PEDIATRIC CRITICAL CARE IN RESOURCE-LIMITED SETTINGS, VOLUME II

EDITED BY: Ndidiamaka L. Musa, Yves Ouellette, Srinivas Murthy, Krishan Chugh and Phuc Huu Phan

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PEDIATRIC CRITICAL CARE IN RESOURCE-LIMITED SETTINGS, VOLUME II

Topic Editors:
Ndidiamaka L. Musa, University of Washington, United States
Yves Ouellette, Mayo Clinic, United States
Srinivas Murthy, University of British Columbia, Canada
Krishan Chugh, Fortis Healthcare, India
Phuc Huu Phan, Vietnam National Children's Hospital, Vietnam

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High-Flow Nasal Cannula Therapy in Children With Acute Respiratory Distress With Hypoxia in A Pediatric Intensive Care Unit–A Single Center Experience

Chih-Ching Chang[1†], *Yi-Chen Lin*[2†], *Tzu-Chun Chen*[2], *Jainn-Jim Lin*[1,2,3,4*], *Shao-Hsuan Hsia*[1,2,3], *Oi-Wa Chan*[1,2,3] *and En-Pei Lee*[1,2,3]

[1] *Department of Respiratory Therapy, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan,* [2] *Chang Gung University School of Medicine, Taoyuan, Taiwan,* [3] *Division of Pediatric Critical Care Medicine and Pediatric Neurocritical Care Center, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan,* [4] *Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan*

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Edited by:
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***Correspondence:**
Jainn-Jim Lin
lin0227@adm.cgmh.org.tw

[†] *These authors have contributed equally to this work*

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Aim: High-flow nasal cannulas (HFNCs) show potential in the application of positive pressure, improving gas exchange, and decreasing work of breathing in patients with acute respiratory distress. The aims of this study were to elucidate the indications for HFNC therapy in children of all ages and diagnoses, and to evaluate the efficacy and risk factors for failure of HFNC therapy in children with acute respiratory distress with hypoxia in a pediatric intensive care unit.

Methods: We conducted this retrospective cohort study at a tertiary pediatric intensive care unit between January 1, 2018 and December 31, 2020. All children, from 1 month to 18 years of age, with acute respiratory distress with hypoxia and HFNC therapy were eligible. The clinical data were reviewed.

Results: One hundred and two children met the eligibility criteria for the study, of whom 57 (55.9%) were male, and the mean age was 7.00 ± 6.79 years. Seventy-eight (76.5%) of the children had underlying disorders. The most common indications for the use of HFNC therapy were pneumonia (40, 39.2%), sepsis-related respiratory distress (17, 16.7%), and bronchiolitis (16, 15.7%). The failure rate was 15.7% (16 of 102 children). Higher initial and maximum fraction of inspiration O2 levels and lower initial and lowest SpO2/FiO2 (S/F) ratio were early and possible signs of failure requiring escalation of respiratory support.

Conclusion: In our population, we found that HFNC therapy could be initiated as the first-line therapy for various etiologies of acute respiratory distress with hypoxia in a pediatric intensive care unit and for all age groups.

Keywords: high-flow nasal cannula, child, acute respiratory distress, pediatric intensive care unit, hypoxic

INTRODUCTION

Acute respiratory distress is the most common cause of pediatric intensive care unit admission. Invasive mechanical ventilation is an established effective supportive therapy for acute respiratory distress. However, it is associated with increased risks of nosocomial infections, lung and airway injuries, length of stay, and sedation-related complications (1–3).

High-flow nasal cannulas (HFNCs) are an increasingly used form of non-invasive respiratory support, and they have shown potential in reducing the need for intubation (4–7). HFNCs enable the administration of high concentrations of oxygen with adequate relative humidity and temperature, and they have been shown to improve airway resistance and lung compliance, achieve a certain level of continuous positive airway pressure (CPAP), eliminate dead space and decrease respiratory work (8–11). HFNC therapy has been used in infants with respiratory distress syndrome and infants with bronchiolitis, and it has been shown to decrease respiratory distress and intubation rates, increase patient comfort and ease of use compared with face masks or traditional cannulas, and shorten the length of stay in pediatric intensive care units (ICUs) (12–15).

Despite increasing evidence supporting the use of HFNCs as respiratory support for children with bronchiolitis, few studies have investigated the indications for HFNC therapy and the epidemiology of disease warranting HFNC therapy in older children in a pediatric ICU (16–25). Thus, the aims of this study were to elucidate the indications for HFNC therapy in children of all ages and diagnoses, and to evaluate the efficacy and risk factors for failure of HFNC therapy.

METHODS

This was a retrospective cohort study using chart reviews of pediatric patients who received HFNC respiratory support at the pediatric ICU of Chang Gung Children's Hospital between January 1, 2018 and December 31, 2020. Acute respiratory distress was defined as hypoxemia (SpO2 < 94%) and signs of respiratory distress despite standard-flow oxygen therapy. All patients received standard-flow oxygen therapy via a traditional nasal cannula at 1–5 L/min, simple mask at 6–10 L/min or oxygen hood with 35–50% oxygen before they were switched to high flow (16, 17). The signs of respiratory distress included increased breathing rate and heart rate, color changes, grunting, nose flaring, retractions, wheezing, and sweating. The eligibility criteria for this study were: (1) age from 1 month to 18 years; and (2) patients with acute respiratory distress with hypoxia who used HFNC respiratory support for any period of time during their pediatric ICU admission. We excluded those who: (1) were older than 18 years and younger than 1 month; (2) had respiratory distress with low-flow oxygen therapy (such as a traditional nasal cannula at 1–5 L/min, simple mask at 6–10 L/min or oxygen hood with 35–50% oxygen) or respiratory failure with invasive mechanical ventilation; (3) required respiratory support post extubation and after weaning from continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP); and (4) had a history of long-term ventilator dependency. This study was approved by the Chang Gung Memorial Hospital Institutional Review Board (IRB number: 201801252B0C502 and 201901701B0).

HFNC Protocol

In January 1, 2018, we initiated an institutional protocol for the use of HFNCs, which was modified from a previous study conducted in a pediatric ICU (**Figure 1**) (3, 6). HFNC was delivered by an Optiflow System® (Fisher & Paykel, Auckland, New Zealand). The protocol includes guidelines for the indications, settings, monitoring and outcomes (success or failure) of HFNC therapy (3, 6). Fraction of inspiration O2 (FiO2) was adjusted to reach a pulse oximetry (SpO2) between 92 and 97%, and the flow setting was based on the patients' body weight: 0–15 kg: 2 L/kg/min; 16–30 kg: 35 L/min; 31–50 kg: 40 L/min; >50 kg: 50 L/min. We also monitored clinical parameters including heart rate, respiratory rate, and SpO2 as well as venous blood gas for pH and CO2. Disease severity and oxygenation were assessed according to the PRISM score, SpO2/FiO2 (S/F) ratio, and ROX index score [(SpO2/FiO2)/RR] (26, 27). The

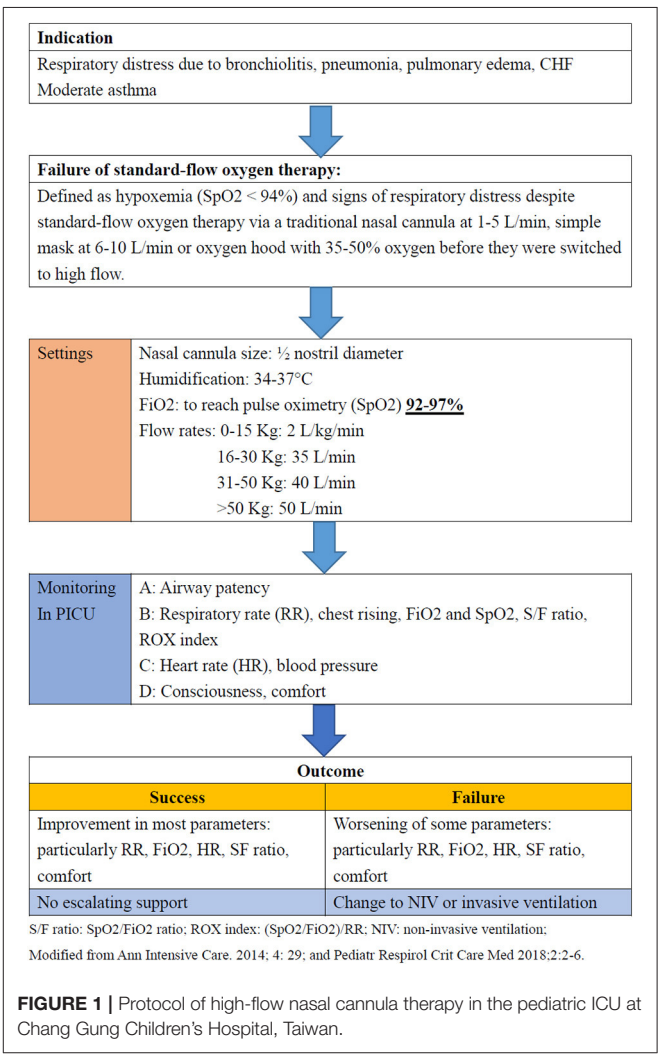

FIGURE 1 | Protocol of high-flow nasal cannula therapy in the pediatric ICU at Chang Gung Children's Hospital, Taiwan.

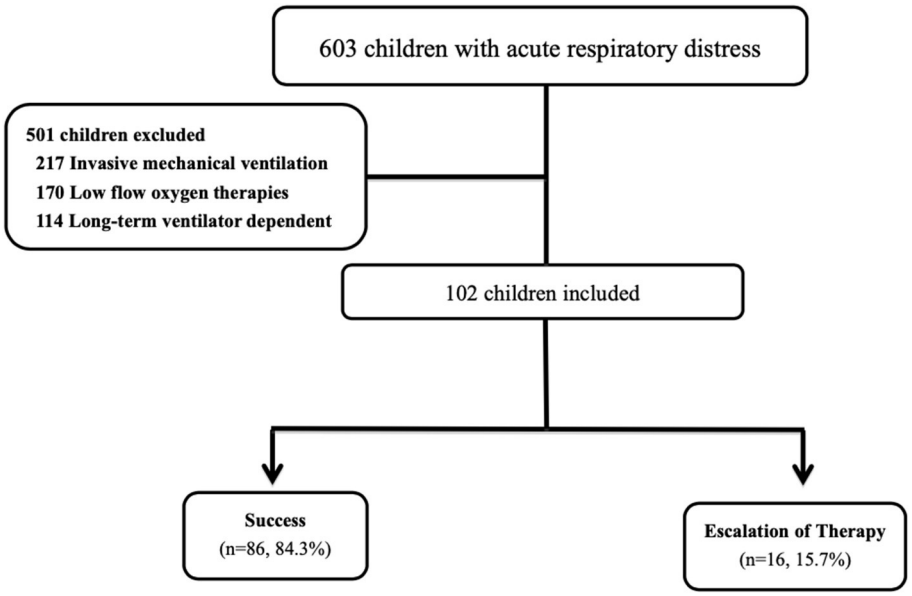

FIGURE 2 | Flowchart of the included patients. During the study period, 102 children with acute respiratory distress were managed with HFNC therapy during their pediatric ICU stay. This represented 16.9% (102 of 603) of all pediatric ICU admissions due to acute respiratory distress over the same time period. The 16 (15.7%) children needed escalation of respiratory support, including five who received non-invasive ventilation and 11 who received intubation with mechanical ventilation.

S/F ratio and ROX index score were calculated initially and every 4 h during the first 48 h after starting HFNC therapy or before stopping HFNC therapy. HFNC failure was defined as the need for escalation to non-invasive ventilation or invasive mechanical ventilation. The treating intensive care physician decided whether escalation of treatment was necessary, but it generally occurred if FiO2 > 0.6 or there was a worsening clinical state, and a similar protocol was followed in the PICU (17).

Data Collection

The following information was collected for all patients: (1) demographics and underlying medical history; (2) primary indication and respiratory infection status; (3) clinical parameters of disease severity, including heart rate, breathing rate, SpO2, venous blood gas from a central venous catheter, including pH and PCO2, as well as Pediatric Risk of Mortality (PRISM) III score, the initial and lowest level S/F ratio and the ROX index score; (4) variables after HFNC respiratory support, including initial and maximum HFNC parameters (FiO2 and flow) and duration of HFNC use; and (5) outcomes. The primary indication was defined according to the discharge summary and treatment modalities used during the ICU stay. The primary outcome was defined as success or failure of HFNC respiratory support, and the second outcome was defined as 1-month mortality, and lengths of pediatric ICU and hospital stay.

Statistical Analysis

The patients' characteristics including demographic and HFNC utilization data are presented as percentage (%) or mean ± standard deviation (SD). We divided the patients into two groups: HFNC respiratory support success, and HFNC respiratory support failure. Between-group differences were analyzed using the chi-square test or Fisher's exact test for categorical variables, and the Student's *t*-test for normally distributed continuous variables. The Mann-Whitney test was used for non-normally distributed data. Associations with outcomes between the success and failure groups were determined using univariate analysis. Receiver operating characteristic (ROC) curves for the initial and lowest S/F ratio were plotted to predict the failure of HFNC respiratory support. The respective areas under the ROC curves and cut-off values were calculated. Statistical analysis was performed using SPSS software, version 23.0 (IBM, Inc., Chicago, IL). A two-sided $p < 0.05$ was considered to be statistically significant.

RESULTS

Demographics

During the study period, 102 children with acute respiratory distress were managed with HFNC therapy during their pediatric ICU stay (**Figure 2**). This represented 16.9% (102 of 603) of all pediatric ICU admissions due to acute respiratory distress over the same time period. Fifty-seven (55.9%) of the 102 children were male, and the mean age was 7.00 ± 6.79 years. There were no significant differences in sex and age between the two groups. Seventy-eight (76.5%) of the 102 children had an underlying medical history. The most common underlying medical history was a neurologic disorder (28, 27.5%), followed by hematologic disorder/malignancy (15, 14.7%), heart disorder (13, 12.7%) and asthma/history of wheezing (7, 6.9%). The most common

indication for the use of HFNC therapy was pneumonia (40, 39.2%), followed by sepsis-related acute respiratory distress (17, 16.7%) and bronchiolitis (16, 15.7%). The initial S/F ratios were 211.87 ± 39.85 and 165.64 ± 46.49 in the success and failure groups, respectively. After disease progression, the lowest S/F ratios were 210.07 ± 41.72 and 147.43 ± 49.86, respectively. There were significant differences in the initial and lowest S/F ratios between the two groups (both $p < 0.001$). There were no other significant differences in underlying medical history, indication, PRISM III score and initial and lowest ROX index score between the two groups. The demographics of the 102 children are summarized in **Table 1**.

Etiologies of Infection

Among the 102 patients, 33 had detectable pathogens (32.3%), including 13 bacterial infections from sputum cultures (7 *Haemophilus influenzae,* 4 *Streptococcus pneumoniae*, and 2 *Staphylococcus aureus*), 13 viruses [5 *Adenovirus* Ag from throat swabs or sputum specimens, 3 *Respiratory syncytial virus (RSV)* Ag from sputum specimens, 2 *Human rhinovirus/Enterovirus* PCR, 1 *Influenza A PCR*, 1 *Influenza B* PCR from throat swabs and 1 *Parainfluenza A* from a throat virus culture] and 5 *Mycoplasma pneumonia* PCR from throat swabs. In addition, two patients had combined bacterial and viral infections (*Haemophilus influenzae* and *Respiratory syncytial virus).*

Initial and Maximum HFNC Parameters and Clinical Parameters

After starting HFNC therapy at the pediatric ICU, the initial FiO2 and flow rates were 44.92 ± 16.71% and 29.13 ± 11.75 L/min, respectively. After disease progression, the maximum FiO2 and flow rates were 46.93 ± 18.82% and 30.05 ± 12.95 L/min, respectively. The flow/body weight ratio was 1.73 ± 0.58 (L/kg). **Table 2** summarizes the details of HFNC therapy by diagnostic indication. There were no significant differences in age, therapeutic interventions during hospitalization, and lengths of stay in the pediatric ICU and hospital between the different diagnostic indications.

The evolution of the clinical parameters and blood gas after the initiation of HFNC is shown in **Table 3**. There were significant improvements in heart rate, breathing rate, pulse oximetry (SpO2), S/F ratio, and ROX index score in the early HFNC period (0.5–8 h) and late HFNC period (8–24 h). No significant differences in pH and PCO2 were observed after the initiation of HFNC in the early HFNC period, however there were significant improvements in pH in the late HFNC period (8–24 h). No air leak syndrome or epistaxis were noted with the use of HFNCs.

Outcomes

Most of the children (86 of 102, 84.3%) were successfully treated with HFNC during their pediatric ICU admission. The other 16 (15.7%) children needed escalation of respiratory support, including five who received non-invasive ventilation and 11 who received intubation with mechanical ventilation. The reasons for treatment failure were a rise in respiratory rate and desaturation in 13 (12.7%) children, and discontinuation of therapy due to discomfort in three (2.9%) children. Of the 16 cases who failed HFNC therapy, 11 (68.8%) failed during the first 24 h following the initiation of HFNC treatment. The mean time to failure was 24.38 ± 30.96 h. The overall 1-month mortality rate was 5.9% (6 of 102 children), and the lengths of stay in the pediatric ICU and hospital were 7.56 ± 6.35 and 20.08 ± 15.90 days, respectively.

Predictors of Failure

Among the data collected at baseline (**Table 1**), univariate analysis revealed that the failure group had significantly higher initial and maximum FiO2 levels than the success group (59.71 ± 21.37 vs. 42.43 ± 14.52%, $p = 0.002$; and 68.64 ± 24.20 vs. 43.27 ± 15.09%, $p < 0.001$, respectively). In addition, the initial and lowest Spo2/Fio2 ratio were also shown to be significant predictors of HFNC failure (both $p < 0.001$). The areas under the ROCs of initial and lowest S/F ratio for HFNC failure were 0.786 and 0.816, respectively, and both cut-off S/F ratio values were 212. Therefore, higher initial and maximum FiO2 levels and lower initial and lowest S/F ratio were early and possible signs of failure requiring escalation of respiratory support. However, there were no significant differences in other baseline data, including sex, age, underlying medical history, and primary indication for HFNC.

DISCUSSION

In this retrospective study, we described the use of HFNC for children with acute respiratory distress at a tertiary pediatric ICU over a 3-year period. We focused on HFNC as the first-line therapy for various etiologies of acute respiratory distress with hypoxia and for all age groups. One hundred and two patients met the eligibility criteria for the study, and the failure rate was only 15.6% (16 of 102 children). In addition, there were no cases of air leak syndrome or epistaxis with HFNC therapy, Therefore, HFNC therapy appears to be a safe and effective method of non-invasive respiratory support.

The Indications for HFNC Therapy

HFNC therapy is most commonly used for infants with acute viral bronchiolitis. However, recent studies have suggested that HFNC therapy can also be effectively and safely used in patients with a wider age range and etiologies of respiratory distress (16–25). Coletti et al. investigated the use of HFNC in 620 children with a wide range of indications in their pediatric ICU, including a significant number of subjects with status asthmaticus (41%) and congenital heart disease with respiratory distress (10%), and they reported that 10.1% of the cases needed escalation of therapy to either non-invasive ventilation or intubation with mechanical ventilation (20). In addition, Baudin et al. described 177 subjects who received HFNC therapy in a similar pediatric ICU population, including 52% with congenital heart disease, 16% with bronchiolitis, and 7% with pneumonia. They reported that HFNC therapy failure occurred in 32 cases (22%), 28 of whom required transition

TABLE 1 | Demographics of 102 children with acute respiratory distress requiring high-flow nasal cannula therapy during the study period.

Characteristics	Total $N = 102$ (%)	Success $N = 86$ (%)	Failure $N = 16$ (%)	*P*-value
Sex				
Male	57 (55.9%)	45 (52.3%)	12 (75%)	0.108
Female	45 (44.1%)	41 (47.7%)	4 (25%)	
Age group				0.093
<23 months	28 (27.5%)	26 (30.2%)	2 (12.5%)	
2–4 years	24 (23.5%)	20 (23.3%)	4 (25%)	
5–12 years	28 (27.5%)	25 (29.1%)	3 (18.8%)	
13–17 years	22 (21.6%)	15 (15.9%)	7 (43.7%)	
Underlying medical history				0.641
Previously healthy	24 (23.5%)	21 (24.4%)	3 (18.8%)	
Neurologic disorder (CP, epilepsy)	28 (27.5%)	24 (27.9%)	4 (25%)	
Hematologic disorder/malignancy	15 (14.7%)	10 (11.6%)	5 (31.3%)	
Asthma/history of wheezing	7 (6.9%)	6 (7.0%)	1 (6.3%)	
Cardiac disorder (pulmonary HTN, CHD)	13 (12.7%)	12 (14.0%)	1 (6.3%)	
Lung disorder (BPD, BO)	7 (6.9%)	6 (7.0%)	1 (6.3%)	
Other	8 (7.8%)	7 (8.1%)	1 (6.3%)	
Primary indication for HFNC				0.508
Pneumonia including aspiration	40 (39.2%)	32 (37.2%)	8 (50.0%)	
Sepsis related	17 (16.7%)	15 (17.4%)	2 (12.5%)	
Bronchiolitis	16 (15.7%)	15 (17.4%)	1 (6.3%)	
Status asthmaticus and pneumonia	5 (4.9%)	4 (4.7%)	1 (6.3%)	
Status asthmaticus	6 (5.9%)	6 (7.0%)	0 (0.0%)	
CHD with respiratory distress	9 (8.8%)	8 (9.3%)	1 (6.3%)	
Neurologic disorders, seizures	9 (8.8%)	6 (7.0%)	3 (18.8%)	
Severity of disease				
PRISM III score	7.76 ± 3.49	7.53 ± 3.40	9.36 ± 3.90	0.104
Initial S/F ratio	205.27 ± 73.73	211.87 ± 39.85	165.64 ± 46.49	<0.001*
Lowest S/F ratio	201.12 ± 48.04	210.07 ± 41.72	147.43 ± 49.86	<0.001*
Initial ROX index	6.68 ± 3.01	6.81 ± 3.14	6.00 ± 2.16	0.325
Lowest ROX index	6.11 ± 2.38	6.29 ± 2.39	5.00 ± 2.03	0.059
Initial HFNC parameters				
FiO2 (%)	44.92 ± 16.71	42.43 ± 14.52	59.71 ± 21.37	0.011*
Flow (L/min)	29.13 ± 11.75	27.86 ± 11.40	36.71 ± 11.35	0.008*
Maximum HFNC parameters				
FiO2, %	46.93 ± 18.82	43.27 ± 15.09	68.64 ± 24.20	0.002*
Flow (L/min)	30.05 ± 12.95	28.34 ± 11.94	40.28 ± 14.47	0.001*
Flow/body weight ratio (L/kg)	1.73 ± 0.58	1.77 ± 0.56	1.48 ± 0.63	0.081
Primary outcome				
Escalation of therapy	16 (15.7%)	–	16 (15.7%)	
Transition to non-invasive ventilation	5 (4.9%)	–	5 (4.9%)	
Tracheal intubation	11 (10.8%)	–	11 (10.8%)	
Duration of HFNC (hours)	65.35 ± 75.45	71.55 ± 78.31	24.38 ± 30.96	0.035*
Secondary outcome				
1-month mortality	6 (5.9%)	0	6 (5.9%)	<0.001*
PICU LOS (days)	7.56 ± 6.35	7.19 ± 6.08	9.60 ± 7.59	0.178
Hospital LOS (days)	20.08 ± 15.90	19.44 ± 15.69	23.86 ± 17.22	0.339

*HFNC, high-flow nasal cannula; CP, cerebral palsy; HTN, hypertension; CHD, congenital heart disease; BPD, bronchopulmonary dysplasia; BO, bronchiolitis obliterans; PRISM, Pediatric Risk of Mortality; S/F ratio, SpO2/FiO2 ratio; FiO2, fraction of inspiration O2; PICU, pediatric intensive care unit; LOS, length of stay. *Statistically significant ($P < 0.05$).*

TABLE 2 | High-flow nasal cannula use by diagnostic indication.

