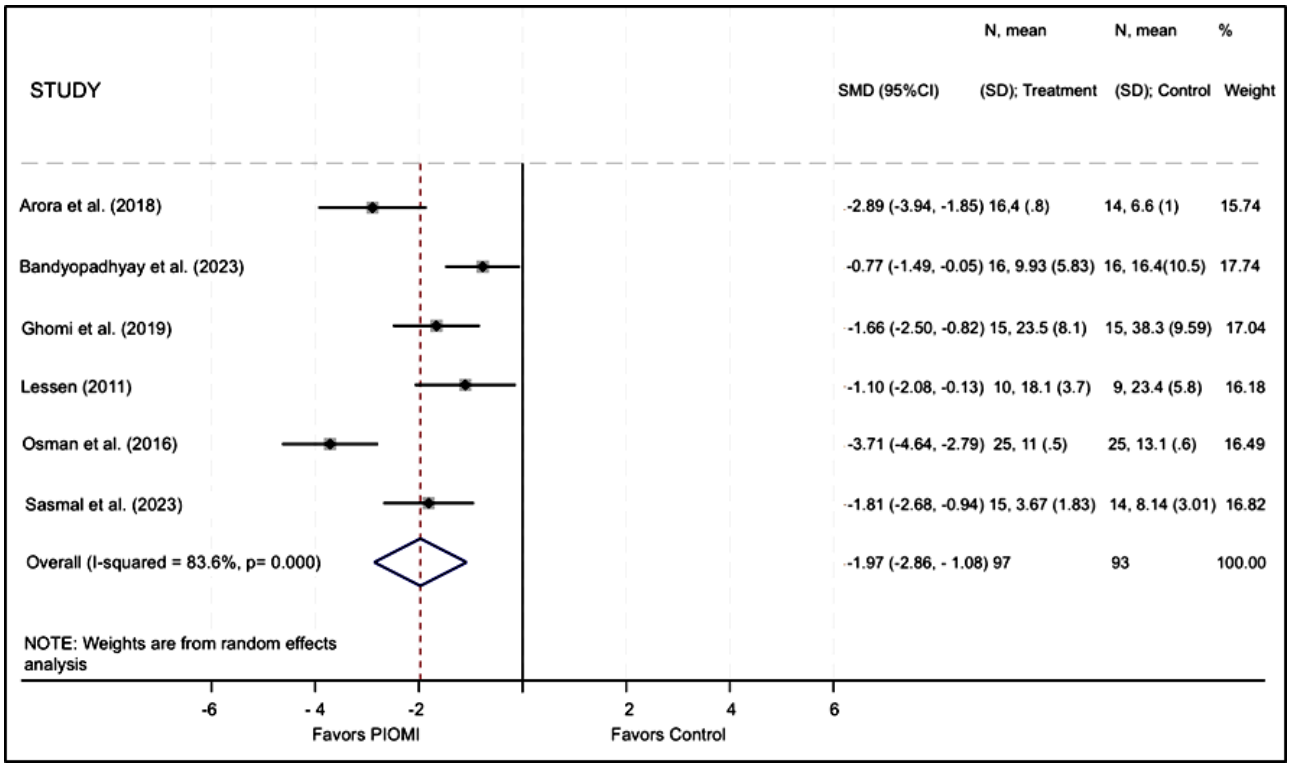


Figure 2b. Risk of Bias Assessment Summary of the Included Studies

Six studies were included in the transition from tube to full oral independent feeding. Figure III shows the pooled standardized mean difference in the transition time to full oral feeding between the PIOMI and the control groups. The random-effects model analysis included 190 participants, 97 in the PIOMI group and 93 in the control group. The forest plot shows that the transition time was 1.97 days shorter in the PIOMI group (SMD=–1.97, z=4.33, p=0.001, 95% CI = –2.86 to –1.08) than in the control group.