Primary indication for HFNC	*n* (%)	Age (years)	Receiving HFNC (hours)	Peak FiO2 (%)	Peak Flow (L/min)	Peak Flow/kg (L/kg)	PICU LOS (days)	Hospital LOS (days)
Pneumonia including aspiration	42 (39.2%)	8.11 ± 7.28	73.85 ± 98.00	43.84 ± 15.60	31.75 ± 11.88	1.76 ± 0.54	7.33 ± 5.35	19.08 ± 13.50
Sepsis-related	17 (16.7%)	8.71 ± 5.56	89.81 ± 87.63	57.37 ± 26.51	36.06 ± 11.86	1.67 ± 0.61	10.69 ± 9.06	34.73 ± 21.26
Bronchiolitis	16 (15.7%)	1.29 ± 1.06	53.47 ± 29.17	39.53 ± 8.64	16.80 ± 7.08	1.99 ± 0.51	5.94 ± 3.45	14.25 ± 11.47
Status asthmaticus with pneumonia	5 (4.9%)	3.58 ± 3.29	57.00 ± 35.19	41.40 ± 4.72	23.20 ± 7.98	1.89 ± 0.65	6.20 ± 3.11	10.00 ± 5.19
Status asthmaticus	6 (5.9%)	2.28 ± 1.90	43.83 ± 33.07	44.66 ± 22.84	28.33 ± 4.08	2.16 ± 0.23	3.50 ± 1.76	10.50 ± 11.07
CHD with respiratory distress	9 (8.8%)	12.50 ± 8.77	43.44 ± 29.29	54.62 ± 14.72	38.63 ± 20.30	1.36 ± 0.60	12.25 ± 10.08	29.13 ± 15.65
Neurologic disorders, seizures	9 (8.8%)	8.58 ± 6.09	42.25 ± 42.53	52.50 ± 26.99	31.37 ± 8.91	1.15 ± 0.49	5.11 ± 4.34	13.50 ± 9.91
Total	102 (100%)	7.00 ± 6.79	65.35 ± 75.45	46.93 ± 18.82	30.05 ± 12.95	1.73 ± 0.58	7.56 ± 6.35	20.08 ± 15.90

PICU, pediatric intensive care unit; LOS, length of stay; HFNC, high-flow nasal cannula; CHD, congenital heart disease.

TABLE 3 | Evolution of clinical parameters and blood gas after initiating high-flow nasal cannula therapy.

Parameters	Baseline (Before HFNC)	Early HFNC Period (0.5–8 h)†	*P*-value§	Late HFNC period (8–24 h)‡	*P*-value§
Clinical parameters					
Heart rate (beats/min)	142 (124–157)	125 (110–142)	<0.001*	128 (107–144)	<0.001*
Breathing rate (breaths/min)	31 (24–41)	28 (24–33)	0.003*	28 (23–37)	0.001*
SpO2 (%)	92 (89–94)	99 (96–100)	0.008*	99 (95–100)	<0.001*
S/F ratio	230 (188–235)	295.5 (244.5–333.0)	<0.001*	291 (250–333)	<0.001*
ROX index	6 (5–8)	11 (6.75–13.25)	<0.001*	10 (7–13)	<0.001*
Venous blood gas					
pH	7.38 (7.34–7.43)	7.40 (7.36–7.44)	0.330	7.39 (7.33–7.45)	0.023*
PCO2 (mmHg)	40.00 (35.10–47.60)	41.5 (36.40–49.57)	0.133	42.75 (36.95–48.57)	0.133

Data are presented as median (IQR); IQR, interquartile range; HFNC, high-flow nasal cannula; h, hours; SpO2, pulse oximetry; S/F ratio, SpO2/FiO2 ratio.
**P < 0.05: statistically significant.*
† Early HFNC period data correspond to the severe values observed between 0.5 and 8 h after HFNC initiation.
‡ Late HFNC period data correspond to the severe values observed between 8 and 24 h after HFNC initiation.
§ Significant difference between baseline and early HFNC period and between baseline and late HFNC period.

to non-invasive ventilation, and five required endotracheal intubation (21). Kelly et al. also reported the use of HFNC therapy in 496 children with respiratory distress in the emergency department, including 46% with bronchiolitis, 28% with pneumonia and 8% with asthma. They reported that 8% of the cases failed therapy and required intubation with mechanical ventilation following HFNC therapy (22). In our study, we also used HFNC therapy for patients with a wide range of diagnoses, including a significant number with pneumonia (39.2%), sepsis-related respiratory distress (16.7%), and acute bronchiolitis (15.7%). Of our patients, 15.7% needed escalation of therapy to either non-invasive ventilation or intubation with mechanical ventilation.

The Risk Factors for Escalation of Therapy With the Use of HFNC Therapy

In clinical practice, it is important to have an objective method to determine if HFNC therapy is working or not. Roca et al. proposed an easy bedside tool using SaO2, FiO2 and respiratory rate to predict the success or failure of HFNC therapy, known as the ROX index (26). The authors found that a higher ROX index score was associated with HFNC success at all time points analyzed, and they concluded that a ROX index value of $\geq$ 4.88 at 12 h after the initiation of HFNC therapy was significantly associated with HFNC success. However, in children, predicting success using the ROX index can be much more difficult, because the respiratory rate can vary with age (27). In our study, there

were no significant differences in initial and lowest ROX index scores between the two groups.

To date, few studies have assessed the risk factors for escalation of therapy to either non-invasive ventilation or intubation with mechanical ventilation, because most of the patients included in these studies have had a variety of indications and did not have severe forms of acute respiratory distress. Kelly et al. reported that failure occurred in the more critical children who presented to the pediatric emergency department with a triage respiratory rate greater than the 90th percentile for age, initial venous PCO2 >50 mm Hg and pH >7.30 (significant respiratory acidosis). A diagnosis of acute bronchiolitis seemed to be protective with respect to intubation following HFNC therapy (22). Kamit et al. reported that a lower SpO2/FiO2 (S/F) ratio at admission was a predictor of HFNC failure, and that achieving S/F > 200 at 60 min significantly predicted successful HFNC therapy (23). Betters et al. also reported that high FiO2 requirement, history of intubation, and cardiac co-morbidities were predictors of HFNC failure (24). Abboud et al. retrospectively analyzed children with viral bronchiolitis who failed HFNC (needing intubation) compared to children who were successfully treated with HFNCs, and found that improved respiratory rate and clearance of repeat pCO2 were predictors of success (25). In our study, higher initial and maximum FiO2 levels and lower initial and lowest S/F ratio were early and possible signs of failure requiring escalation of respiratory support. Therefore, these findings may help guide clinicians who would prefer to use HFNC therapy and avoid a delay in escalating therapy to either non-invasive ventilation or intubation with mechanical ventilation in children at a higher risk of failing HFNC therapy.

Limitations

There are some limitations to this study. First, this is a retrospective study with a limited cohort of children with acute respiratory distress receiving HFNC therapy at a single center. However, very few reports in the pediatric literature have reported HFNC therapy as initial respiratory support in children with acute respiratory distress, especially for pneumonia and sepsis-related respiratory distress. Experience with HFNC therapy for this indication is particularly lacking, and this is a strength of this study. Second, because few studies have assessed the use of HFNCs and the risk of intubation in children, there is low evidence or no guidelines for the escalation of treatment to CPAP or intubation. In our study, the criteria of escalating therapy from HFNC to either non-invasive ventilation or intubation with mechanical ventilation are different in different clinical scenarios. This may have influenced the failure rate, which may limit comparisons with other studies in this field. Third, broad age groups with a small number of cases may further limit the findings of this study. Fourth, in our study, most of the severe cases (217 of 501, 43.3%) of respiratory failure were not initially treated with HFNCs, but received invasive mechanical ventilation. Only 11 patients with borderline moderate to severe respiratory failure initially received HFNC therapy, and they were finally intubated. Because HFNC therapy is being increasingly used in our hospital, the overenthusiastic use leading to delayed intubation cannot be ruled out in this study. Fifth, HFNC has been reported to fail to offer adequate PEEP, even at higher flows, for patients with moderate to severe acute respiratory distress syndrome (28). In our study, FiO2 requirement (initial or maximum) > 60% was a predictor of HFNC failure. The safety and effectiveness of providing high FiO2 (>60%) with HFNCs without adequate PEEP, given the risk of oxygen-induced lung damage at high concentrations must be considered.

CONCLUSIONS

HFNC was used frequently over the 3-year study period for children with a wide range of ages and for a variety of indications. We found that HFNC could be initiated as the first-line therapy all age groups of children with various etiologies of acute respiratory distress in our pediatric ICU. Further prospective studies are needed to confirm the efficacy of HFNC therapy and to evaluate the risk factors of failure in different settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Chang Gung Memorial Hospital Institutional Review Board (IRB number: 201801252B0C502 and 201901701B0). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

C-CC and J-JL: conceptualization and writing—original draft preparation. S-HH, Y-CL, and O-WC: methodology. O-WC: software. J-JL and O-WC: formal analysis. Y-CL, T-CC, O-WC, and E-PL: data curation. J-JL: writing—review and editing. J-JL and S-HH: supervision. All authors contributed to the article and approved the submitted version.

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Nasotracheal vs. Orotracheal Intubation and Post-extubation Airway Obstruction in Critically Ill Children: An Open-Label Randomized Controlled Trial

Vijay Kumar, Suresh Kumar Angurana, Arun Kumar Baranwal and Karthi Nallasamy*

Division of Pediatric Critical Care, Department of Pediatrics, Advanced Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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***Correspondence:**
Suresh Kumar Angurana
sureshangurana@gmail.com

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Background: The data on long-term nasotracheal intubation among mechanically ventilated critically ill children is limited. The purpose of this study was to compare the rate of post-extubation airway obstruction (PEAO) with nasotracheal and orotracheal intubation.

Methods: This open-label randomized controlled trial was conducted in PICU of a tertiary care and teaching hospital in North India from January-December 2020 involving intubated children aged 3 months−12 years. After written informed consent, children were randomized into nasotracheal and orotracheal intubation groups. Post-extubation, modified Westley's croup score (mWCS) was used at 10-timepoints (0-min, 30 min, 1, 2, 3, 6, 12, 24, 36, and 48-h after extubation) to monitor for PEAO. The primary outcome was the rate of PEAO; and secondary outcomes were time taken for intubation, number of intubation attempts, complications during intubation, unplanned extubation, repeated intubations, tube malposition/displacement, endotracheal tube blockade, ventilator associated pneumonia, skin trauma, extubation failure/re-intubation, duration of PICU stay, and mortality.

Results: Seventy children were randomized into nasotracheal ($n = 30$) and orotracheal ($n = 40$) groups. Both the groups were similar in baseline characteristics. The rate of PEAO was similar between nasotracheal and orotracheal groups (10 vs. 20%, $p = 0.14$). The maximum mWCS and mWCS at 10-timepoints were similar in two groups. The time taken for intubation was significantly longer (85 vs. 48 s, $p < 0.001$) in nasotracheal group, whereas other secondary outcomes were similar in two groups.

Conclusion: The rate of PEAO was not different between nasotracheal and orotracheal groups.

Clinical Trial Registration: http://ctri.nic.in, Identifier: CTRI/2020/01/022988.

Keywords: post-extubation stridor, extubation, airway edema, reintubation, post-extubation airway obstruction, nasotracheal intubation

INTRODUCTION

Endotracheal intubation is commonly performed intervention in critically ill children to provide mechanical ventilation in emergency rooms (ERs) and Pediatric intensive care units (PICUs). Orotracheal and nasotracheal intubation are two modes with their own advantages and disadvantages (1–3). Orotracheal intubation is generally preferred and commonly used as it is easier, quicker especially during emergent intubations, and less painful (1, 2). Nasotracheal intubation is commonly used in operating rooms especially during dental, oropharyngeal, and maxillofacial surgeries as it is easier to ventilate the patient and administer anesthetic gases without limiting access to oral cavity and oropharynx (1, 2). Nasotracheal intubation has several advantages as it is easier to secure; moves less, if secured properly; lesser risk of trauma to lips, tongue and larynx; lesser chances of unplanned extubation; more patient comfort; and possibly lower rate of post-extubation airway obstruction (PEAO) (1, 2). However, nasotracheal intubation can cause injury (to nose, turbinate, and nasopharynx), bleeding, and increases the risk of sinusitis (1, 2, 4–10). As nasotracheal intubation is technically challenging and associated with more complications, it is recommended that it should be performed by skilled healthcare providers (1, 2). Due to these reasons, nasotracheal intubation is less commonly practiced (2–5.6% of all endotracheal intubations) among adults and children undergoing mechanical ventilation in ICUs (2, 5, 11–15).

Few studies involving critically ill children on mechanical ventilation documented lower rate of unplanned extubation in nasotracheal group than in orotracheal intubation group (11, 16–18). However, the literature on the long-term nasotracheal intubation among mechanically ventilated critically ill children and its impact on PEAO is not available, despite the theoretical benefits of nasotracheal intubation. Therefore, we conducted this study to compare the nasotracheal and orotracheal routes of endotracheal intubation among mechanically ventilated critically ill children and compared the rate of PEAO between the two groups.

METHODOLOGY

This open-label randomized controlled trial was conducted in a 15-bedded PICU of a tertiary care teaching hospital in North India over a period of 1 year (January 2020 to December 2020) including children aged 3 months−12 years with endotracheal intubation and invasive mechanical ventilation. The children with tracheostomy, raised intracranial pressure, severe acute respiratory distress syndrome (ARDS), refractory septic shock, remained intubated in ER for >24 h, referred intubated to ER from peripheral hospitals, anticipated intubation <24 h, cases requiring re-intubation after one episode of mechanical ventilation, known bleeding disorder, recent nasal surgery or trauma or burns, previous history of epistaxis, chronic lung disease, congenital heart disease, and with nasal and other facial malformation were excluded. The study protocol was approved by the Institute Ethics Committee (PGI/IEC/2019/002796, dated 28-12-2019) and registered with the Clinical Trials Registry-India (CTRI/2020/01/022988). The written informed consent was obtained from the parents/legal guardian before enrolment.

Randomization

Patients were enrolled on the day of admission to PICU or whenever intubation was performed in PICU. The eligible children were randomized into 2 groups (nasotracheal orotracheal intubation groups) by using computer generated randomization table. The slips mentioning the group were placed in serially numbered, sealed, and opaque envelops which were opened at the time of randomization by the primary investigator (VK).

Intubation Procedure

In our unit, we routinely perform orotracheal intubation. Children randomized to nasotracheal group were re-intubated through the nasal route. The primary investigator and senior residents working in the unit were trained in performing orotracheal and nasotracheal intubation. The standard protocol was followed to perform orotracheal and nasotracheal intubation. Adequate sedation, analgesia, and neuromuscular blockade (if needed) were used. Children were pre-oxygenated with bag and mask ventilation. The size (in mm) of endotracheal tube (ETT) was calculated as per the standard formulae for uncuffed (Age in years/4 + 4) and cuffed tube (Age in years/4 + 3.5). The length (in cm) of insertion of ETT was calculated as ETT size x 3 or Age in years/2 + 12 for orotracheal intubation and Age in years/2 + 15 for nasotracheal intubation (1, 19). We used micro-cuffed endotracheal tubes in all cases.

For nasotracheal intubation, the lidocaine jelly (as local anesthetic and lubricant) was applied to the nasal cavity and ETT prior to intubation. The ETT was then passed through nares into nasopharynx under direct laryngoscopy. Once it reached nasopharynx, it was guided into the glottic opening by using Magill's forceps (1, 2). During the procedure, oxygen saturation and heart rate was monitored continuously and time taken for intubation (in seconds) was recorded. The appropriate position of ETT was confirmed by clinical examination (auscultation over stomach and bilateral axilla) and later on by the chest radiograph, as per routine in the unit. The ETT was secured by the using dynaplast. For orotracheal intubation, one strip of dynaplast was pasted to the upper lip and another E-shaped strip was used to secure tube to upper and lower lip. For nasotracheal intubation, one strip of dynaplast was pasted to upper lip and another-Y-shaped strip was used to secure tube to upper lip. Any repositioning of the ETT after intubation was also documented.

General Care

All children were managed and monitored as per unit's existing protocol for management of critically ill children for intubation, mechanical ventilation, sedation and analgesia, hemodynamic monitoring and treatment, nutrition, nursing support, weaning, extubation, and post-extubation care. Routine nursing care was provided in form of strict aseptic precautions, minimal handling, proper fixation of tube, clustering of interventions, and frequent position changes (if not contraindicated). The suction

of endotracheal tube was done every 4–6-h or whenever needed. Enteral feeding was started as soon as possible, preferably within 24 h of admission to the PICU. Among children intubated for >48 h, six dosage of dexamethasone (0.5 mg/kg/dose) were used peri-extubation, with first dose given 24 h prior to extubation (20, 21). Feeding was withheld for 6 h prior to extubation and 4–6 h after extubation.

Post-extubation Monitoring

We used modified Westley's croup score (mWCS) to monitor for PEAO at 10-timepoints (0-, 30-min, 1, 2, 3, 6, 12, 24, 36, and 48-h after extubation) (**Supplementary Table 1**) (20, 22, 23). A mWCS ≥4 suggested administration of adrenaline nebulization (1 mg/ml; 2.5 ml in 2.5 ml saline every 20 min until improvement). The re-intubation (by oronasal route) was performed if there was no response after adrenaline nebulization as evident by audible stridor, marked decreased air entry, severe chest indrawing and/or respiratory acidosis (pH < 7.35 and $PaCO_2$ > 45 mmHg), SpO_2 < 90% at FiO_2 > 40%, bradycardia, or other clinical sign of impending respiratory failure, or mWCS of 7 (extubation failure) (20).

Data Collection

Baseline data (age, sex, diagnosis), admission Glasgow Coma Scale (GCS), pediatric risk of mortality III (PRISM III) score, maximum vasoactive inotropic score (VIS), and sequential organ failure assessment (SOFA) score on day 1, 2, and 7 were noted. Time taken for intubation, number of intubation attempts, complications during intubation (hypoxemia, bradycardia, hypotension or cardiac arrest), unplanned or accidental extubation, repeated intubations, tube malposition or displacement, ETT blockade, skin trauma related to ETT, epistaxis, sinusitis, healthcare associated infections (HCAIs), ventilator associated pneumonia (VAP), post-extubation atelectasis, extubation failure/reintubation, duration of intubation, duration of PICU stay, and final outcome (survival or death) were recorded.

Definitions

The clinically significant *PEAO* was defined as mWCS ≥ 4. *Time taken for intubation* was defined as period from stopping the bag and mask ventilation to starting positive pressure ventilation after insertion of ETT. *Intubation failure* was considered if there was bradycardia (heart rate < 60/min) and/or desaturation (SPO_2 < 90%) or both during the intubation attempt. *Numbers of intubation attempts* defined as number of times procedure was aborted and requiring re-oxygenation and another attempt to intubate. The standard definitions were used for *Sepsis and severe sepsis* (24), and *VAP* (25). The skin trauma related to ETT was classified as per the standardized classification of decubitus lesions by the US National Pressure Ulcer Advisory Panel (NPUAP) (26).

Outcomes

The primary outcome was the rate of PEAO among children in nasotracheal and orotracheal groups. Secondary outcomes were time taken for intubation, number of intubation attempts, complications during intubation, unplanned extubation, repeated intubations, tube malposition/displacement, ETT blockade, VAP, skin trauma related to ETT (injury to skin, nostrils, nasal septum, lip, or tongue), extubation failure/reintubation, duration of PICU stay, and survival or death.

DATA ENTRY AND STATISTICAL ANALYSIS

The sample size was calculated based on the incidence of PEAO (32.8–34%) documented in previous studies from our PICU (21, 23). As a superiority trial, with the incidence of PEAO in nasotracheal group as 15% and β-error of 0.2, the required sample size was 90 cases in each group ($n = 180$).

However, in view of COVID-19 situation, the number of admissions to the PICU and those underwent mechanical ventilation were reduced (585 admissions during study period as compared to 900-100 admissions per year in normal times), leading to slower recruitment. The study was stopped after the end of the study period (with enrolment of 70 cases) as it was a dissertation project of a Pediatric Critical Care Fellow (VK), and the dissertations are time bound in our institute. The Dean of the institute approved to go ahead with the sample size of 70 (letter no. 12396/1TRG/PG-2019/15029, dated 16/12/2020).

Data entry and statistical analysis were performed using Microsoft Excel 2013 (Microsoft, Redmond, WA) and SPSS software version 21(IBM Corp. 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Descriptive

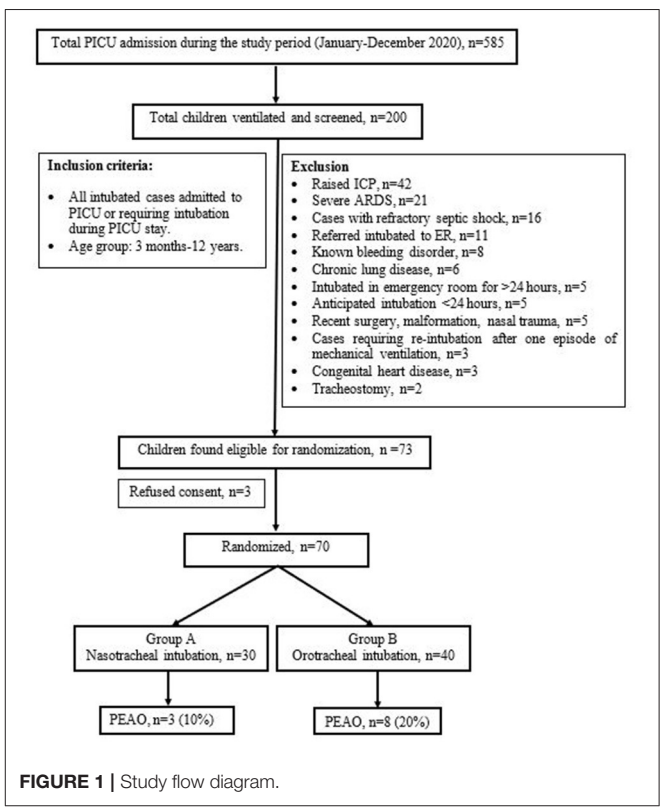

FIGURE 1 | Study flow diagram.

TABLE 1 | Baseline characteristics and severity scores among children in nasotracheal and orotracheal intubation groups.