Figure 3. Pooled Standardized Mean Difference in the Transition Time to Full Oral Feeding between the PIOMI Group and the Control Group



However, there was a significant high between-study variation among the included studies
(χ^2=30.50, p=0.001; I^2=83.60%; τ^2=1.03).

To identify the possible source of heterogeneity in the feeding transition, subgroup analyses were conducted according to four groupings: 1. start of measurement of the transition time to full oral feeding, full gavage feeding vs. first oral feeding, 2. duration of PIOMI (7 Days vs. >7 Days), 3. Frequency of PIOMI (7 Times vs. >7 Times), and 4. age of gestation. Figures IV to VI demonstrate the forest plot of the subgroup analyses.

The subgroup analysis, according to the start of measurement of transition shown in Figure 4, indicated that the heterogeneity

between the included studies was not significantly different (χ^2=3.68, p=0.005). Among those which measured the transition at the start of full gavage feeding, the random-effects model results showed that those in the PIOMI group reached full independent oral feeding 1.72 days shorter than the control group (SMD=–1.72, z=2.91, p=0.004, 95% CI = –2.89 to –0.56). The heterogeneity, however, remained significantly substantial (χ^2=10.97, p=0.004; I^2=81.80%; τ^2=0.86). Similarly, studies that measured transition at the start of the first oral feeding resulted 2.21-day shorter in achieving full independent oral feeding in the PIOMI group compared to control group (SMD=–2.21, z=2.89, p=0.004, 95% CI = –3.71 to –0.71) but still with significant high heterogeneity (χ^2=15.85, p=0.001; I^2=87.40%; τ^2=1.54).

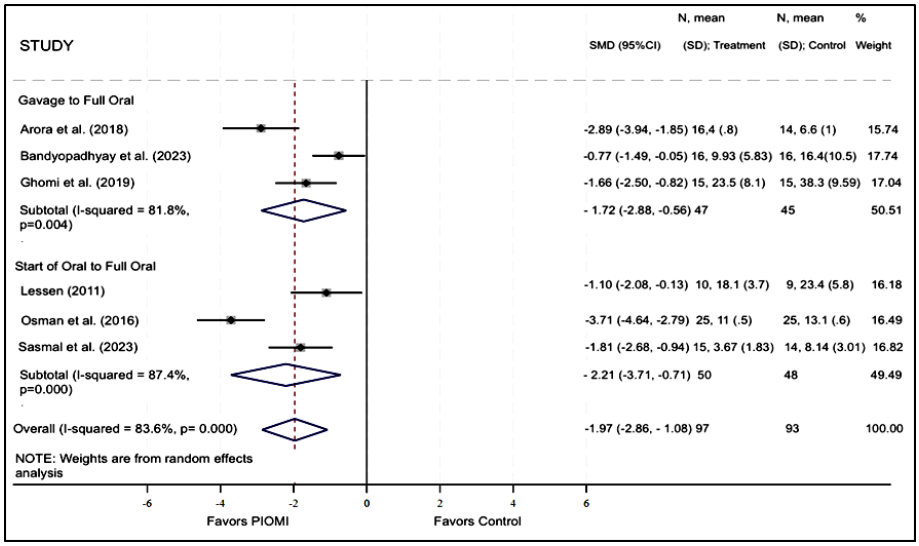


Figure 4. Pooled Standardized Mean Difference in the Transition Time to Full Oral Feeding between the PIOMI Group and the Control Group according to the Start of Measurement of the Transition Time

Figure 5A shows the subgroup analyses according to the duration of PIOMI and indicated that the heterogeneity in the two subgroups were significantly different (χ^2=10.89, p=0.001), with most heterogeneity coming from the 7 days duration subgroup. Studies which had PIOMI for 7 days, showed that the transition was 2.38-day shorter in the PIOMI group (SMD=–2.38, z=4.10, p=0.001, 95% CI = –3.53 to –1.24), and the estimated heterogeneity was significantly high (χ^2=17.10, p=0.001; I^2=82.50%; τ^2=1.11). Similarly, results for the articles which had PIOMI for >7 days indicated that the transition was 1.19-day shorter in the PIOMI group (SMD=–1.19, z=2.66, p=0.008, 95% CI = –2.06 to –0.31). This subgroup did not have a significant substantial heterogeneity (χ^2=2.51, p=0.113; I^2=60.20%; τ^2=0.24).