Patient characteristics	Total ($n = 70$)	Nasotracheal ($n = 30$)	Orotracheal ($n = 40$)	*P*
Male, *n* (%)	41 (58.6)	19 (63)	22 (55)	0.48
Age (month); median (IQR)	36 (12–96)	42 (21–133)	30 (11–85)	0.73
Diagnosis				
Snake envenomation, *n* (%)	13 (18.6)	9 (30)	4 (10)	0.12
Metabolic disorders, *n* (%)	9 (12.9)	4 (13.3)	5 (12.5)	
Sepsis, *n* (%)	8 (11.4)	2 (6.7)	6 (15)	
LGBS, *n* (%)	8 (11.4)	3 (10)	5 (12.5)	
CNS infections, *n* (%)	7 (10)	3 (10)	4 (10)	
Scrub typhus, *n* (%)	7 (10)	2 (6.7)	5 (12.5)	
Poisoning, *n* (%)	7 (10)	3 (10)	4 (10)	
ARDS, *n* (%)	5 (7.1)	1 (3.3)	4 (10)	
Disseminated Staphylococcal sepsis, *n* (%)	2 (2.9)	0	2 (5)	
Electrocution, *n* (%)	2 (2.9)	1 (3.3)	1 (2.5)	
Dengue shock syndrome, *n* (%)	1 (1.4)	1 (3.3)	0	
Tetanus, *n* (%)	1 (1.4)	1 (3.3)	0	
Site of intubation prior to enrolment				0.84
ER, *n* (%)	60 (85.7)	26 (86.7)	34 (85)	
PICU, *n* (%)	10 (14.3)	4 (13.3)	6 (15)	
GCS at admission, median (IQR)	8 (6–10)	7 (5–10)	9 (8–12)	0.02
PRISM III Score, median (IQR)	13 (9–20)	12 (9–15)	16 (11–20)	0.09
Maximum VIS score, median (IQR)	50 (20–62)	43 (13–53)	50 (21–65)	0.73
SOFA score, median (IQR)				
Day 1	6 (4–9)	5 (2–6)	8 (4–9)	0.07
Day 2	3 (2–8.5)	3 (2–4.2)	4 (2–9)	0.07
Day 7	1 (0–2)	1 (0–2)	1 (0–5)	0.42

statistics [mean (SD), median (IQR), range, number, and percentages] were used for baseline variables. Dichotomous outcomes were compared by chi-square test or Fisher's exact-test, as applicable. Continuous variables were compared by Student *t*-test or Mann–Whitney *U*-test. The repeated measure analysis of variance (RM-ANOVA) was used to compare mWCS between 2 groups over 10-timepoints. All tests used were two-tailed and p-value < 0.05 was taken as significant.

RESULTS

During the study period, there were 585 admissions to the PICU, 200 (34.2%) were ventilated, and 70 were randomized to nasotracheal ($n = 30$) and orotracheal ($n = 40$) groups (**Figure 1**).

Baseline Characteristics

There were 58.7% ($n = 41$) males with median (IQR) age of 36 (12–96) months. The most common diagnosis included snake envenomation (18.6%), metabolic disorder (12.9%), sepsis (11.4%), Landry-Guillain-Barre syndrome (11.4%), central nervous system infections (10%), Scrub typhus (10%), poisoning (10%), and ARDS (7.1%). The initial orotracheal intubation was performed in ER among 85.7% cases and in PICU among 14.3% cases. Later, the cases in nasotracheal group were extubated and reintubated through the nasal route. The median GCS at admission was 8 (6–10), PRISM-III score was 13 (9–20), and maximum VIS score was 50 (20–62). The SOFA score on day 1, 2, and 7 were 6 (4–9), 3 (2–8.5), and 1 (0–2), respectively. Both the groups were comparable as far as baseline variables are concerned. However, children in nasotracheal group had lower GCS at admission ($p = 0.02$) (**Table 1**).

Primary Outcome

The overall rate of PEAO was 15% ($n = 11$). The rate of PEAO in nasotracheal and orotracheal groups was 10% ($n = 3$) and 20% ($n = 8$), respectively ($p = 0.14$). The maximum mWCS [mean (SE)] was 1.81 (0.25) and it was comparable in nasotracheal and orotracheal groups [1.62 (0.38) vs. 1.98 (0.33), respectively, $p = 0.47$] (**Table 2**). The serial mWCS in the first 48 h following extubation was also similar in two groups (**Table 2**; **Figure 2**). The RM-ANOVA showed no significant difference in mWCS between 2 groups over 10-timepoints ($p = 0.53$, Wilks Lambda Test).

Secondary Outcomes

The overall time taken [median (IQR)] for intubation was 60 (47–85) s and it was significantly higher in nasotracheal group as compared to orotracheal group [85 (75–90) s vs. 48 (45–60) s, respectively, $p < 0.001$]. Other outcomes like children requiring

TABLE 2 | Primary outcomes in nasotracheal and orotracheal intubation groups.

Outcome parameter	Total ($n = 70$)	Nasotracheal ($n = 30$)	Orotracheal ($n = 40$)	*P*-value
Post-extubation airway obstruction, n (%)	11 (15.7)	3 (10)	8 (20)	0.14
Maximum Westley Croup Score (m WCS), mean (SE)	1.81 (0.25)	1.62 (0.38)	1.98 (0.33)	0.47
WCS, mean (SE)				
0 min	1.17 (0.18)	0.96 (0.21)	1.32 (0.27)	0.32
30 min	1.16 (0.22)	0.97 (0.24)	1.3 (0.33)	0.45
1 h	1 (0.23)	0.87 (0.31)	1.1 (0.03)	0.61
2 h	0.48 (0.14)	0.38 (0.16)	0.56 (0.22)	0.53
3 h	0.23 (0.09)	0.27 (0.13)	0.26 (0.12)	0.94
6 h	0.49 (0.18)	0.44 (0.26)	0.52 (0.26)	0.83
12 h	0.27 (0.13)	0.25 (0.22)	0.29 (0.18)	0.88
24 h	0.21 (0.1)	0.13 (0.11)	0.29 (0.16)	0.37
36 h	0.29 (0.15)	0.07 (0.07)	0.45 (0.25)	0.23
48 h	0.13 (0.79)	0.21 (0.05)	0.08 (0.03)	0.48

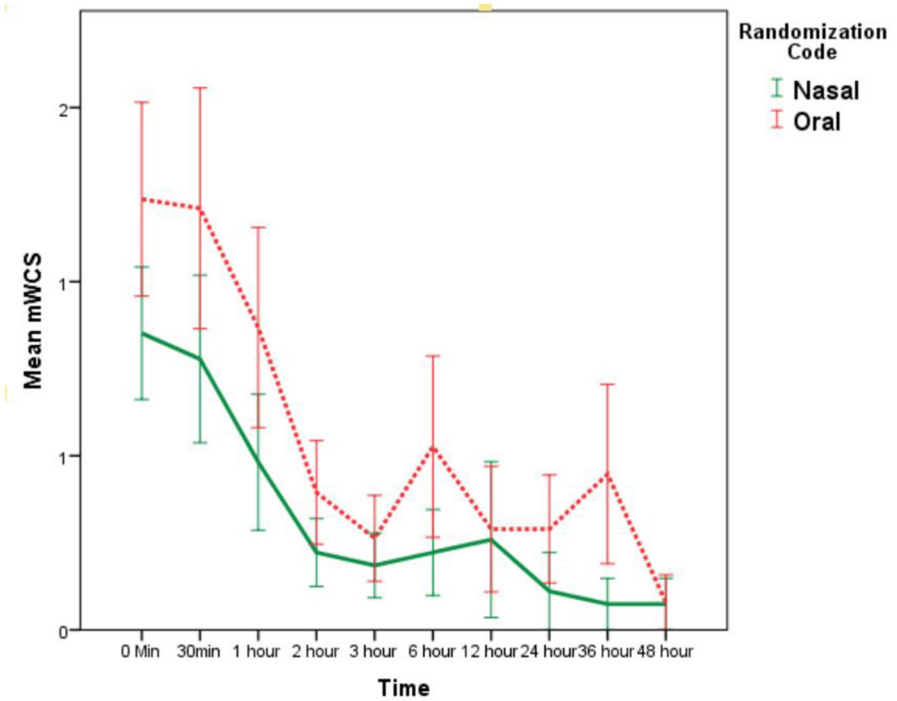

FIGURE 2 | mWCS [mean (SE)] in nasotracheal and orotracheal intubation groups at different time points after extubation.

>1 intubation attempt (10 vs. 2.5%), complications during intubation (3.3 vs. 2.5%), unplanned extubation (10 vs. 15%), repeated intubation (10 vs. 15%), tube malposition/displacement (6.7 vs. 5%), ETT blockade (0 vs. 7.5%), skin trauma (10 vs. 5%), VAP (6.7 vs. 5%), duration of intubation (6.5 vs. 7 days), adrenaline nebulization (10 vs. 20%), post-extubation atelctasis (10 vs. 0%), type of post-extubation respiratory support, extubation failure/reintubation (6.7 vs. 8.5), duration of PICU stay (7.5 vs. 9 days), and mortality (6.7 vs. 12.5%) were similar in two groups (**Table 3**). The time of onset of PEAO in two groups was also similar ($p = 0.22$, Log Rank test).

DISCUSSION

In this open-label RCT, we noted that in critically ill children undergoing mechanical ventilation, the rate of PEAO (10 vs. 20%) and maximum mWCS (1.62 vs. 1.98) were similar in nasotracheal and orotracheal intubation groups. The serial mWCS was also similar in two groups during the first 48 h after extubation. The rate of PEAO (15%) in the index study was within the range of the documented rates of PEAO among critically ill children (18–40%) (20, 23, 27–29). However, the rate of PEAO in index study was lower than the reported rates of

TABLE 3 | Secondary and final outcomes in nasotracheal and orotracheal intubation groups.

Outcome parameter	Total ($n = 70$)	Nasotracheal ($n = 30$)	Orotracheal ($n = 40$)	*P*-value
Time taken for intubation (seconds); median (IQR)	60 (47–85)	85 (75–90)	48 (45–60)	<0.001
Intubation attempts >1, *n* (%)	4 (5.7)	3 (10)	1 (2.5)	0.18
Complication during Intubation Hypoxia/Bradycardia, *n* (%)	2 (2.8)	1 (3.3)	1 (2.5)	0.84
Unplanned extubation, *n* (%)	9 (12)	3 (10)	6 (15)	0.54
Repeated intubation, *n* (%)	9 (12)	3 (10)	6 (15)	0.28
Tube malposition/displacement, *n* (%)	4 (5.7)	2 (6.7)	2 (5)	0.77
Endotracheal tube blockade, *n* (%)	3 (4.2)	0 (0)	3 (7.5)	0.13
Skin trauma related to ETT, *n* (%)	5 (7.1)	3 (10)	2 (5)	0.42
VAP, *n* (%)	3 (4.3)	2 (6.7)	1 (5)	0.14
Duration of intubation, median (IQR)	7 (3–13)	6.5 (3–13)	7 (3–13)	0.81
Adrenaline nebulization, *n* (%)	11 (15.7)	3 (10)	8 (20)	0.14
Post-extubation atelectasis, *n* (%)	3 (4.3)	3 (10)	0 (0)	0.08
Post-extubation respiratory support				
Nasal prongs, *n* (%)	14 (20)	6 (20)	8 (20)	0.62
Nasal CPAP, *n* (%)	29 (41.4)	15 (50)	14 (35)	
BiPAP, *n* (%)	13 (18.7)	5 (16.7)	8 (20)	
High flow nasal cannula, *n* (%)	2 (2.8)	1 (3.0)	1 (1.4)	
Extubation failure *n* (%)	5 (7.1)	2 (6.7)	3 (7.5)	1
Duration of PICU stay, median (IQR)	8 (5–13)	7.5 (4.7–14)	9 (5–13)	0.77
Death, *n* (%)	7 (10)	2 (6.7)	5 (12.5)	0.69

PEAO in the recent studies from our unit (32.8–34%) (21, 23). The lower rate of PEAO could be due to the fact that we used micro-cuffed endotracheal tubes (high-volume-low-pressure) in all cases as these were routinely available from the hospital supply during the study period. The use of micro-cuffed ETT may had led to lesser movement of ETT, lesser chances of unplanned extubation or ETT change, lower risk of laryngeal edema, and hence lower rates of PEAO (15, 30, 31). None of the Pediatric studies looked into the impact of nasotracheal intubation on the rate of PEAO, time taken for intubation, unplanned extubation, extubation failure, and other important clinical outcomes (duration of PICU stay and mortality).

We noted that the nasotracheal intubation took more time than the orotracheal intubation, as it is technically more complex. However, other outcomes like children requiring >1 intubation attempt, complications during intubation, unplanned extubation, repeated intubation, tube malposition/displacement, ETT blockade, skin trauma, VAP, duration of intubation, adrenaline nebulization, post-extubation atelctasis, post-extubation respiratory support, extubation failure, duration of PICU stay, and mortality were similar in two groups. Previous studies also demonstrated that time taken for nasotracheal intubation was significantly longer than orotracheal intubation among critically ill adults and children (32–34). Also, nasotracheal intubation when compared to orotracheal intubation was associated with more changes in heart rate and blood pressure in early post-intubation period (33); need of more number of additional providers, more intubation attempts, and more traumatic intubations (34).

The literature on the outcome of long-term nasotracheal intubation in children on mechanical ventilation is limited. Spence and Barr (35) conducted a systematic review involving 2 randomized trials that compared nasal vs. oral intubation in neonates requiring mechanical ventilation and demonstrated that there were no differences between the orotracheal and nasotracheal route of intubation. One study noted higher rate of intubation failure using the nasal route; and one noted higher rates of post-extubation atelectasis in nasally intubated neonates weighing <1,500 g. The rates of ETT malposition, accidental extubation, tube blockage, re-intubation after extubation, septicemia, clinical infection, and local trauma were similar between two groups. Recently, Christian et al. (11) published a retrospective cohort study (January 2015 to December 2016) involving 121 PICUs in the United States and noted that 53% ($n = 64$) of PICUs had zero nasotracheal intubations during the study period. Out of 12,088 endotracheal intubations, only 5.6% ($n = 680$) were nasotracheal. Among nasotracheal group, the rate of unplanned extubation was significantly less as compared to orotracheal group (0.9 vs. 2.9%, $p < 0.001$). However. The rates of sinusitis and VAP were similar in two groups. Among children in nasotracheal group, majority were <2 years (88.1%), and 82.2% were classified as cardiac cases. Among young cardiac cases, the rate of unplanned extubation was significantly lower in nasotracheal group as compared to orotracheal group (0 vs. 2.1%, $p < 0.001$).

Unplanned extubation is one of the serious adverse events noted in cases with endotracheal intubation and associated with increased mortality, duration of mechanical ventilation,

and ICU stay (16, 18, 36, 37). As ETT is well-secured with nasotracheal intubation, the chances of unplanned extubation are lesser, which has been demonstrated among adults and children (17, 38, 39). However, Piva et al. (40) demonstrated that among children in PICU, the rate of unplanned extubation was similar in orotracheal and nasotracheal group (3.1 vs. 1.6%, respectively, $p = 0.06$). Nasotracheal ETT can lead to blockage of drainage of paranasal sinuses, local trauma, edema, and local infection of nasal mucosa which can leads to sinusitis. The nasotracheal intubation has been identified as an important risk factor for sinusitis among adults and children (5–10). Moreover, the sinusitis can evolve into sepsis, bacteremia, and VAP (41). The rate of unplanned extubation was similar in two groups in the index study and none had sinusitis.

Strength and Limitations

This is the first RCT that compared the nasotracheal vs. orotracheal route of endotracheal intubation in critically ill children receiving invasive mechanical ventilation. All enrolled cases were analyzed for the final outcome. We uniformly used micro-cuffed ETT in all cases. The limitations of this study include open-label trial as blinding of treating team and patients was not possible. The setting during endotracheal intubation was different in two groups, ER (in most cases) in orotracheal group and PICU in nasotracheal group, which is more of a controlled environment. In our units (ER and PICU), all cases underwent endotracheal intubation through orotracheal route first as per the routine practice. Children randomized to nasotracheal route were extubated and then re-intubation through nasal route. Hence, we could not enroll cases before endotracheal intubation and then randomizing them directly to orotracheal or nasotracheal groups. In nasotracheal group, the act of extubation and reintubation through nasal route at the time of enrolment can be a confounder as the number of airway manipulations may had a bearing on the occurrence of PEAO. The long-term outcome after discharge from the PICU was not available, as it was not the part of this study. We could enroll only 38.9% (70 out of 180) of the calculated sample size. To have an adequate answer to the study question, large randomized trial with adequate sample size is needed to assess the impact of nasotracheal intubation on PEAO, other clinical outcomes, and safety among children receiving long-term mechanical ventilation.

CONCLUSION

In this open-label RCT involving critically ill children undergoing mechanical ventilation, we noted that the rate of PEAO was similar in nasotracheal and orotracheal intubation groups. Slower recruitment rate and enrolment of lesser than required sample size are the major limitations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institute Ethics Committee, PGIMER, Chandigarh, India. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

VK prepared the protocol, enrolled cases, collected data, reviewed the literature, and prepared the initial draft of the manuscript. SA conceptualized the study, supervised the preparation of the protocol and conduct of the study, analyzed data, and critically reviewed and finalized the manuscript. AKB supervised the data collection and helped in statistical analysis. KN supervised the data collection and performed literature review. All authors approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.713516/full#supplementary-material

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Evolution of a Bidirectional Pediatric Critical Care Educational Partnership in a Resource-Limited Setting

Sarah E. Gardner Yelton[1], Julia M. McCaw[1], Carolyn J. Reuland[2], Diana A. Steppan[1], Paula Pilar G. Evangelista[3] and Nicole A. Shilkofski[1,4]*

[1] Department of Anesthesiology and Critical Care Medicine, Charlotte R. Bloomberg Children's Center, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2] Johns Hopkins University School of Medicine, Baltimore, MD, United States, [3] Department of Pediatric Critical Care Medicine, Philippine Children's Medical Center, Quezon City, Philippines, [4] Department of Pediatrics, Charlotte R. Bloomberg Children's Center, Johns Hopkins University School of Medicine, Baltimore, MD, United States

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****Correspondence:***
Sarah E. Gardner Yelton
sgardneryelton@luriechildrens.org

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Introduction: Children in resource-limited settings are disproportionately affected by common childhood illnesses, resulting in high rates of mortality. A major barrier to improving child health in such regions is limited pediatric-specific training, particularly in the care of children with critical illness. While global health rotations for trainees from North America and Europe have become commonplace, residency and fellowship programs struggle to ensure that these rotations are mutually beneficial and do not place an undue burden on host countries. We created a bidirectional, multimodal educational program between trainees in Manila, Philippines, and Baltimore, Maryland, United States, to improve the longitudinal educational experience for all participants.

Program Components: Based on stakeholder input and a needs assessment, we established a global health training program in which pediatricians from the Philippines traveled to the United States for observerships, and pediatric residents from a tertiary care center in Baltimore traveled to Manila. Additionally, we created and implemented a contextualized simulation-based shock curriculum for pediatric trainees in Manila that can be disseminated locally. This bidirectional program was adapted to include telemedicine and regularly scheduled "virtual rounds" and educational case conferences during the COVID-19 pandemic. Providers from the two institutions have collaborated on educational and clinical research projects, offering opportunities for resource sharing, bidirectional professional development, and institutional improvements.

Conclusion: Although creating a mutually beneficial global health partnership requires careful planning and investment over time, establishment of a successful bidirectional educational and professional development program in a limited-resource setting is feasible and benefits learners in both countries.

Keywords: children, simulation, medical education, global health, program development

INTRODUCTION

Children in resource-limited settings (RLS) are disproportionately affected by common childhood illnesses, resulting in significant morbidity and mortality (1). Each year, 60,000 children under the age of 5 die in the Philippines, almost a third from sepsis, diarrhea, or pneumonia (1). Providers in RLS frequently need to resuscitate children with critical illness or life-threatening disease processes, but encounter obstacles that include limited pediatric-specific training, inadequate staffing, and equipment and financial constraints (2, 3). Although decreasing child mortality in RLS will require improved training, particularly in the areas of pediatric emergency medicine and critical care, the methods used to effectively enhance education are neither clear nor standardized (3–7).

Various methods to address these educational gaps have historically included (1) observerships in tertiary care hospitals, wherein individuals observe clinical care and participate in didactic education; (2) limited in-country educational programs; (3) telemedicine and telemonitoring programs; and 4) longer-term formalized training programs. Each of these methods has a unique set of barriers. For example, observerships are expensive and do not provide hands-on opportunities (8), and in-country educational efforts face challenges in sustainability, dissemination, and skill-decay (9). At the same time, global health rotations for trainees from North America and Europe have become commonplace, benefitting learners by exposing them to global disease burden, challenges in resource utilization, and different cultural belief systems that influence clinical practice (10). However, residency and fellowship training programs struggle to ensure that these rotations are mutually beneficial; they require careful design, implementation, and ongoing evaluation (10, 11).

Beyond the need to improve pediatric critical care training programs, the World Health Organization (WHO) and experts in the field of pediatric critical care in global health have identified several major target areas that could contribute to better provision of pediatric critical care and decrease child mortality. Examples include standardization of care, such as with the Surviving Sepsis Guidelines and the WHO guidelines for emergency treatment of children, care checklists, and early identification of decompensation both pre-hospital and in-hospital (4, 5, 7, 12, 13).

Using the above framework, we sought to create a long-term bidirectional, multimodal educational program between trainees in Manila, Philippines, and those in Baltimore, Maryland, United States (U.S.), using cross-institutional trainee experiences, formal simulation education development, and a collaborative research relationship. Through this partnership, we aim to improve the longitudinal educational experience for all participants and serve as a model for pediatric critical care education in other venues.

PROGRAM COMPONENTS

We have sustained a relationship between pediatric providers at Johns Hopkins Hospital (JHH) in Baltimore and Philippine Children's Medical Center (PCMC) in Manila for over 30 years. This relationship started with an observership program in which pediatricians from PCMC rotated in the pediatric intensive care unit (PICU) at JHH. The strong relationship that developed over time between the two institutions fostered the creation of a mutually beneficial partnership, which included ongoing needs assessments and programmatic changes to best focus on WHO-identified areas for improving provision of pediatric critical care.

Observership

In 1996, before the establishment of formal pediatric critical care training in the Philippines, faculty from JHH and PCMC collaboratively created an observership program for pediatricians from PCMC interested in additional pediatric critical care training. Each year, two to three pediatricians from PCMC volunteered to participate in a program for several months at JHH. After the development of an accredited pediatric critical care fellowship training program in the Philippines, the senior pediatric critical care fellows from PCMC began traveling to Baltimore in their final year of training to participate in the observership. The 4–8-week-long program includes participation in PICU rounds and all didactic and simulation-based education available to faculty and trainees in the JHH PICU. There is no institutional funding available for this program, so participants are responsible for their own travel expenses.

Since the inception of the program, Johns Hopkins Pediatrics has received over 30 trainees (primarily PICU fellows). 15 of these participants currently hold leadership positions in pediatrics and pediatric critical care across the Philippines as program directors, unit medical directors, committee chairs and division heads. For example, one former trainee is currently head of the PICU at PCMC, serves as director of research and research training at her institution, in addition to maintaining a role in medical education as an assistant program director for the pediatric critical care fellowship. Multiple participants are also active in their national organizations in the Philippines Pediatric Society and the Society of Pediatric Critical Care Medicine, Philippines.