The subgroup analysis according to the frequency of PIOMI (Figure 5B) showed that

that the estimated heterogeneity was statistically significant between the two subgroups (χ^2=4.75, p=0.029), and most of the heterogeneity was detected in PIOMI administered for the seven times subgroup. The results of the studies with PIOMI performed seven times indicated that the transition time between the PIOMI and control groups was not significantly different (SMD=–2.41, z=1.85, p=0.064, 95% CI = –4.97 to 0.14), and with high heterogeneity (χ^2=14.47, p=0.001; I^2=93.10%; τ^2=3.17). On the other hand, the subgroup analysis with PIOMI administered >7 times showed that the transition time in the PIOMI group was significantly 1.73 days shorter (SMD=–1.73, z=4.07, p=0.001, 95% CI = –2.56 to –0.90) than the control group. The subgroup analysis, however, still had a significantly substantial heterogeneity (χ^2=11.29, p=0.010; I^2=73.40%; τ^2=0.53).

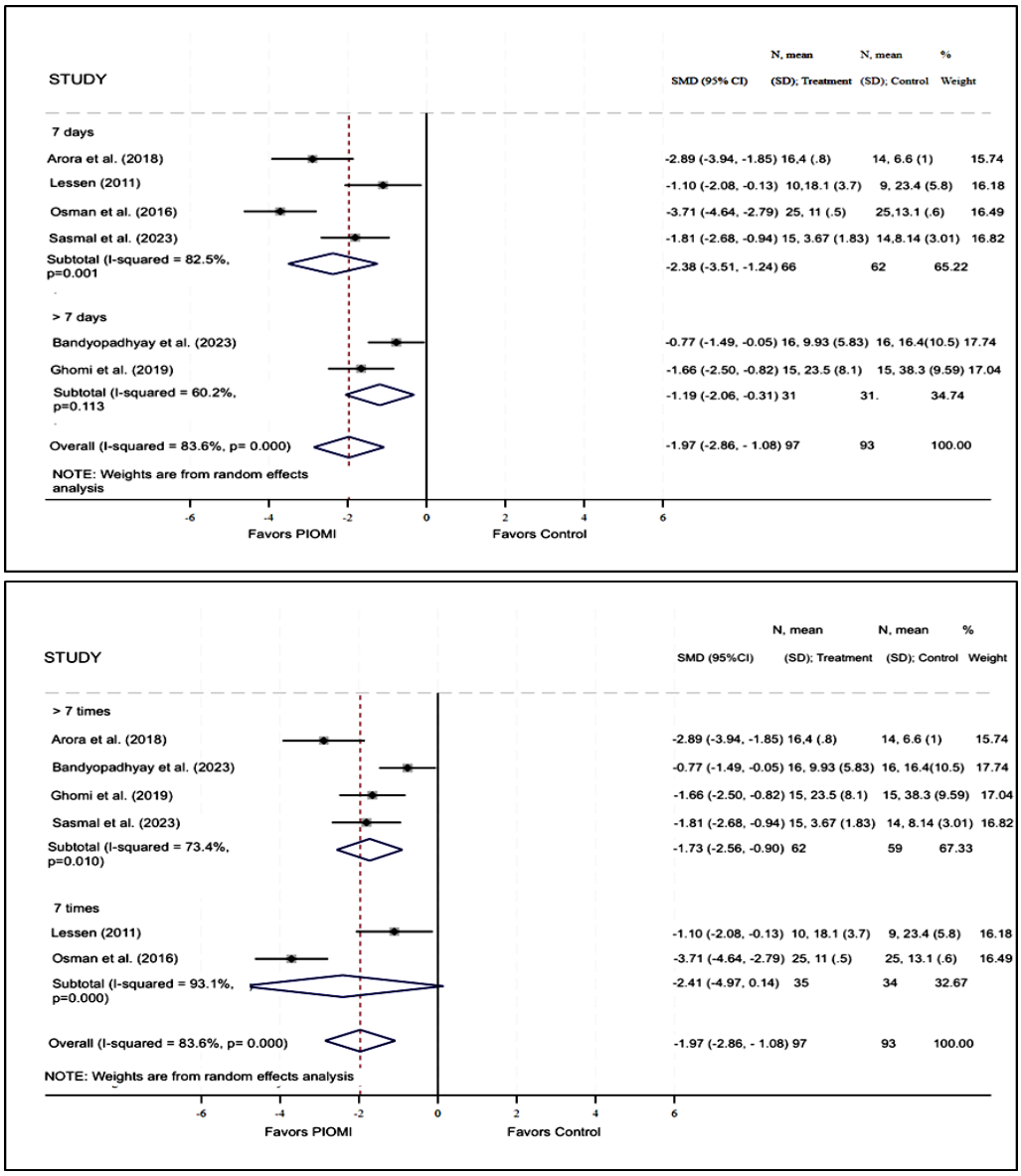


Figure 5. Pooled Standardized Mean Difference in the Transition Time to Full Oral Feeding between the PIOMI Group and the Control Group according to (A) the Duration and (B) the Frequency of PIOMI

The subgroup analysis according to age of

The subgroup analysis according to age of gestation (Figure 6) shows that the heterogeneity between the two groups were significant (χ^2=19.33, p=0.001), and most of the between-study variance was detected in the 30 to 32 weeks of gestation group (76.90%). In the 28 to 29 week of gestation group, the transition time was 1.15-day shorter in the PIOMI group (SMD=–1.15, z=4.17, p=0.001, 95% CI = –1.69 to –0.61) than in the control group, and the heterogeneity in this subgroup was not substantial (χ^2=2.52, p=0.284; I^2=20.60%; τ^2=0.05). The transition time in the subgroup of 30 to 32 weeks of gestation was 2.80-days shorter (SMD=–2.80, z=4.82, p=0.001, 95% CI = –3.93 to –1.66) in the PIOMI group than in the control group, but with substantial heterogeneity (χ^2=8.66, p=0.013; I^2=76.90%; τ^2=0.77).

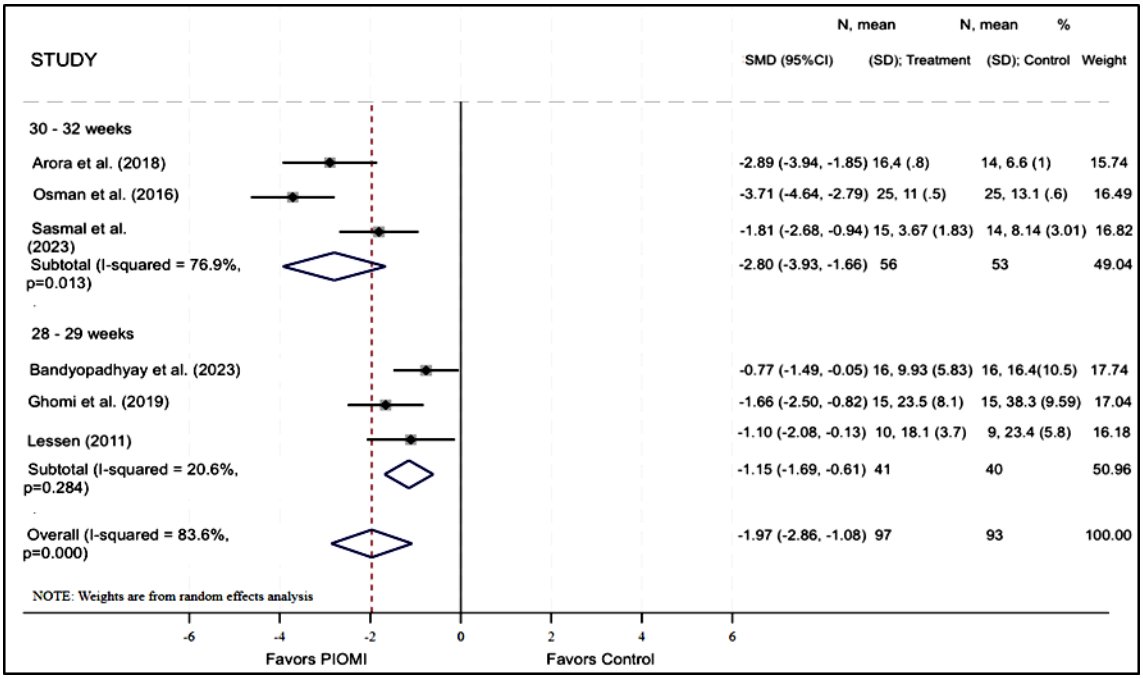


Figure 6. Pooled Standardized Mean Difference in the Age of Gestation between the PIOMI Group and the Control

Pooled Estimate for the Standardized Mean Difference in Weight Gain

The pooled standardized mean difference in weight gain between the PIOMI and the control groups is presented in Figure 7. Fixed-effects model analysis of two studies with 79 participants, 40 in the PIOMI group and 39 in the control group, showed that the weight gain in the PIOMI group was 810 grams significantly higher (SMD=0.81, z=3.45, p=0.001, 95% CI = 0.35 to 1.27) than in the control group. Analyses also indicated that there was no heterogeneity among the included studies (χ^2=0.03, p=0.871; I^2=0.00%, τ^2=0.00).

Pooled Estimate for the Standardized Mean Difference in the Duration of Hospital Stay

Figure 8 depicts the pooled standardized mean difference in the duration of hospital stay between the two groups. There was good homogeneity in the 8 studies that included 290 participants, 147 in the PIOMI group and 143 in the control group (χ^2=5.77, p=0.567; I^2=0.00%; τ^2=0.00); Fixed-effects model analysis showed that the duration of hospital stay was 0.47-day significantly shorter in the PIOMI group (SMD=–0.47, z=3.93, p=0.001, 95% CI = –0.71 to –0.24) compared to the control group.