Education/Simulation

Although observerships are a common method of education in global health, and participants report them to be enjoyable experiences that contribute to professional development, these programs are expensive and inherently lack hands-on opportunities owing to legal and licensure constraints of the U.S. healthcare system (8, 14). It is therefore essential to augment these programs through additional training.

To align with the WHO goal of care standardization and early identification of in-hospital decompensation (5, 7, 13) and to expand access to hands-on training, we created and implemented a contextualized, sustainable simulation-based shock curriculum for pediatric trainees in Manila that can be disseminated locally. This was undertaken as a pilot for a larger scale simulation education program. Simulation programs have been shown to effectively educate individuals in many countries in areas ranging from fluid management for patients in shock to cardiopulmonary resuscitation, improving participant confidence and knowledge (15–17). Greater confidence in skills and improved knowledge

scores can translate into changes in clinical practice, although the effect on outcomes is less well-known (18).

We carried out a needs assessment via in-country meetings with the PCMC pediatric residency program director, pediatric critical care faculty and trainees, and hospital administration, and conducted in person observations in the PICU at PCMC. Hands-on simulation experience with patient management was identified as a priority need for pediatric trainees. We created and implemented a simulation-based shock curriculum by administering a half-day workshop at PCMC with 24 pediatric residents in March 2020. Collaboratively, we chose to focus on shock due to the high contribution of dengue shock, septic shock, and hypovolemic shock to mortality in the Philippines, and early recognition and appropriate management can drastically improve patient outcomes (19). The curriculum included a didactic portion, skills-based stations, and simulation scenarios/objective standardized clinical examinations. After the workshop, confidence in shock concepts and skills and performance on a simulation scenario as measured via a checklist improved significantly for the pediatric residents. The program, created and taught collaboratively by pediatric critical care faculty and fellows from both institutions, was designed to establish a low-cost and accessible model of simulation education in an RLS. Most of the materials and task-trainers used were brought from the U.S. and donated to PCMC. Additionally, PCMC faculty participation in the creation and teaching of the curriculum allowed for these individuals to become master trainers. Together with the donated materials, this served to promote sustainability and dissemination of the curriculum and to allow for provision of frequent refresher training sessions to mitigate skill decay.

Global Health Rotation

To maintain a bidirectional relationship, we also established a global health training program and rotation for pediatric residents from JHH in 2018. Our goal was to obtain maximal educational value for pediatric trainees from the U.S. while allowing for benefit to the host country. Essential components of a successful structured global health rotation include pre-departure orientation and simulation sessions focusing on local epidemiology and disease burden, early establishment of host-country needs and knowledge gaps, on-site mentorship with ongoing program evaluation, and a partnership with formalized longitudinal education and opportunities for professional development (6, 7, 10, 11, 20).

Our global health rotation adheres to these principles through a structured elective rotation in global health for JHH pediatric residents. Therefore, our program incorporates pre-departure training, pediatric training program leadership commitment to global health, and bilateral evaluations of the established relationship between PCMC and JHH. Global health elective rotations, with defined goals and objectives, are used to provide structured education and orientation for JHH residents before and during travel to the Philippines. The elective starts with a pre-departure curriculum and orientation that uses components of the Simulation Use for Global Away Rotations (SUGAR) curriculum, which includes simulations and procedure adaptations for limited-resource settings (21). The pre-departure curriculum also includes lectures on bioethics, professionalism, and Filipino culture from pediatric faculty with experience in global health. While in the Philippines, visiting JHH residents spend 1–2 days observing rounds in each unit at PCMC (PICU, neonatal intensive care unit, emergency department, and general ward); anesthesia-trained residents also have the opportunity to observe in the operating room. PCMC attendings, as well as JHH attendings traveling with residents during the elective abroad, give didactics, specifically case presentations with review of tropical and endemic diseases. PCMC has received 18 residents, fellows and medical students for observerships from Johns Hopkins University School of Medicine (JHUSOM).

Additionally, pediatric residents participating in the global health rotation travel to other regions of the Philippines to teach the simulation-based training programs Helping Babies Breathe (HBB) and Helping Mothers Survive (HMS). The team from JHUSOM has trained 65 midwives, nurses, physicians and nurse midwives as master trainers. The U.S.-based training team and the local master trainers have subsequently trained over 550 nursing students, nurses, midwives, physicians, and emergency first responders as providers in both training programs over the last 5 years. While much of the dissemination work has been focused in the Southern Philippines regions of Mindanao where neonatal and maternal mortality rates are highest in the country, both simulation-based training programs have been disseminated by trainers within Luzon, Visayas and Mindanao, stretching across many regions and various islands in the Philippines, with training materials having been translated into local dialects in these regions by bilingual master trainers.

Given the natural turnover of pediatric residents, relationships between faculty at JHH and PCMC have been key in establishing continuity and sustainability. The JHH pediatric residency director (NAS) has a longstanding relationship with many physicians at PCMC and has personally accompanied groups of residents to PCMC at the start of their global health rotation there. Hence, she has been able to continually assess host-country needs and knowledge gaps of U.S.-based residents, while providing mentorship for residents both in-country and upon return to the U.S. Additional programmatic assessment occurs via post-rotation evaluations by JHH residents on their return to the U.S.

American trainees who have participated in the global health rotation more recently have gone on to fellowship training in specialty fields within pediatrics and several are now in academic positions at major teaching hospitals in the United States, with continued academic focus in global health research and education. Many former trainees from both PCMC and JHUSOM have cited their experience on rotations resulting from the educational exchange as being very influential in their long-term career development, having been a major contributor to their understanding of other healthcare systems within global health settings. One of the trainees from Johns Hopkins stated: "Participating in this program appealed to me due to its sustainability. The opportunity to work with both community providers and specialists during a global health rotation and to experience disparities in care in different settings was part of the draw of the rotation, and something that has led me

to pursue additional work in international settings in order to better understand disparities in healthcare in my own setting and practice. The idea that you are starting a cascade of education that is going to continue far beyond your time in the country is really exciting. The experience will also help me in my future career plans to practice pediatrics in austere settings where resources will be limited."

Research/Professional Development

Finally, providers from the two institutions have collaborated on clinical and educational research projects that have permitted opportunities for bidirectional professional development. This concept of "participatory research," whereby the host country identifies specific research needs, and is partnered with visiting trainees whose skills and interests fill those needs, can lead not only to sustainable community health and hospital initiatives, but also to further understanding of care delivery needs in RLS for both local governments and global health practitioners (20). Additionally, it provides an opportunity for providers from both countries to present together at conferences, co-write manuscripts, and share resources (10, 11).

As previously mentioned, our research collaborative evaluated the efficacy of the simulation-based shock curriculum on skill and knowledge development. After participation in the curriculum, residents improved with respect to confidence and simulated performance in skills associated with shock identification and management. Simulation performance was measured using an original checklist, created based on previously validated checklists (22–24). While knowledge scores did not improve on a written assessment, checklist scores improved significantly following the intervention. Checklists are commonly used in simulation studies as a marker of knowledge acquisition, and may translate more directly to clinical skills than a written evaluation (22–25).

Additionally, the research collaborative evaluated the barriers and facilitators to implementation of a Pediatric Early Warning Score (PEWS) system at PCMC. Globally, pediatric hospitals have implemented PEWS systems to improve early detection of clinical deterioration in pediatric patients by standardizing escalation of care decisions. These scoring systems include various vital signs and other clinical characteristics for quick classification of decompensation risk. They have been shown to accurately predict the need for intensive care unit level of care and are better predictors of clinical deterioration than physician opinion alone (26–34). Implementation studies have shown that clinical outcomes are improved in some settings because the early recognition of patient decline allows for earlier intervention (34). PEWS systems have been modified to fit specific hospital contexts worldwide, including in some RLS (26–28, 30, 35).

We conducted semi-structured interviews with nurses, residents, fellows, and attendings at PCMC to characterize existing systems for escalation of care decisions and attitudes about PEWS implementation. In-person hospital observations by the study team at PCMC served to triangulate interview findings. Barriers within the PCMC workflow included limited bed capacity, delay in referral owing to uncertainty of patient condition severity, patient overflow, limited monitoring equipment, and high patient-to-staff ratio. Facilitators of PEWS implementation included positive attitudes toward PEWS adoption/adaptation and existence of systems for vital sign monitoring across different units. This study showed that tools such as the PEWS system may be feasible for implementation in RLS, and we anticipate that this formal assessment will result in PEWS system implementation at PCMC.

Pediatric faculty and trainees from both JHH and PCMC participated in the creation and implementation of both projects, and resources such as statistical support, editing services, and funding for manuscript submission were shared. The results of collaborative projects have been presented at the International Pediatric Simulation Society Virtual Workshop, the World Federation of Pediatric Intensive & Critical Care Societies (WFPICCS) Virtual Conference, and the Society for Critical Care Medicine Annual Congress. Additionally, manuscripts have been submitted for publication, allowing for multi-institutional authorship and bidirectional networking opportunities (36).

Distance mentorship has been a core component of the bidirectional exchange for several years, both in areas of clinical practice and within research. Specialists in both institutions have spoken and presented posters and abstracts together at national and international conferences on various topics in pediatric critical care medicine. Difficult case presentations and clinical conundrums have been discussed between the care teams in both institutions, as a form of distance mentoring for both fellows and early career faculty. Research mentorship in study design/execution and research ethics from faculty in both institutions has been a core tenet of all collaborative research and quality improvement endeavors undertaken by the two institutions, with input from institutional review boards in both countries. These opportunities have allowed, for example, one pediatric critical care attending to participate in the quality improvement process at her home institution through the PEWS project, attend WFPICCs and serve as a senior author on three oral presentations at the conference, in addition to authoring multiple manuscripts currently submitted for publication in major medical journals.

CHALLENGES

COVID-19 Pandemic

When the COVID-19 pandemic restricted travel, both the observership program and the global health rotation required substantial adaptation. Medical education became increasingly provided via telemedicine throughout the pandemic (37), and we began using this technology in the fall of 2020 to sustain the program. Participants from PCMC were invited to attend regularly scheduled virtual PICU rounds and educational conferences remotely. To facilitate proper social distancing at JHH, both rounds and conferences were already conducted in a remote fashion through videoconferencing software using a tablet on wheels with video and microphone capabilities. This setup not only allowed for continued implementation of the observership in a virtual format, but also decreased costs associated with an in-person observership, while expanding

access in an interdisciplinary/interprofessional fashion to other individuals at PCMC, including nursing and respiratory therapy.

When residents and fellows could no longer travel to Manila, pre-departure lectures were converted to a virtual format and expanded to include topics such as disaster medicine and tropical disease identification and management. SUGAR simulations were also adapted for appropriate social distancing and cleaning between groups. In addition to the development of the remote observership as described above, the 2-week-long global health rotation also featured shared synchronous lectures and case discussions between the global health residents and PCMC residents. The ability to adapt the curriculum to a virtual format and schedule shared lectures between programs—even when in-person observerships are not possible—highlights the positive relationship between JHH and PCMC and the sustainability of this partnership.

Research Approval

We have struggled throughout the development of this program with timely implementation, in addition to inclusion of non-physician disciplines. The reasons for this are multifactorial, including cultural differences in communication styles, and lack of familiarity with institutional approval processes. While U.S. physicians are highly reliant on e-mail communication, this is not the case in the Philippines. Through early visits to PCMC, we were able to find alternative and more efficient methods of communication to improve collaboration, such as via phone messenger applications. The approval process commonly required in-person meetings or provision of hard-copies of paperwork. Travel to the country prior to implementation of the project was therefore essential to meet face-to-face with administration for a clear understanding of the process, find meeting proxies, and determine how best to transfer required paperwork.

Additionally, the research approval process to enroll physicians versus non-physician disciplines was different. While we were able to interview nurses for the PEWS project, we did not have approval to enroll nurses in our simulation-based education program in time for implementation. Future visits should include a focus on meeting with nursing leadership and a better understanding of the best process for nursing involvement, as inclusion of nursing in educational or clinical interventions is essential for meaningful and long-term change.

DISCUSSION

Establishing a mutually beneficial relationship between an institution in a resource rich setting and one in a RLS requires time, commitment, and stakeholder investment. We have been successful in sustaining a multimodal partnership via cross-institutional trainee experiences, simulation education development, and collaborative research. This partnership may serve as a model for educational programs in other RLS.

Although observerships are not the most effective method of education, we have endeavored to make them more fruitful by improving accessibility through telemedicine and adding hands-on education via simulation. Our resident global health elective adheres to ethical standards with ongoing reassessment that benefits both institutions. We have laid the groundwork for continued simulation education at PCMC that could be elaborated upon to encompass other topics and scenarios beyond shock in a contextualized manner.

Individuals from both institutions have benefited from resource-sharing in the realm of professional development via international conferences, publications, and participatory research on topics that address WHO goals of early identification of decompensation and standardization of care, as well as stakeholder-identified topics such as implementation of a simulation-based education program or PEWS system. Local identification of education, research, and improvement projects have contributed to sustainability because of buy-in from hospital healthcare providers and leadership.

PCMC is a large academic institution with a pediatric critical care training program, resources such as ventilators and sub-specialists, and trainees who are comfortable speaking English in medically complex situations. The generalizability of this program is limited to other regions or countries with similar resources and epidemiology of disease burden. Additionally, a relationship such as this has been fostered over decades of modification. Although it would likely present different challenges, implementing a similar design in another environment would be feasible and likely benefit from a similar framework that includes ongoing needs assessments with stakeholder buy-in, longitudinal educational programs, structured global health experiences and observerships, and a research collaborative that fosters professional development. Our ability to transition many educational components to virtual platforms may allow us to further expand program access to other institutions in the future. However, the in-person experiences remain essential, and must be reincorporated as international circumstances allow.

Additionally, though portions of the program have been evaluated formally, such as the simulation program and the global health rotation, most markers of our success are subjective or anecdotal, in the form of perceived improved relationships across institutions and positive verbal feedback. To best determine next steps for this program, a more formal assessment should be undertaken. Monitoring clinical improvement in patient outcomes over time would be beneficial. However, advances in medicine and variable availability of technologies, staffing, or funding serve as confounding factors that decrease the validity of outcomes as markers of programmatic success.

By adhering to guidance from the WHO and focusing on improving training in pediatric critical care, we aim to decrease obstacles associated with the health care of children with critical illness and the associated morbidity. We have built a successful collaboration between physicians across institutions who continue to assess the relationship and identify areas for improvement. Changes in clinical outcomes will require widespread and long-term use of an educational program

that comes from local stakeholder commitment and institutional buy-in.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Johns Hopkins Hospital IRB and the Philippine Children's Medical Center Office of Research Development. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Pain Assessment and Management in Pediatric Intensive Care Units Around the World, an International, Multicenter Study

Michelle Grunauer[1,2], Caley Mikesell[1], Gabriela Bustamante[1], Gissela Cobo[1], Sebastián Sánchez[1], Ana María Román[1], Andrea P. Icaza-Freire[1], Antonio W. D. Gavilanes[3], Nancy Ewen Wang[4] and The PICU-MIC Research Group[†]*

[1] School of Medicine, Universidad San Francisco de Quito USFQ, Quito, Ecuador, [2] Pediatric Intensive Care Unit, Hospital de los Valles, Quito, Ecuador, [3] Department of Pediatrics, University Medical Center Maastricht, Maastricht, Netherlands, [4] Emergency Medicine, Stanford University School of Medicine, Stanford, CA, United States

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***Correspondence:**
Michelle Grunauer
mgrunauer@usfq.edu.ec

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The adequate assessment and management of pain remains a challenging task in the Pediatric Intensive Care Unit (PICU). Our goal is to describe how pain is assessed and managed in PICUs around the world and to examine how human and material resources impact achievement of this goal. An international multicenter cross-sectional observational study was designed with the participation of 34 PICUs located in urban, suburban, and rural areas of 18 countries. We evaluated how PICUs around the world assessed and managed pain according to the Initiative for Pediatric Palliative Care recommendations, and how human and material resources impacted achievement of this goal. Data was collected for this study from 2016 to 2018 using questionnaires completed by medical doctors and nurses. In this paper, we focus on the indicators related to how pain is managed and assessed. The average achievement of the goal of pain relief across all centers was 72.2% (SD: 21.1). We found a statistically significant trend of more effective pain management scores, routine assessment, proper documentation, and involvement of pain management experts by increasing country income. While there are efforts being made worldwide to improve the knowledge in pain assessment and management, there is a lack of resources to do so appropriately in low-middle-income countries. There is a mismatch between the existing guidelines and policies, which are mainly designed in high income countries, and the resources available in lower resourced environments.

Keywords: pain, pediatric critical care units, pediatric palliative care, under resourced settings, pediatric

INTRODUCTION

An inevitable consequence of a child's admission to the intensive care unit is the experience of pain, either because of the need for painful procedures or because of the disease itself. In this context, prevention of pain and pain management is fundamental (1). All critical care providers receive training in pain control and should apply it in an integrated model of care considering the principles related to palliative care: the active total care of the child's body, mind and spirit (2). In this context, Cicely Saunders, a founder of the discipline of Palliative Care, developed the concept of addressing

"total pain" or the importance of addressing pain not only from a physical standpoint, but also from psychological, social, and spiritual aspects of life (3, 4). This approach to pain management has been demonstrated to positively affect the patient-family unit care, provide symptom control, and also improved survival among pediatric patients with life limiting and life-threatening conditions (1, 2). Nevertheless, a significant number of children still experience a lack of optimal pain management, which can lead to long and short-term psychological and physiological disturbances (5).

Despite the fact that these conversations and definitions are gaining prominence in both the scientific literature and in clinical settings, in 2008, the World Health Organization (WHO) estimated that, ∼80% of the worldwide population has scant or no access to treatment for moderate to severe pain of various etiologies (1). The challenge for health care professionals is to find a way to assess and manage pain despite the fact that the sensation of pain is subjective and that there is poor use of standardized methods to evaluate pain in children (6). The gold-standard for diagnosing pain in the pediatric population is the use of self-reported scales. However, this method has limitations depending on the patient's age or acuity (5). For example, in very young children and in neonates, pain assessment includes scales that consider behavioral observations and physiological measures (7). As an alternative, Franck et al. (6) mentions that parents and non-professionals are more accurate than healthcare providers in identifying expressions and responses related to pain in children. Furthermore, there are multiple factors that affect pain perception including: anxiety, fear, stigma, comorbidities, and concern of separation from family, strange environments, and barriers in verbal communication (8).

Thus, the adequate assessment and management of pain remains a challenging task in Pediatric Intensive Care Units (PICUs). This can be attributable to complications in pain assessment and management in pediatric patients arising from a variable understanding of illness and death depending on the age of the child, as well as different stages of cognitive and emotional development (9, 10). Age-related differences in expressing pain also make assessment challenging (10). There are many barriers that practitioners confront in everyday practice, including access to validated tools to assess and treat pain, deficient practitioner training, a lack of pain experts, lack of time required to properly assess pain, and interruptions in the supply of pain medications (1, 11, 12).

Another aspect to consider while analyzing pain, is how racial bias can influence pain perception, defined as: an inequality in pain treatment between races despite showing similar levels of pain (13). Furthermore, social and cultural differences affect the way patients experience and exhibit pain. For instance, in some cultures, expression of emotions and acknowledgment of the pain is valued, whereas in others, stoicism is valued (14). Additionally, several studies have demonstrated that boys are rated as experiencing more pain than girls when undergoing the same medical procedures. Therefore, gender stereotypes, such as boys being more stoic than girls, also becomes a limitation (15).

The lack of proper assessment of pain leads to inadequate pain relief. Pain can limit the ability to perform daily activities of living. This can trigger psychosocial instability manifested as depression, anxiety, and a patient-family unit's inability to participate in work or studies (1, 4). Finally, spiritual pain as part of total pain is recognized as anger, hopelessness, and a sense of injustice (3).

In order to provide care to children living with life-threatening conditions, as well as their families with an integrated approach, the Initiative for Pediatric Palliative Care developed 6 quality domains including relief of pain (16). As part of an international multicenter cross-sectional study, we assessed how PICUs around the world assessed and managed pain in relation to the Initiative for Pediatric Palliative Care recommendations, and examine how human and material resources impact achievement of this goal.

MATERIALS AND METHODS

The international PICU-Model of Integrated Care (PICU-MIC) multicenter study identified institutions through medical societies, the Pediatric Acute Lung Injury and Sepsis Investigators Network, publication database searches and team contacts (17). An international multicenter cross-sectional observational study was designed with the participation of 34 PICUs located in urban, suburban and rural areas of 18 countries. Each institution designated a representative investigator who oversaw the study protocol and acquired Institutional Review Board (IRB) approval. Data collection took place from 2016 to 2018, and consisted of two questionnaires with multiple choice and open-ended questions completed by medical doctors and nurses directly caring for children from the 34 PICUs in the PICU-MIC network (18). Each PICU had a designated site coordinator who ensured that surveys were completed. Participants were encouraged to complete questionnaires on REDCap, (19) an encrypted, password-protected online platform. Respondents who could not use REDCap because of a lack of reliable internet sent de-identified responses *via* email. For each center, a two-week period was established to complete the requested questionnaires. The authors did not specifically take into account which caretakers were responsible for pain scoring and management. The first questionnaire collected data related to PICU infrastructure, technology, and provider ratios. The second questionnaire asked providers to answer questions related to providers' practices and center policies based on the Initiative for Pediatric Palliative Care's (IPPC) curriculum that describes domains, goals and indicators for the provision of pediatric palliative care. Each health provider that completed the questionnaire did so while considering the admitted child and the questions related to the domains applied in the care of each child. These questionnaires included 10 to 25 admitted children in each PICU with a 100% survey completion rate. De-identified data were collected using encrypted software (REDCap). This project received approval by the Universidad San Francisco de Quito's Ethics Committee for Research on Human Beings/IRB (2016-0911N) and by ethics committees at all sites [Clinical registry number: ISRCTN12556149 (DOI 10.1186/ISRCTN12556149)].

The IPPC curriculum domains include: (1) holistic care, (2) family support, (3) child-family unit involvement, (4) pain

and symptom control, (5) continuity of care, and (6) grief and bereavement support. In this paper, we focus exclusively on the individual indicators related to how pain is managed and assessed. The pain domain assesses four items (a) Is pain evaluated? (b) What tools are used for pain evaluation? (c) Is pain level reported in the patient's chart? (d) Is pain assessment focused on a specific marker such as expressed, observed, physiological indicators, family reports or the child's ability to participate in activities of daily living? Questions regarding appropriate pain treatment and planning were also addressed: (a) Is there a dynamic therapeutic plan for the patient's pain with a wide range of pharmacologic and non-pharmacologic management strategies? (b) Are there specialists/experts involved in pain management? (c) Does the unit have policies regarding treatment of pain?

Each item had a possible response of "yes," "no," and "sometimes." To analyze adherence to the pain domain of the Initiative for Pediatric Palliative Care curriculum, we constructed a partial score for each subcategory. A numeric value was assigned to each answer within each subcategory: "yes" = 1, "sometimes" = 0.5, and "no" = 0. Scores from all items were summed and a range from 0 to 100 was produced. A model using the mean and standard deviation (SD) of the results was created.

We grouped the centers by income level according to the World Bank definitions for low-middle-income countries, upper-middle-income countries, and high-income countries to be able to determine whether a country's financial stability alters the availability and/or quality of pain management between institutions. The mean of the results of pain assessment and management were juxtaposed with the World Bank income group. The evaluation of these dissimilarities was determined with the application of multilevel generalized linear models (GLM) with a Gaussian distribution modified by age of the child and gender, with clustering by center. While utilizing the high-income country group as reference, the World Bank income group was modeled categorically and ordinally while using the high-income country group as a reference group to determine the existence of a linear trend across income groups. Additionally, we examined if the patient or center characteristic were associated with Initiative for Pediatric Palliative Care-adherence scores using univariate and multivariable multilevel GLM using the center as a clustering variable. Age, race, gender, comorbidities, and shift length were all included in the adjusted model. For demographic information and other patient characteristics we included age, gender, race, length of stay (LOS), diagnosis, and history of comorbidities. In regard to the centers, we reported information on percent of daily bed use, beds per critical care nurse/doctor, health care provider shift lengths and frequency of pain assessment. We determined associations with univariate and multivariable multilevel GLM utilizing the center as a clustering variable. The statistical analysis was made with Stata v14.1.

We included concepts of content analysis and grounded theory as a part of a mixed-methods methodology to analyze the participants' open-ended answers. The responses were stratified by World Bank income level following the extraction and categorization of responses by question. Later, we classified answers by categories, removed duplicates, and condensed answers when feasible. Lastly, we analyzed participants' responses by World Bank country income level to associate data received in open-ended answers to results from our statistical analysis and literature review.

RESULTS

The PICU-MIC study included 34 PICUs from 18 countries: Asia (15), Latin America (7), North America (5), Europe (5), and Africa (2), to analyze the achievement of "relief of pain and other symptoms". PICUs were classified according to their income: low and lower middle income (LIC/LMIC) (23·5%), upper middle income (UMIC) (44·1%) and high income (32·4%).

As shown in **Table 1**, the average achievement of the goal of pain relief across all centers was 72·2% (SD: 21·1). We found a statistically significant trend of increasing pain management scores by increasing country income: LICs/LMICs showed 62·6% (SD: 27·6), while UMICs 70·1% (SD: 20·0), and high-income countries showed 80·4% (SD: 13·8; *p*-value for trend: 0·03).

We also observed this overall trend of higher scores with increasing country income in several of the individual items assessed for relief of pain (**Table 1**). When routine assessment was analyzed the average score for centers in LICs/LMICs was 89·0% (SD: 26·2), compared to 97·1% (SD: 13·4) in UMICs and 99·4% (SD: 7·6) in high-income countries (*p*-value for trend: 0·004). Proper documentation of a pain assessment was achieved in 77·0% (SD: 38·5) among centers from LICs/LMICs, 92·5% (SD: 21·3) among centers from UMICs and 94·7% (SD: 17·2) for those in high-income countries (*p*-value for trend: 0·02). This data reveals increased frequency of routine pain assessment, as well as increased frequency of documented pain assessment in higher income countries in comparison to low-income countries.

We did not find differences across centers by country income in three other indicators, including the focus of pain assessment (i.e., expressed pain, observed pain, physiological indicators, family reports, child's ability for daily activities), having an appropriate treatment plan, and the existence of guidelines and policies for pain relief in each center (**Table 1**). However, we did find that centers in high income countries had higher scores for the involvement of pain management experts with a 73·7% (SD: 42·8), compared with 55·5% (SD: 46·5) in low-income/low-middle-income countries (*p*-value for trend: 0·04).

Table 2 represents the achievement of pain relief by sociodemographic characteristics of the patients and the centers included in the study. We did not find any statistically significant associations between patient and center characteristics and relief of pain in the fully adjusted model. However, in the univariate model, we found that teenagers (>11–18 years) had higher scores for pain relief compared to children of preschool age (>1–5 years). Similarly, there was a tendency identified in the univariate model of longer shifts having lower scores of pain relief compared with shifts of <8 h (*p*-value for trend 0·08).

Finally, **Table 3** shows that centers in countries of different incomes assess pain in PICU patients at different frequencies (Chi-square *p*-value <0·001). In general, providers working in centers in high income countries reported that they assessed pain

TABLE 1 | Average scores for initiative for pediatric palliative care indicators of relief of pain and other symptoms (*each child living with a life-threatening condition receives effective pain and symptom management*) by World Bank income level (16).

Relief of pain and other symptoms—quality indicators	Score‡	World bank income level			
		Low and lower middle income	Upper middle income	High income	All centers
Overall	Mean	62.6	70.1	80.4	72.2
	(sd)	(27.6)	(20.0)	(13.8)	(21.1)
	*p-trend**				***0.03***
Routine assessment	Mean	89.0	97.1	99.4	96.3
	(sd)	(26.2)	(13.4)	(7.6)	(15.9)
	*p-trend**				***0.004***
Assessment documented	Mean	77.0	92.5	94.7	90.2
	(sd)	(38.5)	(21.3)	(17.2)	(25.4)
	*p-trend**				***0.02***
Pain assessment focus:					
Expressed pain	Mean	84.0	85.5	80.7	83.5
	(sd)	(35.4)	(34.0)	(28.8)	(36.0)
	*p-trend**				*0.50*
Observed pain	Mean	93.0	96.3	95.6	95.4
	(sd)	(23.6)	(14.8)	(20.2)	(18.7)
	*p-trend**				*0.27*
Physiological indicators	Mean	84.0	90.1	82.2	86.1
	(sd)	(34.7)	(29.0)	(37.0)	(33.2)
	*p-trend**				*0.79*
Family report	Mean	68.5	71.1	71.6	70.8
	(sd)	(36.0)	(43.3)	(43.7)	(42.0)
	*p-trend**				*0.97*
Child's ability to perform daily activities	Mean	37.0	42.1	57.9	46.5
	(sd)	(45.8)	(47.5)	(48.3)	(48.1)
	*p-trend**				*0.55*
Appropriate treatment plan	Mean	67.5	52.4	85.1	66.7
	(sd)	(42.9)	(38.3)	(32.5)	(40.0)
(pharmacologic and non-pharmacologic)	*p-trend**				*0.20*
Pain management experts involved	Mean	55.5	57.3	73.7	62.6
	(sd)	(46.5)	(47.8)	(42.8)	(46.5)
	*p-trend**				***0.04***
Guidelines and policies	Mean	33.5	69.2	68.7	61.8
	(sd)	(69.2)	(44.8)	(44.7)	(47.0)
	*p-trend**				*0.40*

‡*Scores range from 0–100%-points.*

**p-trend, p-value for linear trend estimated using GLMs adjusted for child's age and gender, and using the center as a clustering variable.*

sd, standard deviation.

Bold values represent statistically significant with a p-value of < 0.05.

in the majority of their patients every 1–3 h (29%) or every 4–8 h (28%). Meanwhile, centers in upper-middle-income countries more frequently reported that they assessed pain "continuously," "regularly" or "always" (37%), as opposed to assessing at a specific time interval. Centers in lower-middle-income countries did not show an identifiable response pattern with some assessing every 1–3 h (21%) or once/twice per day (25%).

DISCUSSION

Average achievement of routine assessment and proper documentation for the relief of pain and other symptoms, were found to be inversely related to country income (**Table 1**). The involvement of pain management experts and the time dedicated to the assessment of pain were also associated with high-income countries (**Tables 1**, **3**). These results are consistent with the literature. Matula et al. (20) discuss considerations regarding relief of pain in low-middle-income countries, including deficient knowledge, adverse beliefs in regard to a child's pain and its treatment, as well as specific cultural beliefs. There is also a strong influence and preference of traditional or alternative treatments in some of these regions, possibly leading to a delay in the pain assessment or to the refusal of medication (19). Furthermore, the lack of material and human resources in these settings result in a scarcity of pain medications, a shortage of appropriate pediatric formulations, and inadequate understanding of

TABLE 2 | Associations between patient and center characteristics, and overall scores for initiative for pediatric palliative care indicators of relief of pain and other symptoms.

			pain		
Patient Characteristics	**N**	**%**	**Mean (sd)**	***p-value*‡**	***Adj. p-value***
Characteristics					
Age					
Newborn (0–1 m)	34	6.8	65.8 (27.4)	*0.95*	*0.50*
Infant (>1–12 m)	122	24.5	72.4 (19.8)	*0.60*	*0.97*
Preschool (>1–5 y)	150	30.1	70.4 (21.5)	*Ref.*	*Ref.*
School age (>5–11 y)	103	20.7	71.3 (19.9)	*0.25*	*0.35*
Teen (>11–18 y)	89	17.9	78.1 (19.6)	***0.03***	*0.12*
Gender					
M	285	57.2	71.9 (22.1)	*Ref.*	*Ref.*
F	213	42.8	72.5 (19.6)	*0.65*	*0.97*
Race					
White	173	34.7	74.3 (18.6)	*Ref.*	*Ref.*
Asian	111	22.3	78.3 (15.0)	*0.58*	*0.62*
Black	54	10.8	59.6 (30.4)	*0.19*	*0.22*
Indian	31	6.2	82.3 (11.3)	*0.96*	*0.81*
Mestiza	57	11.4	70.9 (27.3)	*0.61*	*0.64*
Middle-eastern	67	13.5	62.4 (16.6)	*0.44*	*0.99*
Other	4	0.8	82.0 (6.73)	*0.67*	*0.70*
Days in PICU					
<30 days	427	85.7	72.8 (21.1)	*Ref.*	*Ref.*
≥ 30 days	71	14.3	68.5 (20.9)	*0.22*	*0.50*
Comorbidities					
Single condition	133	26.7	70.7 (20.3)	*Ref.*	*Ref.*
Multiple comorbidities	365	73.3	72.7 (21.3)	*0.16*	*0.16*
Main diagnosis					
Acute	242	48.9	71.6 (20.8)	*Ref.*	*Ref.*
Chronic	253	51.1	72.7 (21.4)	*0.76*	*0.74*
CENTER CHARACTERISTICS					
Percent daily bed use					
<80%	139	30.2	76.4 (20.5)	*Ref.*	*Ref.*
≥80%	322	69.8	69.9 (21.0)	*0.88*	*0.89*
Beds/critical care doctor					
<2 beds per doctor	319	68.5	70.8 (20.1)	*Ref.*	*Ref.*
≥2 beds per doctor	147	31.5	72.0 (23.4)	*0.77*	*0.69*
Beds/nurse					
<2 beds per nurse	245	54.8	77.5 (19.3)	*Ref.*	*Ref.*
≥2 beds per nurse	202	45.2	65.1 (21.1)	*0.10*	*0.12*
Shift length					
<8 h	102	20.5	78.0 (12.4)	*Ref.*	*Ref.*
8 to 12 h	241	48.4	76.3 (19.4)	*0.99*	*0.60*
13 to 18 h	42	8.4	43.0 (19.1)	***0.01***	*0.04*
19 to 24 h	20	4.0	49.8 (31.4)	***0.05***	*0.32*
Multiple	93	18.7	72.9 (17.3)	*0.40*	*0.89*
p-value for trend				*0.08*	*0.39*

‡*p-values were estimated using univariate and multivariable multilevel GLMs using center as a clustering variable. The adjusted model included all characteristics listed in the table. Bold values represent statistically significant with a p-value of < 0.05.*

pediatric dosing which in turn can cause suboptimal pain relief (20). These issues pertain especially to rural areas due to a paucity of pain specialists, who tend to practice in major cities (19). Moreover, there are misunderstandings among health care providers working in lower-middle-income countries regarding the adverse effects of opioid analgesics, the validity of self-reported pain scales, as well as a lack of institutional policies and guidelines (20). In contrast, high income countries possess the resources to treat pain in pediatric populations with the help of specialists or other physicians with pain management training. They offer a wide arrange of services including medication, procedures, psychological and physical therapy, and alternative medicine (21).

There was not a statistically significant difference present by country income in the indicators of pain assessment focus, appropriate treatment plan, and existence of guidelines and policies. This finding could translate to the new efforts being made worldwide to improve the knowledge in pain assessment and management, but the lack of resources to do so appropriately in lower-middle-income countries. There is a mismatch between the existing guidelines and policies of palliative care and pain management, which are mainly designed in high income countries, and the resources available in lower resourced environments (21). Due to this, low-income countries should

TABLE 3 | Frequency of pain assessment as reported by centers of different World Bank income levels.

Frequency of pain assessment*	Low and lower middle income		Upper middle income		High income		All centers	
	n	%	n	%	n	%	n	%
Every 1–3 h	21	21.0	17	7.5	50	29.2	88	17.7
Every 4–8 h	10	10.0	45	19.8	48	28.1	103	20.7
Once/twice per day	25	25.0	48	21.1	15	8.8	88	17.7
Continuously/regularly	18	18.0	85	37.4	16	9.4	119	23.9
At each clinical evaluation	0	0.0	8	3.5	21	12.3	29	5.8
As needed	4	4.0	7	3.1	6	3.5	17	3.4
Missing	22	22.0	17	7.5	15	8.8	54	10.8
Total	100	100	227	100	171	100	498	100

**p-value <0.001 using a Chi-square test.*

prioritize their focus on the development of multidisciplinary teams that could apply low-cost treatment plans and educate professionals and family members alike, when the cultural context requires it (21).

Finally, the univariate model showed a higher prevalence of pain relief in teenagers in comparison to children in the preschool age. For context, the assessment of pain can be approached in the pediatric population by three different methods: self-report scales, observed behavioral changes and measured physiological indicators. Unfortunately, the number of available methods diminish progressively as the age of the child decreases. Preschool children are not developmentally able to utilize self-report scales and require alternative techniques to assess their pain (22). However, these scales are the easiest to use for untrained professionals who do not have the proper knowledge in regard to pain assessment and management. Thus, hindering evaluation and reducing the possibility of pain relief. Furthermore, the behavioral tools applied to younger children can be affected by severity of disease, stage of development and in neonates, gestational age. Additionally, older infants and toddlers could deliberately change the nature and intensity of their responses in function of pain anticipation (22).

This study has some limitations. Our sample was not generalizable. Centers were diverse, located in countries with different income levels and in different parts of the world. However, our sample offered insight into areas often excluded from research as a consequence of geographic, linguistic or resource barriers. Furthermore, we were not able to differentiate centers by public, private or public-private institutions, nor urban, suburban or rural localities.

CONCLUSIONS

Pain management remains a challenging task in the pediatric population, especially in the severely ill child. Furthermore, very young children and neonates have less available tools for the assessment of pain. Evidence suggests that the implementation of adequate pain assessment and treatment not only directly benefits the child by providing symptom control and quality of life, but also improves family and the health care professional's wellbeing. Our findings indicate that health care professionals already complete many palliative care tasks in PICUs around the world, independent of income. Despite this, there is an evident difference in fulfillment when World Bank income level is considered. Development, education, and barriers related to the implementation of evidence-based guidelines likely shaped Initiative for Pediatric Palliative Care pain scores. Moreover, there is a deficiency of material and human resources in countries with lower World Bank income levels, making it harder to implement the guidelines.

Understanding application of and adherence to pediatric palliative care guidelines can maximize the implementation effective interventions like the Initiative for Pediatric Palliative Care pain scores. Additionally, these recommendations should be adapted to each setting's available resources and inherent characteristics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidad San Francisco de Quito's Ethics Committee for Research on Human Beings/IRB (2016-0911N) and by ethics committees at all sites [Clinical registry number: ISRCTN12556149 (DOI: 10.1186/ISRCTN12556149)]. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MG, CM, GB, and NW: substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work. MG, CM, GB, GC, SS, AR, AI-F, AG, and NW: critical revision for important

intellectual content and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MG, CM, GB, GC, SS, AR, and NW: final approval of the version to be published. NW: critical revision for important intellectual content. GC, SS, and AR: literature review. PICU-MIC Research Group investigators: substantial contributions to the conception or design of the work and the data acquisition. All authors contributed to the article and approved the submitted version.

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PICU-MIC INVESTIGATORS

Jorge López González, Jesús López-Herce: Hospital General Universitario Gregorio Marañón-UCIP, Facultad de Medicina Universidad Complutense de Madrid, Madrid, Spain; Emanuele Rossetti, Chiusolo Fabrizio: Ospedale Pediatrico Bambino Gesù-PICU, Roma, Italy; Oliver Karam, Marie Saint-Faust: Geneva University Hospitals-HUG PICU, Geneva, Switzerland; Paolo Biban, Silvia Carlassara: Azienda Ospedaliera Universitaria Integrata Verona-PICU, Verona, Italy; Bettina von Dessauer, Nadia Ordenes: Hospital de Niños Roberto del Río Unidad de Paciente Crítico Pediátrico, Santiago, Chile; Fabiola Figueroa Urízar, Adriana Wegner A: Hospital Sótero Del Río-UCIP, Santiago, Chile; Michael Canarie, Yale-New Haven Children's Hospital's Pediatric Intensive Care Unit, New Haven, CT, United States, Kathryn Miller: University Hospitals Cleveland Medical Center-PICU, Cleveland, OH, United States. José Irazuzta; Nicolas Chiriboga: University of Florida COM-PICU, Jacksonville, FL, United States; Daniel Tawfik, Barbara Sourkes, Nancy Ewen Wang, Hursuong Vongsachang: Division of Pediatric Critical Care Medicine at Stanford University Medical Center-PICU, Stanford, CA, United States; Elizabeth W. Tucker, Nicole Shilkofski: The Johns Hopkins Children's Center PICU, Baltimore, MD, United States; 王文超Wang, Wenchao RN, Zhang Yuxia RN: Pediatric Hospital of Fudan University-PICU—Fudan, China; Lucy Lum Chai See, Sister Priscilla: University Malaya Medical Center-PICU, Kuala Lumpur, Malaysia; Recep Tekin, Fesih Aktar: Dicel University Medical Hospital-PICU, Diyarbakir, Turkey; Duygu Sönmez Düzkaya, Istanbul University Faculty of Medicine PICU; Istanbul, Turkey; Oguz Dursun, Ebru Atike Ongun: Akdeniz University-Faculty of Medicine PICU, Antalya, Turkey; Resul Yilmaz, Gaziosmanpasa University School of Medicine Tokat-PICUTokat, Turkey; Dincer Yildizdas, Çukurova University, Faculty of Medicine; Balcali Hospital, PICU- Adana, Turkey; Hakan Tekgüç, Koru Hospital-PICU; Ankara, Turkey; Vitaliy Sazonov, Timur Tsoy: PICU of City Children Hospital; Astana, Kazakhstan; Vitaliy Sazonov, Askhat Saparov: PICU of National Research Center for Maternal and Child Health, Astana, Kazakhstan; Vitaliy Sazonov, Elizaveta Kalmbakh: PICU of Karaganda Regional Children's Hospital, Karaganda, Kazakhstan; Michelle Grunauer, (USFQ/HDLV); Ernesto Quiñones, Hospital de los Valles, Quito Ecuador; Luis Eguiguren, Universidad San Francisco de Quito, Quito, Ecuador; Killen Harold Briones Claudette, Centro Fisiológico-Respiratorio Briones-Claudett, Guayaquil, Ecuador; ICU Hospital General del IESS de Babahoyo, Babahoyo, Ecuador; Yaneth Tovilla, Unidad Pediátrica de Quemados de los Servicios de Salud del Estado de Puebla, Puebla, México; Sandra Tania Ventura Gómez, UCIP del Hospital Regional de Alta Especialidad de Ixtapaluca, Ixtapaluca, México; Silvio Fabio Torres, Pediatric Intensive Care Unit, Hospital Universitario Austral, Buenos Aires, Argentina; Paul Cobarrubias, Amang Rodriguez Memorial Medical Center-PICU, Manila, Philippines; Dmytro Dmytriiev, Vinnitsa National Medical University-PICU, Vinnitsa, Ukraine; Alejandro Martínez, Gustavo Guzaman, Rudy Sanabria: Hospital del Niño Manuel Ascencio Villarroel, Cochabamba-UTIP, Cochabamba, Bolivia; Ravikumar Krupanandan, Bala Ramachandran: PICU, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India; Nirmal Choraria, Jignesh Patel: PICU—Nirmal Hospital, Ltd., Surat, India; Puneet A Pooni, Karambir Singh Gill: Dayanand Medical College & Hospital-PICU, Punjab, India; John Adabie Appiah, Komfo Anokye: Teaching Hospital—PICU, Kumasi, Ghana; Tigist Bacha Heye, Rahel Argaw, Asrat Demtse, Israel Abebe Admasu: Addis Ababa University, College of Health Sciences-PICU, Addis Ababa, Ethiopia.

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Availability and Quality of Grief and Bereavement Care in Pediatric Intensive Care Units Around the World, Opportunities for Improvement

Michelle Grunauer[1,2], Caley Mikesell[1], Gabriela Bustamante[1], Danielle Aronowitz[3], Kevin Zambrano[1], Andrea P. Icaza-Freire[1], Antonio W. D. Gavilanes[4], Rafael Barrera[3] and the PICU-MIC Research Group*

[1] School of Medicine, Universidad San Francisco de Quito, Quito, Ecuador, [2] Pediatric Intensive Care Unit, Hospital de los Valles, Quito, Ecuador, [3] Department of Surgery, Long Island Jewish Medical Center, Northwell/Hofstra University School of Medicine, New Hyde Park, NY, United States, [4] Department of Pediatrics, University Medical Center Maastricht, Maastricht, Netherlands

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***Correspondence:**
Michelle Grunauer
mgrunauer@usfq.edu.ec

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Pediatric Intensive Care Units (PICUs) provide multidisciplinary care to critically ill children and their families. Grief is present throughout the trajectory of illness and can peak around the time of death or non-death losses. The objective of this study was to assess how PICUs around the world implement grief and bereavement care (GBC) as part of an integrated model of care. This is a multicenter cross-sectional, prospective survey study. Questionnaires with multiple-choice and open-ended questions focusing on unit infrastructure, personnel, policies, limited patient data, and practices related to GBC for families and health care professionals (HCPs) were completed by on-site researchers, who were HCPs on the direct care of patients. PICU fulfillment of GBC goals was evaluated using a custom scoring based on indicators developed by the Initiative for Pediatric Palliative Care (IPPC). We compared average total and individual items fulfillment scores according to the respective country's World Bank income. Patient characteristics and details of unit infrastructure were also evaluated as potential predictors of total GBC fulfillment scores. Statistical analysis included multilevel generalized linear models (GLM) with a Gaussian distribution adjusted by child age/gender and clustering by center, using high income countries (HICs) as the comparative reference. Additionally, we applied principals of content analysis to analyze and summarize open-ended answers to contextualize qualitative data. The study included 34 PICUs from 18 countries: high-income countries (HICs): 32.4%, upper middle-income countries (UMICs): 44.1%, low middle-income and low-income countries (LMI/LICs): 23.5%. All groups reported some compliance with GBC goals; no group reported perfect fulfillment. We found statistically significant differences in GBC fulfillment scores between HICs and UMICs (specifically, HCP grief support), and between HICs and LMICs (specifically, family grief support and HCP grief support). PICUs world-wide provide some GBC, independent of income, but barriers include lack of financial support, time, and training, overall unit culture, presence of a palliative

care consultation service, and varying cultural perceptions of child death. Disparities in GBC for families and HCPs exist and were related to the native countries' income level. Identifying barriers to support families and HCPs, can lead to opportunities of improving GBC in PICUs world-wide.

Keywords: grief, bereavement, pediatric palliative care, pediatric critical care, end of life

INTRODUCTION

Patients, families, and healthcare providers (HCPs) experience grief and bereavement in response to loss of life or changes in quality of life (1), both of which frequently occur in pediatric intensive care units (PICUs). Evidence suggests that the traumatic experience of life-threatening illness in a child, subsequent new or worsening disability, and childhood death are all associated with increased risk of developing grief-related disorders among the bereaved (2). Both patient families and HCPs are at risk for such adverse sequelae and can experience grief differently from one another.