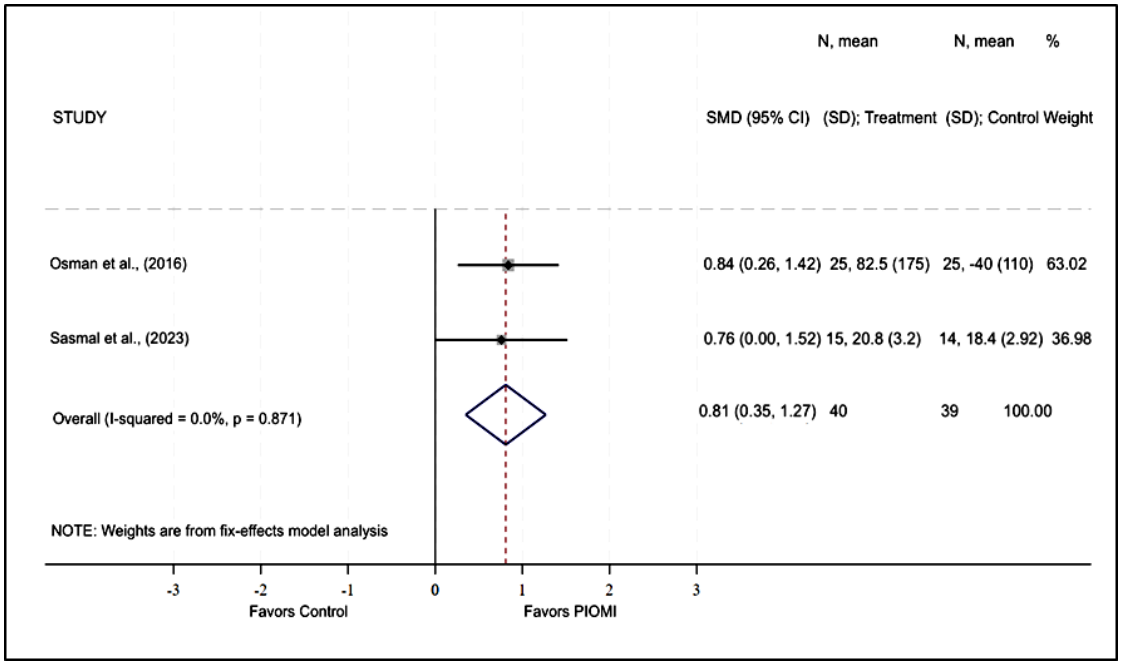


Figure 7. Pooled Standardized Mean Difference in the Weight Gain between the PIOMI Group and the Control Group

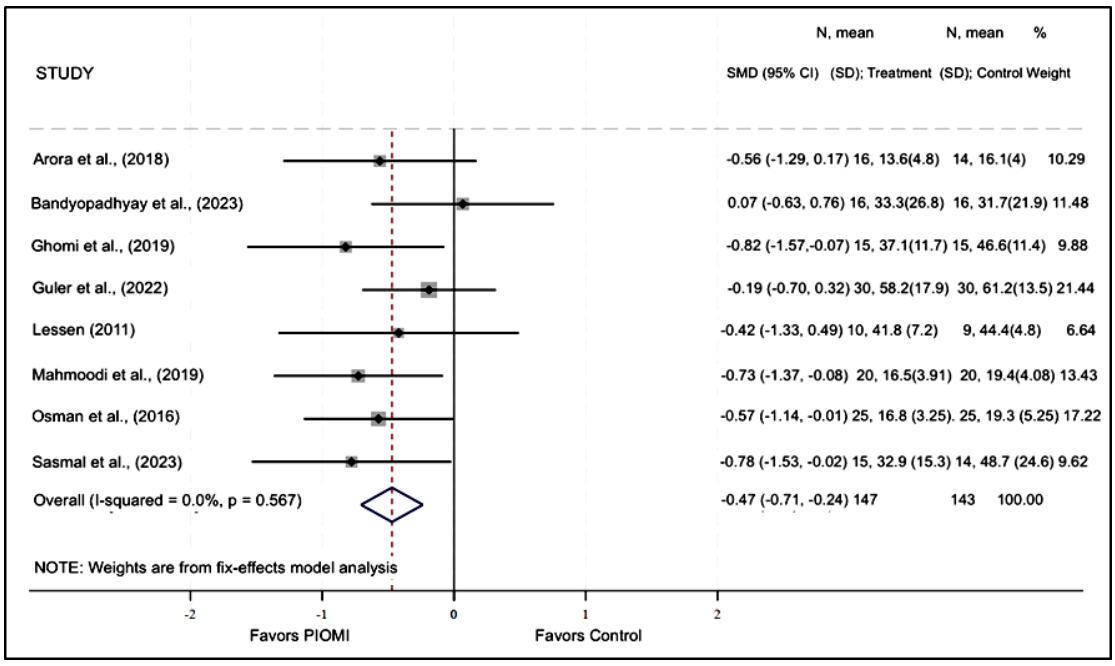


Figure 8. Pooled Standardized Mean Difference in the Duration of Hospital Stay between the PIOMI Group and the Control

Publication Bias

The graphical analyses of publication bias using contour-enhanced funnel plots are shown in Figure 9. These plots show funnel asymmetry for the transition time to full oral feeding and weight gain. The formal statistical tests for publication bias using Begg's adjusted rank correlation test and Egger's regression asymmetry test showed that the likelihood of publication bias for the outcomes of transition to oral feeding and weight gain (p>0.05) were unlikely.