Numerous studies underscore the importance of providing grief and bereavement care (GBC) for the patient-family unit and HCPs (2–7), however this type of care is often inaccessible and of variable quality throughout the world (8). Inadequate GBC places families at risk of developing psychological morbidities, familial disruption, and economic hardship. Similarly, without accessible GBC, HCPs are at risk of burnout, impaired judgment, and depression (2, 3). Furthermore, data on the availability and quality of GBC in PICUs around the world is limited (9). Efstathiou et al. conducted a systematic review of bereavement support in adult ICUs in five western high-income countries (HICs) and found that this type of care was unstandardized, irregularly available, and overall insufficient to meet projected needs (8). Similarly, in their review of the need, accessibility, and quality of pediatric palliative care (PC) in low- and middle-income countries (LMICs), Sasaki et al. reported inverse relationships between country income and both GBC and PC availability (10).

Although evidence indicates that GBC is inaccessible and insufficient in most critical care units across the world (8, 9), at least one study found that units with access to in-hospital PC consultants were eight times more likely to provide GBC than those lacking these services (11). Similarly, evidence suggests that training HCP staff in PC principles as part of an integrated model of care can improve GBC accessibility (2, 3), overall quality of care (12), family satisfaction with care (13), and HCP well-being (3), perhaps even more than a PC consultation service (12, 13). In such an integrated model of care, HCP staff are trained in GBC and can identify and respond to grieving needs independent of external PC consultants (12, 14). Though less commonly used than external consultation models (12, 15, 16), the integrated model of care is increasingly described as a standard of care for seriously ill children (3, 17) and may be particularly effective in under-resourced environments (12).

To address the growing need for a standardized integrated model of pediatric PC, the Initiative for Pediatric Palliative Care (IPPC) developed a novel PC curriculum that describes six essential "domains" that inform the care of vulnerable children, their families, and their HCPs (18). The six domains are: (1) holistic care of the child; (2) support of the family unit; (3) involvement of child and family in communication, decision making, and care planning; (4) relief of pain and other symptoms; (5) continuity of care; and (6) grief and bereavement support. The sixth domain is further sub-categorized into 6A and 6B. Domain 6A consists of five actions that can be used to specifically support the child's family, including: (1) assessing the needs of the family, (2) supporting grief and bereavement-related rituals, (3) providing supportive resources, (4) employing grief and bereavement-specific support professionals and (5) instituting policies and guidelines to support the family needs. Domain 6B consists of three actions that can be used to specifically support the child's healthcare team, including: (1) establish and disseminate processes for grief and bereavement support for HCPs, (2) provide resources to address grief and bereavement needs for HCPs, and (3) have mechanisms in place to obtain feedback from grieving HCPs (13).

The objective of this multicenter cross-sectional study was to assess how PICUs around the world implement GBC as part of an integrated model of care relative to the IPPC curriculum (with a focus on domain 6). The secondary objective was to assess whether unit characteristics (physical environment, technology, and human resources), country World Bank (WB) income level (19), or patient characteristics (race, first language, age, sex, and presence of comorbidities) are associated with differences in GBC provision. Finally, this study used mixed-methods analysis to develop richer descriptions of how individual units provide GBC. Our team hypothesized that all units would at least partially comply with IPPC recommendations for GBC, independent of country income, unit characteristics, and patient characteristics.

MATERIALS AND METHODS

The international Pediatric Intensive Care Unit Model of Integrated Care (PICU-MIC) study is a multicenter cross-sectional study inclusive of 34 participating PICUs/NICUs in 18 countries. Participating centers were identified through medical societies, research networks including the Pediatric Acute Lung Injury and Sepsis Investigators Network, publication database searches, and team contacts. Each individual institution appointed a representative researcher who reviewed the study protocol and obtained local Institutional Review Board (IRB) approval. Participants were medical doctors and nurses from PICUs; HCPs not employed in PICUs were excluded. Two questionnaires with multiple choice and open-ended questions were distributed to the HCPs who were in charge of the care

of each hospitalized child by the designated representative. They were distributed both in Spanish and in English. The first survey inquired about the systematic infrastructure of each unit. The second questionnaire gathered information about patient characteristics and model of care (MOC) in relation to IPPC guidelines as it applied to the care of patients who had been admitted at the time of survey distribution. Each center was requested to complete 10–25 copies of the model of care questionnaire; if centers included additional patients, we did not exclude them. A total of 498 pediatric patients were included across all centers. For each study site, 2-weeks were predefined to complete the questionnaires. Participants had a 100% response survey completion rate. We prompted survey respondents to complete the survey on REDCap which is an encrypted, password-protected online platform that allows the user to create, share, analyze and store data coming from questionnaires. Those participants who were not able to use this platform in the absence of reliable internet connection, were able to fill the de-identified questionaries via email.

The Universidad San Francisco de Quito Ethics Committee for Research of Human Beings/IRB approved this research (2016-091IN). This study was approved by Ethics Committees at all sites and its clinical trial registry number is ISRCTN12556149 (DOI 10.1186/ISRCTN12556149).

To evaluate adherence to domain 6 of the IPPC curriculum, we constructed a partial score for each item listed as subcategories under IPPC domains 6A and 6B. For each recommendation item within each subcategory, we assigned a numeric value to each answer: "yes" = 1, "sometimes" = 0.5, and "no" = 0. To create a partial score within each domain goal, we summed scores for all items and converted them to a percent such that the range of potential scores was 0–100. Lastly, a total index was created by calculating the average of the percent scores of each domain (potential final scores 1–100) (20). The arithmetic mean and standard deviation (SD) were used to summarize these scores.

To assess whether financial stability affects the availability and/or quality of GBC between institutions, we grouped institutions by income level according to the WB definitions for LMICs, UMICs, and HICs. We then compared the average scores for adherence to IPPC domain 6 among institutions at each income level. Statistical analysis included multilevel generalized linear models (GLM) with a Gaussian distribution adjusted by child age/gender and clustering by center. WB income group was modeled categorically (also using the HIC group as the reference group) and ordinally to assess the presence of a linear trend across income groups. Further, we explored whether patient or center characteristics are associated with total IPPC-adherence scores using univariate and multivariable multilevel GLM using the center as a clustering variable. The adjusted model included age, gender, race, comorbidities, and shift length. All statistical analysis was conducted using Stata v14.1. For patient characteristics, we considered age, gender, race, length of stay (LOS), diagnosis, and presence of comorbidities. For center characteristics, we considered the number of ventilators and resuscitation equipment, percent of daily bed use, beds per critical care provider (doctor or nurse), and provider shift lengths.

To better understand questionnaire answers, we also provided participants with the opportunity to provide detailed responses regarding items about GBC policies, rituals, and personnel. While the aggregate data from these open-ended questions was not detailed or extensive enough to perform an independent qualitative study, we applied concepts of content analysis to contextualize quantitative data. The results of this analysis are not generalizable but provide richness to our study results and may help orient further research and clinical considerations. We also applied concepts of content analysis and grounded theory as part of a mixed-methods methodology to analyze the participants' open-ended responses. After extracting and categorizing answers by question, answers were stratified by WB income level. Next, we assigned responses to categories, eliminated duplicates, and summarized responses when possible. Categories included: (1) support of, engagement with, and attitudes about patient-family GBC rituals, (2) individuals with experience in grief and loss available to provide GBC support, and (3) policies and guidelines established to ensure grief and loss support is provided to patients and families by country income level. Then, we compared original participant responses to ensure each answer was represented. Finally, we compared differences in the participants' answers according to WB country income level in order to connect data provided in open-ended responses to findings from our statistical analysis and literature review. We have included tables and a summary of results regarding centers' support of rituals, GBC facilitators, and GBC policies/guidelines by country income level group (**Supplementary Material**).

RESULTS

The PICU-MIC collaboration included 34 participating PICUs from 18 countries across Asia (15), Latin America (7), North America (5), Europe (5), and Africa (2). HIC units made up 32.4% of the sample, UMICs made up 44.1%, and lower middle-income/lower-income countries LMIC/LICs made up 23.5%.

Across all centers, fulfillment of the IPPC recommendations in offering family-specific grief and bereavement support (goal 6A) reached an average score of 37.5% (SD: 28.1) (**Table 1**). Scores increased with respect to income group, and ranged from 22.1% among the LIC/LMICs to the highest average score of 48.0% among HICs (p-value for trend: 0.02). This trend was not observed for each individual indicator of goal 6A. We found that the availability of appropriate services to support grief and bereavement of the family was higher among units in HICs (61.4%) compared to LICs (24.5%, p-value for trend: 0.004). Similarly, policies and guidelines for grief support were more often reported by units in HICs vs. LIC/LMICs (31.9 vs. 3.0%, p-value for trend: 0.001).

Centers achieved an average fulfillment score of 42.1% (SD: 35.3) for the IPPC recommendation to offer grief and bereavement support for HCPs (goal 6B, **Table 1**). Similarly, overall scores for goal 6B increased from 22.3% in LIC/LMICs to 64.1% in HICs (p-value for trend: 0.001). However, unlike goal 6A, we found evidence of an increasing trend in scores for each individual indicator of goal 6B as detailed in **Table 1**.

TABLE 1 | Grief and bereavement support goals (6A and 6B) and indicators according to World Bank income level classification.

Goals and indicators	Low and lower middle income	World bank income level		
		Upper middle income	High income	All centers
	Mean (sd)[a] *p*-trend[b]	Mean (sd)[a]	Mean (sd)[a]	Mean (sd)[a]
6A—Family				
Overall	25.1 (21.6) **0.02**	34.9 (23.8)	48.0 (32.2)	37.5 (28.1)
Family grief needs	49.0 (47.1) 0.89	46.0 (44.9)	49.4 (48.2)	47.8 (46.0)
Support of rituals	36.5 (43.7) 0.75	69.8 (41.6)	50.0 (49.1)	56.3 (46.6)
Grief support resources	24.5 (37.9) **0.004**	33.0 (46.2)	61.4 (45.4)	41.1 (46.8)
Grief professional support	12.5 (32.1) 0.09	17.0 (35.6)	43.9 (46.7)	25.3 (41.4)
Policies for grief support	3.0 (15.6) **0.001**	4.8 (21.0)	31.9 (44.6)	13.8 (33.2)
6B—Health care providers				
Overall	22.3 (24.0) **0.001**	32.8 (29.1)	64.1 (35.8)	42.1 (35.3)
Processes for HCP grief support	19.5 (31.7) **0.02**	18.7 (35.7)	64.0 (45.5)	34.3 (44.1)
Resources for HCP grief support	17.0 (28.6) **0.002**	21.1 (40.4)	69.3 (43.8)	36.8 (46.0)
Feedback from grieving HCP	28.5 (41.6) 0.08	41.6 (42.0)	54.7 (47.0)	43.5 (44.7)

[a]*Mean and standard deviation (sd), Scores range from 0 to 100%-points.* [b]*p-trend: p-value for linear trend estimated using GLMs adjusted for child's age and gender, and using the center as a clustering variable. HCP, health-care provider. The bold values are statistically significant with a p-value of < 0.05.*

Institutions located in HICs more frequently reported the existence of processes, resources and feedback mechanisms to support grieving HCPs (*p*-value for trend: 0.02, 0.002, and 0.08, respectively).

Associations between overall adherence scores for goals 6A and 6B and both sociodemographic characteristics of the patients and structural characteristics of the centers were identified and summarized in **Table 2**. For goal 6A (grief and bereavement support of the family), we found that units reported higher scores for children with PICU stays longer than a month compared to children with shorter stays (adjusted *p*-value: 0.03). Similarly, units reported higher levels of grief and bereavement support for families of children with multiple vs. single morbidities (adjusted *p*-value: 0.002). In terms of center characteristics, the only factor associated with fulfillment of goal 6A was the length of shifts but not the availability of equipment or specialized personnel. After adjusting for patient demographics and other center characteristics, scores consistently decreased as shift lengths increased (adjusted *p*-value for trend: 0.03).

For goal 6B (GB support of HCPs), we found an association between overall scores and patients' age and race without a clear pattern (**Table 2**). Units reported slightly higher levels of GBC for HCPs who cared for patients with multiple comorbidities compared to patients with a single morbidity (adjusted *p*-value: 0.002). In general, we did not find that center personnel or infrastructural characteristics were associated with the fulfillment of goal 6B. However, units with longer shift lengths had lower scores in goal 6B than units with shorter shift lengths (adjusted *p*-value for trend: 0.02).

Regarding detailed responses about policies, rituals, and personnel for grief and bereavement support, some participants in HICs mentioned that families are allowed as much time as they consider needed for their morning process and rituals. Others mentioned that all cultural/religious rituals and beliefs can take place as long as it is not life-threatening to the patient. Personnel from UMICs centers had similar responses. Answers pertaining which individuals with experience in grief and loss care were available to provide support varied greatly among centers from HICs, UMICs or LMICs/LICs. While responses coming from HICs included a wide variety of available personnel like psychologists, intensivists, nurses, rehabilitation services, pain management teams, social workers, interpreters and others, responses from LMICs/LICs included only a handful of those experts. Lastly, participants from HICs and UMICs mentioned the existence and use of specific guidelines dedicated to ensuring grief and loss support in their centers, despite considering them lacking in some instances. Contrastingly, LMICs/LICs did not specify any guidelines used.

TABLE 2 | Associations between patient and center characteristic, and overall scores for domains 6A and 6B of the Initiative for Pediatric Palliative Care's recommendations.

Characteristics of the patient	Family GBC			HCP GBC		
	Mean (sd[a])	*P*-value	Adj. *P*-value	Mean (sd)	*P*-value	Adj. *P*-value
Age						
Newborn (0–1 m) *N* = 33 (7.2%)	34.4 (28.8)	0.62	0.93	36.8 (39.1)	0.69	0.96
Infant (>1–12 m) *N* = 113 (24.5%)	35.9 (26.9)	0.23	0.54	38.7 (32.8)	**0.04**	**0.02**
Preschool (>1–5 y) *N* = 142 (30.8%)	39.6 (27.6)	Ref.[a]	Ref.	41.1 (37.6)	Ref.	Ref.
School (>5–11 y) (*N* = 92) (20%)	34.5 (26.3)	0.84	0.48	32.5 (35.7)	0.40	0.30
Teen (>11–18 y) *N* = 81 (17.6%)	37.1 (26.8)	0.91	0.88	40.1 (34.5)	0.40	0.56
Gender						
M, *N* = 262 (56.8%)	36.3 (27.8)	Ref.	Ref.	35.1 (34.3)	Ref.	Ref.
F, *N* = 199 (43.2%)	37.6 (26.1)	0.65	0.90	42.4 (36.9)	0.56	0.41
Race						
White, *N* = 165 (35.9%)	44.2 (29.3)	Ref	Ref.	50.4 (39.8)	Ref.	Ref.
Asian, *N* = 82 (17.8%)	30.7 (20.9)	0.64	0.35	20.4 (23.0)	0.55	0.87
Black, *N* = 54 (11.7%)	25.4 (27.3)	0.71	0.82	41.0 (36.4)	**0.01**	**0.001**
Indian, *N* = 31 (6.7%)	37.4 (9.99)	0.77	0.42	18.3 (18.9)	0.41	0.3
Mixed-race, *N* = 57 (12.4%)	37.5 (34.1)	0.66	0.61	33.6 (29.3)	0.31	0.48
Middle eastern, *N* = 67 (14.6%)	37.9 (23.2)	0.60	0.92	45.8 (36.3)	0.86	0.76
Other, *N* = 4 (0.9%)	10.0 (20.0)	0.20	0.26	50.0 (19.2)	0.71	0.56
Days in PICU						
<30 days, *N* = 390 (84.6%)	36.1 (27.11)	Ref.	Ref.	38.3 (36.2)	Ref.	Ref.
>30 days, *N* = 71 (15.4%)	41.5 (26.8)	**0.05**	**0.03**	38.3 (32.3)	0.69	0.21
Comorbidities						
Single MDC[b], *N* = 126 (27.6%)	36.2 (26.9)	Ref.	Ref	36.7 (35.8)	Ref.	Ref.
Multiple, *N* = 331 (72.4%)	37.1 (27.2)	**0.01**	**0.002**	38.8 (35.6)	**0.01**	**0.002**
Characteristics of the center						
Number of ventilators						
<1 per bed, *N* = 201 (43.6%)	34.7 (22.9)	Ref.	Ref.	32.6 (33.6)	Ref.	Ref
>1 per bed, *N* = 260 (56.4%)	38.8 (30.3)	0.89)	0.52	43.4 (36.7)	0.91	0.12
Resuscitation equipment						
<0.5 per bed, *N* = 323 (70.1%)	37.4 (26.5)	Ref.	Ref.	38.1 (38.4)	Ref.	Ref.
>0.5 per bed, *N* = 138 (29.9%)	35.4 (28.4)	0.95	0.23	38.8 (27.2)	0.99	0.98
Percent daily bed use						
<80%, *N* = 139 (30.2%)	39.7 (28.5)	Ref.	Ref.	45.6 (43.8)	Ref.	Ref.
>80%, *N* = 322 (69.88%)	35.3 (26.2)	0.77	0.59	34.2 (29.5)	0.50	0.14
Beds/critical care doctor						
<2 beds per doctor, *N* = 282 (65.7%)	36.1 (27.2)	Ref.	Ref.	38.3 (37.2)	Ref.	Ref.
>2 beds per doctor, *N* = 147 (34.3%)	38.0 (21.7)	0.80	0.80	38.9 (34.6)	0.64	0.75
Beds/nurse						
<2 beds per nurse, *N* = 208 (50.7%)	41.1 (30.3)	Ref.	Ref.	39.5 (39.1)	Ref.	Ref.
>2 beds per nurse, *N* = 202 (49.3%)	30.6 (23.1)	0.15	.83	35.9 (32.6)	0.55	0.64
Shift length						
<8 h, *N* = 102 (22.1%)	59.2 (24.4)	Ref.	Ref.	50.0 (41.4)	Ref.	Ref.
8–12 h, *N* = 241 (52.3%)	34.2 (28.3)	**0.01**	**0.001**	43.0 (33.3)	0.73	0.99
13–18 h, *N* = 42 (9.1%)	27.1 (26.2)	**0.02**	**0.009**	50.8 (40.8)	0.95	0.52
19–24 h, N=20 (4.2%)	12.0 (12.8)	**0.001**	**0.001**	17.5 (18.3)	0.17	0.30
Multiple, *N* = 56 (12.2%)	29.0 (8.61)	**0.01**	**0.008**	11.8 (13.4)	**0.04**	**0.02**
p-value *for trend*		**0.01**	**0.03**		**0.02**	**0.02**

‡*p-values were estimated using univariate and multivariable multilevel GLMs using center as a clustering variable. The adjusted model considers all factors in the table.* [a]*sd, standard deviation; Ref, reference category.* [b]*MDC, Major diagnostic category. The bold values are statistically significant with a p-value of < 0.05. ‡P-value headers.*

DISCUSSION

This international multicenter study revealed a statistically significant inverse relationship between country income level and the availability and quality of GBC to PICU patients, families, and HCPs. These findings echo what is already known from the literature (10) and reveal the precise aspects of GBC which vary between countries of different income levels in our sample. Similarly, a survey made in 2010 in 58 countries found that bereavement care for pediatric oncologic patients was available only in 28.3% of their sample with a statistically significant difference by income level in availability and existence of laws or institutional policies regarding GBC (21).

Regardless of income level, about half of all centers reported that they asked families about their needs for GBC both during the child's hospitalization and after their death. However, access to supportive resources for the family-patient unit, including specially trained staff and holistic care related to death and disease, varied greatly between centers (**Table 1**). Other studies have also found that most HCPs consider this type of service as necessary for pediatric palliative care practice, including those working in LMICs/LICs, despite having a different availability of resources to do so (21). In our sample, UMICs reported the highest amount of GBC rituals available to families, although mixed-methods analysis showed that HICs described providing more types of rituals, having more diverse on-site professional support, and generally more active participation in rituals. Participants generally reported support for diverse end of life rituals as long as these did not risk the well-being of the patient or others. Participants sometimes saw the facilitation of rituals as the responsibility of other specialists (e.g., chaplain, psychologist, religious leaders), though others described the accommodation and regulation of rituals as an important facet of intensive care. Some respondents specified that rituals were restricted to cases of imminent death, prior to death, and upon request.

With respect to timing of GBC, standard of care guidelines dictate that PC should be available from the moment of diagnosis (22), and not reserved for instances of imminent death as reported by some centers. Furthermore, evidence shows that rituals may improve family and HCP capacity to cope with the devastating situation, accept unanticipated losses, experience positive feelings following grief, and restore feelings of control (23, 24). Future studies are needed to further determine the best mechanisms of implementing and standardizing GBC such that hospital resources are allocated efficiently to optimize patient-family outcomes.

This study also identified differences in the availability of professionals to provide GBC by country level income. While the differences did not reach statistical significance, HICs (43.9) reported the greatest availability of GBC professionals, followed by UMICs (17.0), and then LMICs/LICs (12.5). This trend was reflected in the mixed-methods analysis (**Table 1**). Overall, HICs described having more availability of multidisciplinary professionals working in their centers in comparison to UMICs, which, in turn, reported more multidisciplinary professionals available than LMICs/LICs.

Additionally, we observed differences in the use of established policies and guidelines for GBC according to country income level. This finding was also reflected in the mixed methods analysis. HICs were most likely to report using established GBC policies/guidelines and reported a greater variety of standardized policies than units of other income levels. Notably, although not explicitly asked, professionals in UMICs reported disagreements and worries about the suitability of official guidelines in their units (e.g., lack of universal applicability, lack of standardization, a complete absence of guidelines, or not knowing if there were guidelines). UMICs also reported the use of more unit-specific and non-standardized guidelines than HICs. Some units in both HICs and UMICs reported substitutes (e.g., experience, routines, "tacit agreements") for the use of standardized guidelines. Other participants saw grief and loss support as the responsibility of other departments. LMICs/LICs did not specify the policies/guidelines used.

Evidence shows that standardizing many facets of critical care may improve outcomes, reduce care costs, and minimize length of stay, but practices to ensure standardization of care are not widely implemented (25). The establishment of GBC guidelines that are acceptable to professionals especially for centers in UMICs, LMICs, and LICs may represent a low-cost method to improving quality of care, patient-family outcomes, and satisfaction with care. Furthermore, evidence suggests that, particularly in LMICs, local government and community organizations can improve the availability and quality of grief and bereavement support in the healthcare system by supporting the implementation of such guidelines (10).

Our study also found differences in GBC for HCPs by country income level. Overall, HICs reported more diverse opportunities supporting healthcare professionals to express their GBC needs, more formalized services, and more regular support opportunities than units in other income groups. Important variations in support opportunities included the frequency of opportunities (e.g., regularity, formality, and prioritization of care opportunities), specialization of facilitators (e.g., psychologists, trained peers, informal support between colleagues), cost of services (e.g., free, independently paid, or unspecified), nature of opportunities (e.g., preventative vs. reactionary), and accessibility (e.g., regularly or sporadically available, unregulated informal support online, 24/7 hotlines). Participants similarly described differences in the resources dedicated to staff (e.g., reserved time, space, professionals) and diversity of services (e.g., only one type of support, or a combination of psychological, religious, spiritual, social work, general health, social, other support). Finally, participant responses reflected a diversity of attitudes regarding how HCPs are perceived by others with regard to their GBC needs (e.g., second victims, professionals) and who is responsible for providing GBC (e.g., individual, team/unit, institution). Normalizing and formalizing GBC for PICU professionals is important because unaddressed grief among HCPs may contribute to maladaptive coping, unhealthy work environments, burnout, and other psychosocial issues (26), as well as ultimately affect the patient-family unit's quality of care (2, 3).

While the present study was completed prior to the COVID-19 pandemic, evidence suggests a dramatically growing need for GBC for patients, families, and HCPs (27) affected by COVID-19. The disparities and insufficiencies of GBC in PICUs around the

world highlighted in our research will likely worsen as a result of this international crisis. Our findings highlight the need to develop interventions to improve the GBC for patients, families, and PICU professionals, irrespective of country income.

Our study has strong points. We analyzed various possible variables determining grief and bereavement care. These included unit characteristics, human resources, patient characteristics and country World Bank Income classification. In addition, we included data from centers located in areas which are not frequently considered in scientific research, either due to geographic or resource limitations or due to language barriers. However, our study has limitations. Responses coming exclusively from centers are not a reliable representative for IPPC curriculum adherence in the whole country. Moreover, we did not request the involved institutions to declare whether they were from urban, suburban or rural areas. Neither did we ask to specify if the centers had public, private or public-private funding. Furthermore, opinions on availability and provision of grief and bereavement care may vary depending on the seniority of the medical professional answering the questionnaires and we did not include this variable in our survey. Finally, determining GBC fulfillment exclusively via assessment of the IPPC curriculum may not be fully representative of how this service is practiced and offered in the countries evaluated.

CONCLUSION

Independent of ultimate patient outcomes, the experience of PICU hospitalization is associated with diverse psychosocial and physical sequelae amongst pediatric patients and their families (28). HCPs are also at risk for burnout, psychiatric illness, etc. The often-undertreated grief and bereavement needs of patients, families, and HCPs are intertwined with the development of these sequelae and thus merit standardized attention within in the PICU. The present study highlighted disparities in GBC provision for both the patient-family unit and HCPs in PICUs across the globe. Accessibility and quality of GBC were inversely related to country income level. Furthermore, our mixed-methods analysis identified specific care techniques used by different PICUs around the world as well as future areas of research. Thus, we provide evidence related to ways in which care practices may vary by country income group as well as points of consideration for further research.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidad San Francisco de Quito Ethics Committee for Research of Human Beings/IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

PICU-MIC INVESTIGATORS

1. Jorge López González, MD; Jesús López-Herce, MD—Hospital General Universitario Gregorio Marañón-UCIP; Facultad de Medicina Universidad Complutense de Madrid, Madrid, Spain.
2. Emanuele Rossetti, MD; Chiusolo Fabrizio, MD—Ospedale Pediatrico Bambino Gesù-PICU, Roma, Italy.
3. Oliver Karam, MD, PhD, Marie Saint-Faust, MD—Geneva University Hospitals-HUG PICU, Geneva, Switzerland.
4. Paolo Biban, MD; Silvia Carlassara, MD—Azienda Ospedaliera Universitaria Integrata Verona- PICU, Verona, Italy.
5. Bettina von Dessauer, MD; Nadia Ordenes, MD—Hospital de Niños Roberto del Río Unidad de Paciente Crítico Pediátrico, Santiago, Chile.
6. Fabiola Figueroa Urízar, MD; Adriana Wegner A, MD—Hospital Sótero Del Río-UCIP, Santiago, Chile.
7. Michael Canarie, MD—Yale-New Haven Children's Hospital's Pediatric Intensive Care Unit, New Haven, Connecticut, USA.
8. Kathryn Miller, MD—University Hospitals Cleveland Medical Center-PICU, Cleveland, Ohio, USA.
9. José Irazuzta, MD; Nicolas Chiriboga, MD—University of Florida COM-PICU, Jacksonville, Florida, USA.
10. Daniel Tawfik, MD, MS; Barbara Sourkes, PhD; Nancy Ewen Wang, MD; Hursuong Vongsachang—Division of Pediatric Critical Care Medicine at Stanford University Medical Center-PICU, Stanford, CA, USA.
11. Elizabeth W. Tucker, MD; Nicole Shilkofski, M.D., M.Ed.; The Johns Hopkins Children's Center PICU, Baltimore, MD, USA.
12. 王文超 Wang Wenchao, RN; Zhang Yuxia, RN, PhD; Pediatric Hospital of Fudan University-PICU—Fudan, China.
13. Lucy Lum Chai See, MD; Sister Priscilla—University Malaya Medical Center-PICU, Kuala Lumpur, Malaysia.
14. Recep Tekin, MD; Fesih Aktar, MD—Dicel University Medical Hospital-PICU; Diyarbakir, Turkey
15. Duygu Sönmez Düzkaya, CPN, PhD—Istanbul University Faculty of Medicine PICU; Istanbul, Turkey.
16. Oguz Dursun, MD; Ebru Atike Ongun, MD—Akdeniz University-Faculty of Medicine PICU; Antalya, Turkey.
17. Resul Yilmaz, MD—Gaziosmanpasa University School of Medicine Tokat- PICUTokat, Turkey.
18. Dincer Yildizdas, MD—Çukurova University, Faculty of Medicine; Balcali Hospital, PICU- Adana, Turkey.
19. Hakan Tekgüç, MD—Koru Hospital-PICU; Ankara, Turkey.
20. Vitaliy Sazonov, MD; Timur Tsoy, MD—PICU of City Children Hospital; Astana, Kazakhstan.
21. Vitaliy Sazonov, MD; Askhat Saparov, MD—PICU of National Research Center for Maternal and Child Health; Astana, Kazakhstan.

22. Vitaliy Sazonov, MD; Elizaveta Kalmbakh, MD—PICU of Karaganda Regional Children's Hospital, Karaganda, Kazakhstan.
23. Michelle Grunauer, MD, PhD (USFQ/HDLV); Ernesto Quiñones, MD (HDLV); Luis Eguiguren, MD (USFQ); Killen Briones, MD (UG, CFRBC, ICU, ICU IESS); UCIP/UCIN del Hospital de los Valles, Quito, Ecuador; Universidad San Francisco de Quito, Facultad de Medicina, Quito, Ecuador; Universidad de Guayaquil, Facultad de Ciencias Médicas, Guayaquil, Ecuador; Centro Fisiológico-Respiratorio Briones Claudett, Guayaquil; ICU Panamerican Clinic, Guayaquil; ICU IESS de Babahoyo, Ecuador.
24. Yaneth Tovilla, MD—Unidad Pediátrica de Quemados de los Servicios de Salud del Estado de Puebla, Puebla, México.
25. Sandra Tania Ventura Gómez, MD—UCIP del Hospital Regional de Alta Especialidad de Ixtapaluca, Ixtapaluca, México.
26. Silvio Fabio Torres, MD, MSc—Pediatric Intensive Care Unit, Hospital Universitario Austral; Buenos Aires, Argentina.
27. Paul Cobarrubias, MD—Amang Rodriguez Memorial Medical Center-PICU, Manila, Philippines.
28. Dmytro Dmytriiev, MD—Vinnitsa National Medical University-PICU, Vinnitsa, Ukraine.
29. Alejandro Martínez, MD; Gustavo Guzaman, MD; Rudy Sanabria, MD—Hospital del Niño Manuel Ascencio Villarroel, Cochabamba-UTIP, Cochabamba, Bolivia.
30. Ravikumar Krupanandan, MD; Bala Ramachandran, MD—PICU, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India.
31. Nirmal Choraria, MD; Jignesh Patel, MD; PICU—Nirmal Hospital, Ltd.; Surat, India.
32. Puneet A Pooni, MD; Karambir Singh Gill, MD—Dayanand Medical College & Hospital-PICU; Punjab, India.
33. John Adabie Appiah, MD; Komfo Anokye Teaching Hospital—PICU, Kumasi, Ghana.
34. Tigist Bacha Heye, MD; Rahel Argaw, MD; Asrat Demtse, MD; Israel Abebe Admasu, MD—Addis Ababa University, College of Health Sciences-PICU, Addis Ababa, Ethiopia.

AUTHOR CONTRIBUTIONS

MG, CM, and GB contributed to, substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work, critical revision for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DA: contributed to, critical revision for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KZ contributed to, literature review, wrote the first draft, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AI-F, AG, and RB contributed to, critical revision for important intellectual content, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PICU-MIC investigators: substantial contributions to the conception or design of the work and the data acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Clinical Characteristics and Outcomes of Children With Extracorporeal Membrane Oxygenation in a Developing Country: An 11-Year Single-Center Experience

Wirapatra Iamwat[1], *Piya Samankatiwat*[2], *Rojjanee Lertbunrian*[1] *and Nattachai Anantasit*[1]*

[1] Division of Pediatric Critical Care, Department of Pediatric, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [2] Division of Cardiothoracic Surgery, Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

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Krishan Chugh,
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Washington University School of Medicine in St. Louis, United States

***Correspondence:**
Nattachai Anantasit
nattachai032@hotmail.com

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Introduction: Extracorporeal Membrane Oxygenation (ECMO) is a lifesaving procedure for patients with refractory cardiac or respiratory failure. The indications for ECMO are growing, and it is increasingly being used to support cardiopulmonary failure in children. However, the risks and benefits of ECMO should be weighed before deploying it on the patients. The objectives of this study were to identify the mortality risk factors and to determine the ECMO outcomes.

Methods: The retrospective chart reviews were done for all patients aged 1 day−20 years old receiving ECMO between January 2010 and December 2020.

Results: Seventy patients were enrolled in the study. The median age was 31.3 months. The incidence of VA and VV ECMO was 85.7 and 14.3%, respectively. The most common indication for ECMO was the failure to wean off cardiopulmonary bypass after cardiac surgery. Pre-existing acute kidney injury (OR 4.23; 95% CI 1.34–13.32, $p = 0.014$) and delayed enteral feeding (OR 3.85, 95% CI 1.23–12.02, $p = 0.020$), and coagulopathy (OD 12.64; 95% CI 1.13–141.13, $p = 0.039$) were associated with the higher rate of mortality. The rates of ECMO survival and survival to discharge were 70 and 50%, respectively.

Conclusion: ECMO is the lifesaving tool for critically ill pediatric patients. Pre-existing acute kidney injury, delayed enteral feeding, and coagulopathy were the potential risk factors associated with poor outcomes in children receiving ECMO. However, ECMO setup can be done successfully in a developing country.

Keywords: extracorporeal membrane oxygenation, pediatric, risk factors, outcome, neonatal

INTRODUCTION

Extracorporeal Membrane Oxygenation (ECMO) is a life-saving procedure that is used to treat patients who have failed to respond to the conventional treatments for cardiac or respiratory failure (1–3). According to the Extracorporeal Life Support Organization (ELSO) report 2016, 24% of all ECMO implants were performed on children, and newborns accounted for 47% of the total cohort (4). Prior to ECMO initiation, the patient's risks and benefits should be outlined. Hemorrhagic and thrombotic complications are among the most common complications associated with ECMO. Nosocomial infections are also common in patients receiving ECMO and are associated with poor outcomes, especially in the neonatal population. Bartlett et al. performed the first neonatal ECMO in 1975, saving the life of a 1-day-old neonate with severe meconium aspiration syndrome (5). Following that, ECMO had been evolved in terms of equipment and management. Furthermore, this sophisticated technology had been successfully used to perform emergency cardiopulmonary resuscitation (E-CPR) (1, 6, 7). The Extracorporeal Life Support Organization (ELSO) gathered data and reported on the global growth, outcomes, and complications of the ECMO technology. In neonatal and pediatric patients, two primary ECMO circuits are used: venovenous (VV) and venoarterial (VA) ECMO. Vascular access is determined by the patient's condition and the surgeon's experience. While VA ECMO maintains both the hemodynamic and the respiratory function, VV ECMO only supports the respiratory function. ECMO is never recommended in the presence of lethal chromosomal or syndromic abnormalities, as well as severe irreversible brain or multiorgan failure.

The most common short-term complications in patients receiving ECMO were hemorrhagic and thrombotic events, cardiac depression, seizures, and acute kidney injury (AKI) (8–10). Long-term complications included hearing loss, delayed development, and decreased lung volume, particularly in patients with respiratory failure (10–13). Our hospital has been developing an ECMO program since 2003. Our center is the tertiary referral center in Bangkok, Thailand. Many patients have multiple conditions, including those who have undergone cardiac surgery, severe acute respiratory distress syndrome, solid organ transplantation, and heart transplantation. Each year, the number of pediatric patients receiving ECMO at our center increases. The objective of this study was to assess the outcomes of ECMO and to identify the risk factors for mortality in neonatal and pediatric patients receiving ECMO.

MATERIALS AND METHODS

This study was performed in a tertiary care referral center. We retrospectively analyzed the medical records of children aged 1 day−20 years who received ECMO from January 2010 to December 2020. This study was approved by the Institutional Review Board. Incomplete medical records were excluded. The demographic and baseline characteristics of the patients were collected, including their age, gender, body weight, immunological status, underlying disease, The Pediatric Risk of Mortality III, length of intensive care unit stays, and in-hospital mortality. Additionally, the characteristics of ECMO were reviewed, including indication, type of ECMO, duration of cannulation, and complications.

Initially the ECMO program was run by an individual attending cardiothoracic surgeon who reviewed the ELSO guideline and literature. Since 2015, our center has established an ECMO committee which comprised of pediatric intensivists, cardiothoracic surgeons, anesthesiologists, perfusionists, and certified ECMO nurses to assess the risks and benefits of ECMO in each patient. A cardiothoracic surgeon was initially ECMO program director with responsibility for overall operation. Two to three medical directors were responsible for locating an ECMO fund, establishing ECMO facilities and equipment, training in ECMO education, and preparing an annual ECMO summary. As the financial restrictions, the selected ECMO patients were required to undergo ECMO under the supervision of two of three ECMO committee members other than the patient's attending staff. These patients would be waived the ECMO expense from our center. Additionally, ECMO patients would have shortened the duration of the initial ECMO. As the lack of perfusionists, our center had only four to seven perfusionists who were responsible for cardiopulmonary bypass (CPB) and ECMO machine in both adults and children. Occasionally, we had three ECMO patients in the same period. There were insufficient perfusionists to cover all ECMO patients during 24-h on-call period. We had initiated a local basic and advanced ECMO course to train ICU nurses to become certified ECMO nurses capable of caring for the ECMO machine in place of the perfusionist. We had annually local ECMO meeting and workshop to keep updated ECMO knowledge and skills to the certified ECMO physicians and nurses. The indications of ECMO were patients who had the potentially reversible causes of severe cardiopulmonary failure such as pediatric acute respiratory distress syndrome with oxygen index $>$ 30 for 6 h or $>$40 for 2 h, acute fulminant myocarditis, failure to weaning from CPB, progressive ventricular failure, or severe pulmonary hypertensive crisis. The location of ECMO cannulation was specified as an operating room or pediatric intensive care unit (PICU). Cannulation configurations were classified as central (sternotomy) for patients undergoing cardiopulmonary surgery or peripheral vessel for patients undergoing medical cardiopulmonary failure. We had the initial standing order in place for the ECMO-selected patients. The ECMO circuits were primed with packed red blood cells if the patient's weight was $<$10 kg. Heparin 100 unit/kg was given as a bolus infusion with a goal of an activated clotting time of 300 s. The initial pump flow rate was 20–30 mL/kg/min and increased gradually to the target flow of 2.4–3 L/m^2/min. Typically, the initial sweep gas flow rate was equal to the blood flow rate (1:1), and the sweep flow was adjusted according to the $PaCO_2$ level of each patient. Adjustment of pump flow was used to ensure adequate systemic perfusion (central venous oxygen saturation $>$ 70%, normal arterial lactate, and adequate mean arterial blood pressure). The anticoagulant was using unfractionated

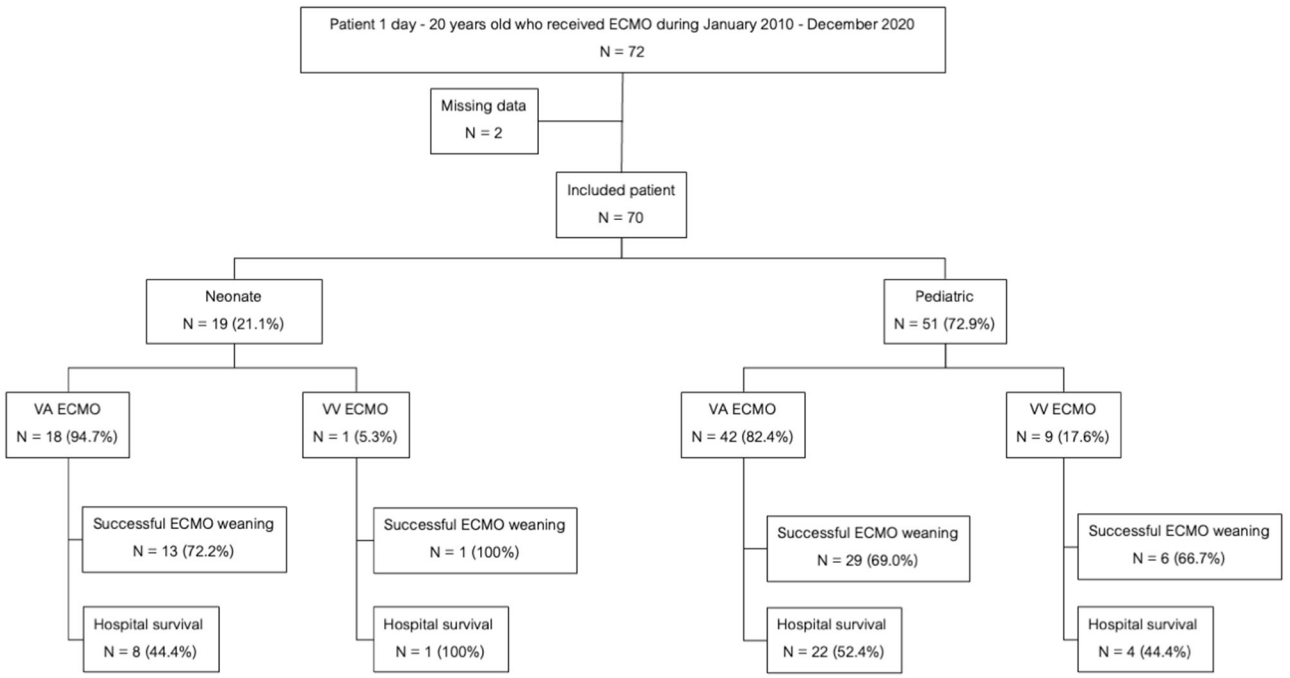

FIGURE 1 | Flow chart of pediatric ECMO patients in this study.

heparin with monitoring *via* activated clotting time, activated partial thromboplastin time, and antiXa level. We had the multidisciplinary team including ICU physicians, ICU nurses, certified ECMO nurses, perfusionists, pediatric nutritionists, pediatric hematologists, clinical pharmacists. Weaning from ECMO was initiated when the following criteria were met: improvement in clinical course, recovery of end-organ function, and stable respiratory and hemodynamic status. Weaning from the VA ECMO was accomplished by decreasing the ECMO flow to 30 mL/kg/min, bridging ECMO for 1 h, and monitored the hemodynamic status and central venous oxygen saturation. If successful bridging was achieved, the decannulation of ECMO was performed. The protocol for weaning from VV ECMO was to decrease the FiO_2 in the ECMO to 0.21 and weaned the sweep gas to zero. We then monitored the oxygen saturation and the arterial blood gases. If the oxygen saturation was >92% and the arterial blood gases were within the normal range, the VV ECMO could be then decannulated.

DEFINITIONS

Successful ECMO weaning was defined as the patients who survived for more than 72 h after successful cessation of ECMO support (14).

Hospital survival was defined as the patients who were successfully weaned off from ECMO and continued to survived until hospital discharge.

Early enteral feeding was defined as enteral feeding within 48 h after ECMO cannulation, whereas delayed enteral feeding was defined as enteral feeding after 48 h of ECMO cannulation.

The definition of acute kidney injury (AKI) was defined according to the Kidney Disease Improving Global Outcome (KDIGO) (15). The pre-existing AKI was defined as patients who had developed AKI within 48 h prior to initiate ECMO or after 48 h of ECMO initiation.

STATISTICAL METHODS

Data were analyzed using PASW Statistics, version 21 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as frequency, distribution, and percentage. Differences in the frequencies of discrete variables were tested using Pearson's Chi-square test or Fisher's exact test. Logistic regression was used to measure the association between the clinical variable and hospital mortality. Risk factors determined to be clinically significant a priori on the bivariable analyses were identified as candidate variables for the multivariable model. A log-rank test was used to analyze the survival of patients who received ECMO. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 70 children underwent ECMO support during the study period. Fifty-one patients (72.8%) were among the pediatric group while the remaining 19 (27.2%) were in the neonatal

TABLE 1 | Baseline characteristics.

	Total (*N* = 70)	Survivors (*N* = 35)	Non-survivors (*N* = 35)	*p* - value
Median age (months; IQR)	31.3 (0.9–46.4)	13.4 (1–52.1)	7.4 (0.7–45)	0.443
Gender: Male, *n* (%)	41 (58.6)	21 (60.0)	20 (57.1)	0.808
Median body weight (kg; IQR)	8.5 (3.3–15.2)	8.5 (3.8–15.0)	7.4 (3.2–15)	0.750
Underlying disease, *n* (%)				
Heart disease	51 (72.9)	25 (71.4)	26 (74.3)	0.764
Healthy	10 (14.3)	6 (17.1)	4 (11.4)	
Other	9 (12.9)	4 (11.4)	5 (14.3)	
Median PRISM III score (IQR)	15.5 (13–19)	16 (13–18)	14 (14–19)	0.522
Indications for ECMO, *n* (%)				
Failure to weaning from CPB	24 (34.3)	10 (28.6)	14 (40.0	0.461
Ventricular failure	24 (34.3)	15 (42.9)	9 (25.7)	
Pulmonary hypertensive crisis	12 (17.1)	5 (14.3)	7 (20.0)	
Severe ARDS	9 (12.9)	4 (11.4)	5 (14.3)	
In-hospital cardiac arrest	1 (1.4)	1 (2.9)	0	
ECMO year 2015–2020	66 (94.3)	34 (97.1)	32 (91.4)	0.364
ECMO type, *n* (%)				
Venoarterial	60 (85.7)	30 (85.7)	30 (85.7)	1.000
Venovenous	10 (14.3)	5 (14.3)	5 (14.3)	
Delayed enteral feeding, *n* (%)	33 (47.1)	11 (31.4)	22 (62.9)	0.008*
Pre-existing AKI, *n* (%)	29 (41.4)	9 (25.7)	20 (57.1)	0.008*

PRISM III, The Pediatric Risk of Mortality III; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury.
*Median (interquartile range), *p-value < 0.05.*

TABLE 2 | Outcomes and complications of ECMO.