Table 3. Statistical Assessment of Publication Bias of the Different Study Outcomes

Outcomes	Number of Studies	Begg's Test		Egger's Test	
		Estimate	p-value (Two-Tailed)	Bias Estimate	p-value (Two-Tailed)
Transition Time to Full Oral Feeding (Days)	6 Studies	1.13	0.26	–11.82	0.176
Weight Gain (Grams)	2 Studies	0.00	1.00	–0.87	1.000
Duration of Hospital Stay (Days)	8 Studies	0.37	0.71	–1.59	0.436
*Significant at 0.05 †Significant at 0.01					

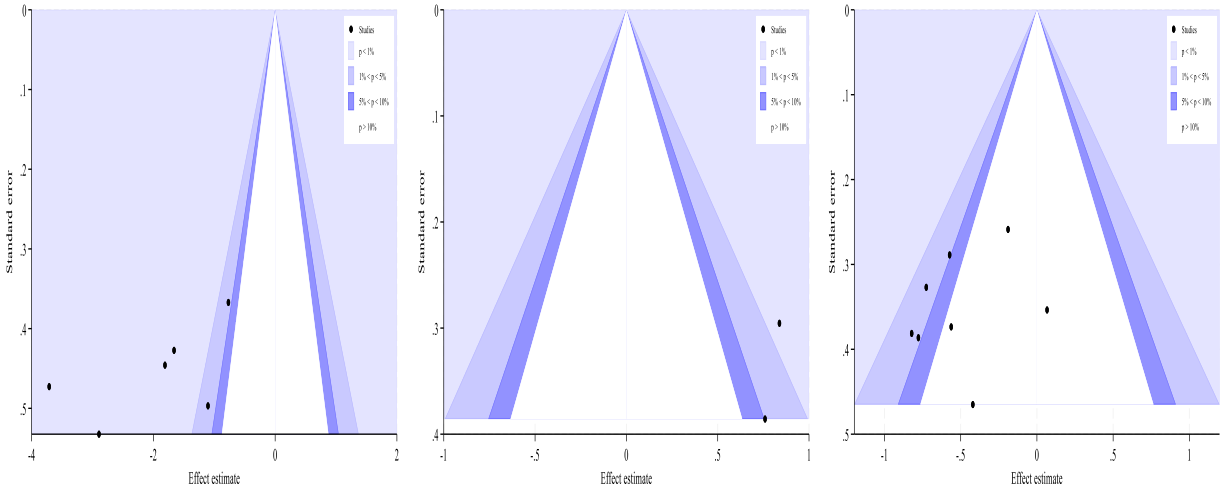


Figure 9. Contour-Enhanced Funnel Plots for the Analysis of Publication Bias for the Pooled Estimates of the Transition Time to Full Oral Feeding (Left Plot), Weight Gain (Middle Plot), and Duration of Hospital Stay (Right Plot) between the PIOMI Group and the Control Group

DISCUSSION

The survival of preterm infants has dramatically improved with medical innovation. In line with this, NICU's best practices should also parallel these developments to minimize long-term complications associated with prematurity.

Independent feeding is the most common barrier to discharge and is a significant factor for prolonged hospitalization.(5) Randomized controlled trials and meta-analysis studies on various oral motor interventions among preterm infants have shown benefits in transitioning to full oral feeding and length of hospital stay. (9,8)

The study was conducted to determine if PIOMI as an oral motor intervention among preterm infants born 32 weeks gestational age or less improves transition to full oral feeding, length of hospital stay, and weight gain. We excluded articles that involved preterm infants more than 32 weeks of gestational age and employed other multiple oral motor techniques. PIOMI was chosen over the other OMS because it requires less time to administer and is tolerated by preterm infants as early as 29 weeks without an unfavorable response.(9) It also has a standardized training method, published intervention fidelity (27), and can be administered by non-professionals comparably to professionals (11). The meta-analysis by Gonzalez et al. specified that PIOMI may be the best intervention for improving oral motor function in preterm infants among the oral motor interventions. (28) In contrast to the meta-analysis done by Jyoti et al. on PIOMI (29), preterm infants over 32 weeks of gestation were excluded to minimize the bias associated with the maturation of the suck-swallow-breathing reflex with increasing gestational age. No reviews on the effect of PIOMI among preterm infants 32 weeks gestational age or less have been found to date.

The Cochrane risk of bias was used to assess the methodological quality of the eight studies. Performance bias is about 40% due to the lack of blinding of participants and personnel. The lack of blinding of the participants cannot affect the results because the target population was preterm infants. Most of the studies involved the primary investigator administering the PIOMI. Since the outcomes are objective measures and assessors were blinded by the allocation, the non-blinding of the primary investigator may not have significantly affected the results. There is almost a 60% unclear risk of reporting bias, specifically for the outcome of weight gain, where only two studies reported the numerical values. The rest of the parameters have a low-risk bias.

Six studies included for the feeding transition showed that the PIOMI group significantly decreased transitioning to full feeding. However, there was high heterogeneity among the studies; thus, four subgroup analyses were performed based on the start of transition (full gavage vs. first oral), duration and frequency of PIOMI administration, and age of gestation at birth. Figures 3-5 show that the timing of the start of the transition and the duration and frequency of PIOMI have high heterogeneity. Figure 6 showed non-substantial heterogeneity among those 28 to 29 weeks of gestation. The results suggest that neither the duration nor frequency of PIOMI administration affected the transition to full oral feeding. The same findings were reported by Chen et al. in which there was a significant reduction in the transition to oral feeding but with high heterogeneity even in the subgroup analyses based on age, country, and duration of intervention.(8) The different practices in oral feeding among preterm infants in the neonatal intensive care units may have contributed to the high heterogeneity in the feeding transition. However, this factor cannot be examined since only one study described the feeding progression protocol (9), and the others stated that no standard feeding protocol was used and oral feeding initiation and progression were based on the discretion of the attending neonatologist. Future studies are needed to investigate the effect of PIOMI among preterm infants using a standard oral feeding protocol for a more objective assessment of feeding initiation and progression.

Five studies reported weight gain as one of the outcomes, but only 2 reported the numerical values (27,28) and the other studies only stated a significant weight gain in the PIOMI group . The pooled analysis showed a significant weight gain in the PIOMI group. The same findings in weight gain were observed by Chen et al. and Greene et al. (8,20), while other studies did not show significant results (9,29).

The length of hospital stay showed a significant decrease in the PIOMI group and homogeneity among the eight studies. Other meta-analyses reported similar results with homogeneity among the included studies. (8,-10, 20)

Three studies showed that PIOMI significantly improved the feeding readiness scale. (14,28,30) Only one study reported adverse events such as sepsis, apnea, and desaturation, but no differences were found between the control and PIOMI groups. (21)

Our findings can guide in implementing an oral feeding protocol in preterm infants, especially in extremely and very preterm infants, in the neonatal intensive care units. The study only included research written in English and with small sample sizes; thus, may affect the credibility of the pooled analysis.

Conclusion

The study suggests that PIOMI can reduce the transition to independent feeding and hospital stay and increase weight gain among preterm infants 32 weeks of gestation or less. However, careful consideration of its clinical use in neonatal intensive care units is warranted due to study variations.

Recommendation

Future well-designed randomized clinical trials on PIOMI may include standard oral feeding protocol in the initiation and progression of feeding to minimize methodological limitations or variations in the results. Studies on the impact of PIOMI on breastfeeding at discharge and at six months of life and long-term neuro-developmental outcomes, as well as the adverse events of PIOMI administration in the extremely and very preterm infants, are also recommended.

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Philippine Children's Medical Center

Quezon Ave., Quezon City

8588-9900 local 1308

crd@pcmc.gov.ph

www.pcmc.gov.ph/research