	Total (*N* = 70)	Survivors (*N* = 35)	Non-survivors (*N* = 35)	*p*-value
Duration of ECMO support (days, IQR)	6.5 (4–12)	6 (4–8)	8 (4–13)	0.069
Length of stay in ICU (days, IQR)	24 (15–36)	23 (15–36)	24 (14–40)	0.784
Length of stay in hospital (days, IQR)	30 (18–35)	37 (25–61)	24 (14–40)	0.395
Upper gastrointestinal bleeding, *n* (%)	6 (8.6)	1 (2.9)	5 (14.3)	0.088
Acute kidney injury, *n* (%)	10 (14.3)	3 (8.6)	7 (20.0)	0.172
Continuous renal replacement therapy, *n* (%)	4 (5.7)	1 (2.9)	3 (8.5)	0.303
Immediate complications, *n* (%)				
Surgical site bleeding	7 (10.0)	2 (5.7)	5 (14.3)	0.232
Pneumothorax	6 (8.6)	2 (5.7)	4 (11.4)	0.415
Hemopericardium	3 (4.3)	1 (2.9)	2 (5.7)	0.555
Infectious complications, *n* (%)				
CRBSI	5 (7.1)	2 (5.7)	3 (8.6)	0.643
VAP	8 (11.4)	3 (8.6)	5 (14.3)	0.452
Neurological complications, *n* (%)				
Seizure	10 (14.3)	5 (14.3)	5 (14.3)	1.000
Cerebral hemorrhage	7 (10.0)	4 (11.4)	3 (8.6)	0.690
Stroke	1 (1.4)	1 (2.9)	0	0.314
ECMO mechanical complications, *n* (%)	5 (7.1)	3 (8.6)	2 (5.7)	0.643
Coagulopathy, *n* (%)	8 (11.4)	1 (2.9)	7 (20.0)	0.024*

ICU, intensive care unit; CRBSI, catheter-related blood stream infection; VAP, ventilator associated pneumonia.
*Median (interquartile range), *p-value < 0.05.*

TABLE 3 | Logistic regression analysis for associated risk factors with mortality.

Variables	Univariate analysis Odd ratios (95%CI)	Multivariate analysis Odd ratios (95%CI)	*p*-value
Age	1.005 (0.994–1.016)	1.003 (0.989–1.018)	0.663
PRISM III	0.932 (0.841–1.032)	0.904 (0.784–1.042)	0.904
Delayed enteral feeding	3.692 (1.372–9.933)*	3.848 (1.232–12.021)*	0.020
Pre-exiting AKI	3.852 (1.401–10.590)*	4.227 (1.341–13.324)*	0.014
Coagulopathy	8.500 (0.986–73.276)	12.644 (1.133–141.127)*	0.039

PRISM III, The Pediatric Risk of Mortality III; AKI, acute kidney injury.
**p-value < 0.05.*

group. There were 60 (85.7%) patients required VA ECMO and 10 patients (14.3%) required VV ECMO. The flow chart of all patients receiving ECMO support in this study was shown in **Figure 1**. There were 4 and 66 patients who received ECMO support during 2010–2015 and 2015–2020, respectively. The mortality rate was not significantly different between two periods (75 vs. 48.5%, $p = 0.326$). The baseline characteristics were shown in **Table 1**. Central cannulation was the most frequently used site for cannulation in neonatal and children. Central cannulation was performed in 71% of cases. The mean age was 31.3 (0.9–46.4) months, and 58.6% of participants were male. Forty-nine (70%) patients were successfully weaned from ECMO. Overall hospital mortality was 50%. Among the pediatric group, the mortality rate was 25 of 51(52.6%) patients while the neonatal group suffered a mortality rate of 10 of 19 (49%) patients. The mortality rate of VA ECMO and VV ECMO were 50 and 50%, respectively. The most common comorbidity was congenital heart disease. The three major indications for ECMO support the failure to wean off cardiopulmonary bypass (CPB) (34.3%), ventricular failure (34.3%), and pulmonary hypertensive crisis (17.1%). Twenty-nine patients (41.1%) had pre-existing AKI stage 2 or above. Two patients who required

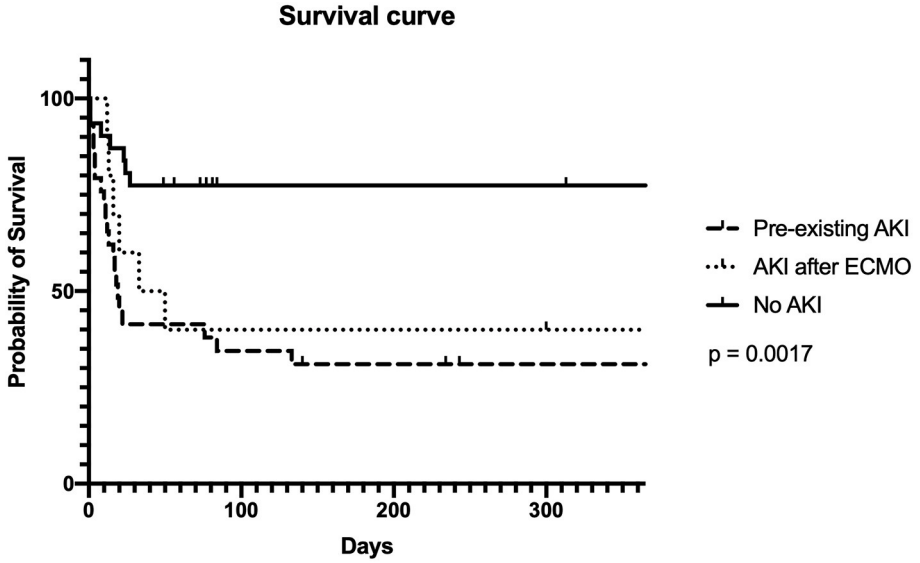

FIGURE 2 | Survival curve.

ECMO for bridging to heart transplantation and both of them survived.

The median duration of ECMO support was 8.3 days (range 3 h−27 days). The median length of stay in ICU was 29.8 days (range 3–134 days). The most frequently encountered complications were hematological (28.6%) and neurological in nature (28.6%). **Table 2** summarized the outcomes and associated complications. The delayed enteral feeding was found to be higher among the non-survivors than survivors (62.9 vs. 31.4%, $p = 0.008$). Coagulopathy was found to be more prevalent in the non-survivors than the survivors (20 vs. 2.9%, $p = 0.024$). Only those who died in the hospital had disseminated intravascular coagulation (DIC). There were 5 patients with thrombocytopenia, 2 patients with heparin-induced thrombocytopenia (HIT) and only 1 patient with heparin resistance. Multiple logistic regression analysis to adjust for the clinical variables significantly associated with hospital mortality (age, PRISM III, delay enteral feeding, pre-existing AKI, and coagulopathy) confirmed that delayed enteral feeding [Odds ratio (OR) 3.85; 95% confidence interval (CI) 1.23–12.02; $p = 0.020$], pre-existing AKI [OR 4.23; 95% CI 1.34–13.32, $p = 0.014$], and coagulopathy [OD 12.64; 95% CI 1.13–141.13, $p = 0.039$] were potential risk factors for increasing mortality (**Table 3**).

Fifty percent of the neonatal and pediatric patients on ECMO support survived until discharge. The leading cause of in-hospital death was septicemia (54.3%). Other causes of death included heart failure (28.6%), brain death (5.7%), and renal failure (1.4%). The overall 1-year survival rate of our patients was 47.8%. Survival rates were 31.0, 30, and 73.3%, respectively, in the pre-existing AKI, AKI after ECMO, and the non-AKI group ($p = 0.050$) (**Figure 2**).

DISCUSSION

In this study, the distribution of age group among patients requiring ECMO varied similarly to the previously reported studies by ELSO, 85.7% in pediatric age group and 14.3% in neonates. This study found that the neonates with congenital heart disease had a higher rate of requiring VA ECMO implantation than the general population, which was consistent with the previous research (13). The most common indication for ECMO within this cohort was the failure to wean off cardiopulmonary bypass following cardiac surgery. The number of patients who received ECMO support climbed rapidly after the ECMO committee established. The mortality rate was slightly decreased but no significant difference in two period due to the very low number of ECMO patients in pre-ECMO committee program period. The ECMO survival rate and survival rate to discharge were 70 and 50%, respectively, which were comparable to the previous studies (12, 13, 16, 17). This study found the ECMO survival rate to discharge in VA and VV were 50%, while the ELSO registry summarized that the mortality rate of VA ECMO was 51.9% and VV ECMO was 61.8% in Asia pacific registration (18). Our ECMO program used unfractionated heparin as the routine anticoagulant. Our study found ECMO patients had HIT 2.8% and heparin resistance 1.4%. An overall incidence of immune-mediated HIT with unfractionated heparin was 2.6% by a meta-analysis (19). Bivalirudin is an alternative anticoagulant in ECMO for patients with HIT or heparin resistance (20). To our knowledge, this study was the first study to report the clinical characteristics, risk factors, and outcomes in pediatric patients with ECMO in Thailand.

The incidences of AKI in neonatal and pediatric ECMO patients were estimated to be between 50 and 62% in a multicenter retrospective observational cohort study (21).

Additionally, patients with AKI were shown to require a longer duration of ECMO support, longer ventilator days, and had a higher mortality rate (17, 21, 22). A recent meta-analysis study in 3,523 pediatric patients on ECMO demonstrated that AKI was significantly associated with reduced survival outcome (23). AKI was the most frequently encountered complication in this study and was associated with a significant increase in mortality rate, particularly in those with pre-existing AKI. Additionally, we also found that the non-AKI group had a higher 1-year survival rate than the AKI group (31 vs. 73%, $p = 0.050$).

Providing optimal nutrition to critically ill children is also an important aspect of a favorable outcome. There were few nutritional support studies in pediatric patients who received ECMO even though they were nutritionally vulnerable (24, 25). A prior retrospective study showed that early enteral feeding was associated with a lower hospital mortality rate (25). Our study found that late enteral feeding after 48 h was associated with an increased risk of mortality.

Septicemia was the leading cause of death in our patients. The most prevalent pathogen was bacteria, particularly those with extensive drug resistance, which was consistent with other studies (26, 27).

Our study had several strengths. We reported the first clinical characteristics and outcomes of pediatric ECMO in Thailand. This study demonstrated a successful ECMO program that developing countries might use to drive the establishment of their own programs and improve patient outcomes. This program utilized an established ECMO committee to select ECMO patients, create certified ECMO nurses as ECMO specialists, establish ECMO training and continue annual ECMO training.

This study had some limitations. First, this was a retrospective study with some variables having missing data. Second, because this study was conducted in a single center with a small sample size, it cannot be generalized. Our center, on the other hand, was a large referral center that may represent the region. Finally, the federal government imposes spending limits on ECMO patients. ECMO may be initiated late in the course of some patients' illnesses. However, our center utilized an ECMO committee to determine which patients would receive ECMO, which likely shortened the time required to initiate ECMO. Additionally, this financial crisis may be comparable to that of other developing countries. Additional collaborative and prospective research are required to validate risk factors and outcomes in developing countries.

CONCLUSION

ECMO is the lifesaving treatment for rescuing neonatal and pediatric patients with refractory cardiopulmonary failure. Pre-existing acute kidney injury and delayed enteral feeding were associated with an increased mortality rate. Nosocomial infection was the leading cause of death in hospitals. An ECMO program could be done successfully with a multidisciplinary team in developing country.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WI and NA contributed to design of the study, data collection, data analysis, and manuscript drafting. PS and RL contributed to design of the study. NA critically revised it for important intellectual content. All authors gave final approval of the version to be published.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Delayed Presentation and Mortality in Children With Sepsis in a Public Tertiary Care Hospital in Tanzania

Audrey Marilyn Smith[1], Hendry R. Sawe[2], Michael A. Matthay[3], Brittany Lee Murray[4], Teri Reynolds[5] and Teresa Bleakly Kortz[1,6]*

[1] Institute for Global Health Sciences, University of California, San Francisco, San Francisco, CA, United States, [2] Department of Emergency Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania, [3] Departments of Medicine and Anesthesia, Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA, United States, [4] Department of Pediatrics and Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA, United States, [5] World Health Organization, Geneva, Switzerland, [6] Division of Critical Care, Department of Pediatrics, University of California, San Francisco, San Francisco, CA, United States

Background: Over 40% of the global burden of sepsis occurs in children under 5 years of age, making pediatric sepsis the top cause of death for this age group. Prior studies have shown that outcomes in children with sepsis improve by minimizing the time between symptom onset and treatment. This is a challenge in resource-limited settings where access to definitive care is limited.

Methods: A secondary analysis was performed on data from 1,803 patients (28 days−14 years old) who presented to the emergency department (ED) at Muhimbili National Hospital (MNH) from July 1, 2016 to June 30, 2017 with a suspected infection and ≥2 clinical systemic inflammatory response syndrome criteria. The objective of this study was to determine the relationship between delayed presentation to definitive care (>48 h between fever onset and presentation to the ED) and mortality, as well as the association between socioeconomic status (SES) and delayed presentation. Multivariable logistic regression models tested the two relationships of interest. We report both unadjusted and adjusted odds ratios and 95% confidence intervals.

Results: During the study period, 11.3% ($n = 203$) of children who presented to MNH with sepsis died inhospital. Delayed presentation was more common in non-survivors ($n = 90/151$, 60%) compared to survivors ($n = 614/1,353$, 45%) ($p \leq 0.01$). Children who had delayed presentation to definitive care, compared to those who did not, had an adjusted odds ratio for mortality of 1.85 (95% CI: 1.17–3.00).

Conclusions: Delayed presentation was an independent risk factor for mortality in this cohort, emphasizing the importance of timely presentation to care for pediatric sepsis patients. Potential interventions include more efficient referral networks and emergency transportation systems to MNH. Additional clinics or hospitals with pediatric critical care may reduce pediatric sepsis mortality in Tanzania, as well as parental education programs for recognizing pediatric sepsis.

Keywords: pediatric sepsis, pediatric critical care, global health, pediatric emergency medicine, sub-Saharan Africa, health disparities, resource-limited

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****Correspondence:***
Audrey Marilyn Smith
Audrey.Smith@ucsf.edu

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INTRODUCTION

Sepsis is a clinical syndrome defined as a systemic inflammatory response associated with an infection (1). If untreated, sepsis can lead to septic shock, a condition that can result in multi-organ system failure and death (2, 3). Over 40% of the global burden of sepsis occurs in children under 5 years of age, with 20.3 million cases in 2017, causing the highest burden of mortality for this age group (2.9 million deaths in 2017) (4, 5).

Sepsis is the common final pathway for most infectious disease-related deaths, indicating that regions with higher burdens of pediatric communicable diseases have higher burdens of sepsis, such as South-East Asia and sub-Saharan Africa (4, 6, 7). Pediatric sepsis data are sparse in low- and middle-income countries (LMICs), making it difficult to assess trends in pediatric sepsis cases and mortality. Health facilities in LMICs sometimes lack the resources necessary to recognize and treat pediatric sepsis, such as sufficient intensive care unit beds, monitoring devices, medications, or health professionals trained in pediatric emergency or critical care (8–12). The lack of data on sepsis is a barrier to improving pediatric outcomes in resource-limited settings.

Basic acute and critical care and evidence-based therapies such as antibiotics and fluid resuscitation have been shown to reduce the likelihood of negative outcomes for septic children (1, 4, 6, 8, 13–17), and longer treatment delays result in higher morbidity and mortality (8, 13–19). Current pediatric sepsis guidelines recommend immediate (within 1 h) administration of antibiotics, because delayed treatment with antibiotics is an independent predictor of mortality and organ dysfunction (13, 14, 18). Familial SES has also been shown to influence pediatric sepsis outcomes as well as delayed presentation to care (6). However, most studies on pediatric sepsis in resource-limited settings focus on timely administration of treatment within the hospital rather than delays in arrival.

The objective of this secondary analysis was to assess SES as a possible risk factor for delayed presentation to definitive care, as well as the association between delayed presentation and mortality within this pediatric sepsis cohort.

MATERIALS AND METHODS

Study Design

This is a secondary analysis of a prospective cohort study conducted at Muhimbili National Hospital (MNH) in Tanzania. The study population was children 28 days to 14 years of age who presented to the ED of MNH over 12 months from July 1, 2016 to June 30, 2017. Eligible children were screened for suspected infection and at least two of the criteria for Systemic Inflammatory Response Syndrome (SIRS) adapted for resource-limited settings (**Figure 1**) (20).

Children were excluded for lack of consent, acute trauma, active cardiopulmonary resuscitation (CPR), lack of English of Kiswahili fluency of the guardian, and death prior to approach. In total, 2,031 children were included in the study, and 1,803 (88.8%) had outcome data (**Figure 2**).

Study Site

The National Hospital at Muhimbili University of Health and Allied Sciences is a public, tertiary-level referral hospital located in Dar es Salaam, Tanzania. At the time of the study, MNH had the only 24 h, public ED in the country. MNH receives hundreds of pediatric sepsis cases each month, and patients travel from every region of Tanzania, some over 1,000 km, for definitive care. While there are other emergency departments in Tanzania that can provide aspects of definitive care such as antibiotics and fluid resuscitation, MNH is the only public hospital with pediatric subspecialty care, meaning it has pediatricians with advanced training in emergency medicine. With respect to resources, it is one of the few hospitals in Tanzania equipped to provide emergency and critical care to children (21).

Data Collection and Management

Research personnel collected data from electronic medical records, paper charts, care providers, and guardians during the study period (22). Data were entered into and managed using REDCap (Research Electronic Data Capture) tools version 7.2.2 hosted at MNH. Data were deidentified prior to analysis. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

Statistical Analysis

All statistical analyses were performed using R Statistical Software (version 1.4.1717; R Foundation for Statistical Computing, Vienna, Austria, 2021). Descriptive statistics assessed patient baseline characteristics including pertinent demographic data, proxies for SES, clinical characteristics, and hospital pre-arrival information, such as mode of transport to the hospital and fever duration (**Tables 1**–**3**). Univariate statistics were generated to assess these characteristics in the full cohort. Bivariate tests compared survivors and non-survivors using Fisher's exact tests for categorical variables with skewed distributions and chi-squared tests for categorical variables with normal distributions. Wilcoxon rank-sum tests compared the medians of continuous variables with skewed distributions. P-values ≤ 0.05 were considered statistically significant.

Delayed presentation to definitive care was determined by measuring the time between onset of fever to the time the child reached the ED of MNH, as reported by the guardian. The definition for delayed presentation to definitive care was a fever duration >48 h from fever onset to arrival at the ED.

The proportion of children that were underweight, had wasting, and had stunting were calculated based on the WHO's official guidelines for child anthropometry (**Table 1**) (23). The R package *zscorer* (version 0.3.1) was used to calculate z-scores

Systemic inflammatory response syndrome (SIRS) clinical criteria for resource-limited settings (20)
Proven or suspected infection with ≥ 2 of the following criteria: - Temperature > 38.5 or < 36.0°C - Tachycardia (average heart rate > 2 standard deviations above normal heart rate for child's age group) or bradycardia for infants (average heart rate ≤ 10th percentile for age) - Tachypnea (respiratory rate > 2 standard deviations above normal rate for child's age group), hypoxia, on mechanical or positive-pressure ventilation - Ill-appearing, in distress, or not responsive

FIGURE 1 | SIRS criteria.

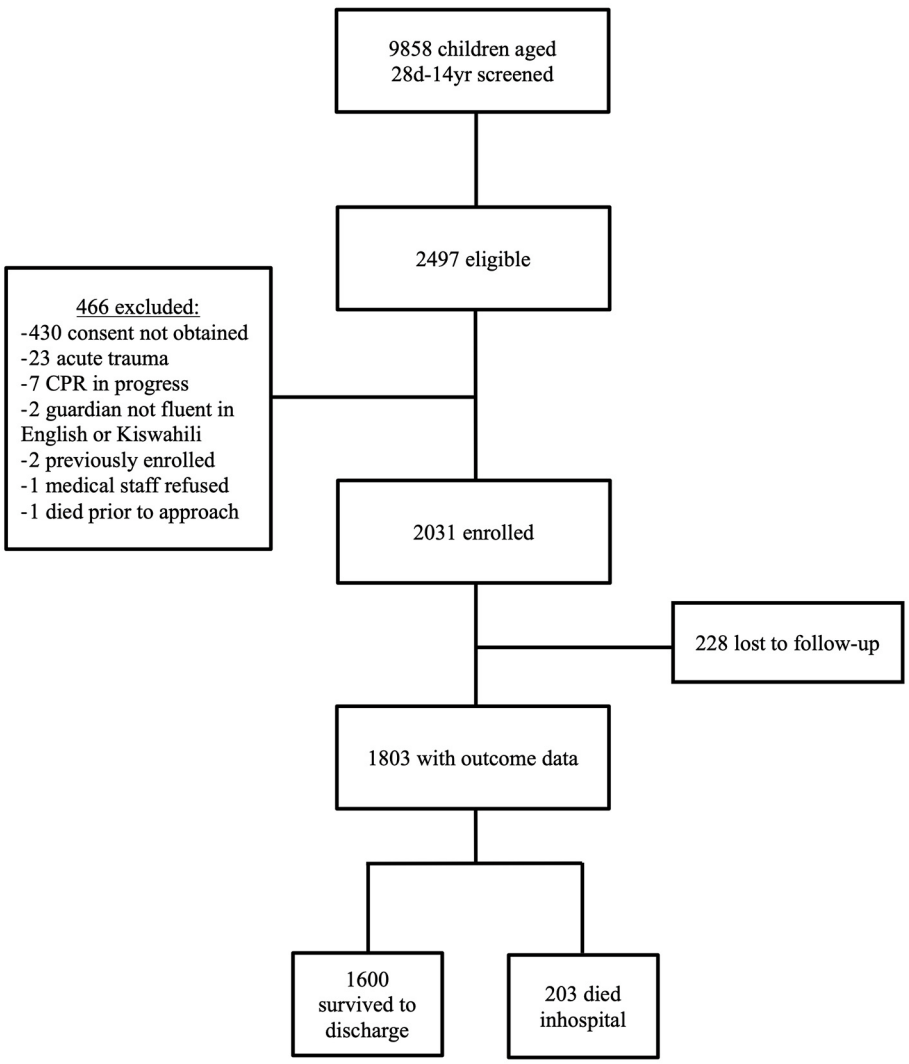

FIGURE 2 | Flow-chart depicting enrollment for this study, including criteria for exclusion, children lost to follow-up, and mortality outcomes.

TABLE 1 | Descriptive statistics for the full cohort and a comparison of demographic characteristics by mortality outcome.

Demographic characteristic	Total $N = 1803$	Survivors ($n = 1,600$)	Non-survivors ($n = 203$)	*P*-value
Age, months, median (IQR)	24.9 (13.1–53.1)	25.8 (13.8–54.6)	17.1 (7.7–37.0)	$P < 0.001$
Age, *n* (%)				
<2 years	854 (47.4)	732 (45.8)	122 (60.1)	$P < 0.001$
2–5 years	540 (30.0)	498 (31.1)	42 (20.7)	$p \leq 0.01$
>5 years	409 (22.7)	370 (23.1)	39 (19.2)	$p = 0.24$
Male sex, *n* (%)	1033 (57.3)	920 (57.5)	113 (55.7)	$p = 0.67$
Regional address, *n* (%)				
Dar es Salaam	1394 (77.3)	1237 (77.3)	157 (77.3)	$p = 1.00$
Neighboring regions	240 (13.3)	210 (13.1)	30 (14.8)	$p = 0.59$
Mid-distance regions	97 (5.4)	88 (5.5)	9 (4.4)	$p = 0.64$
Far regions	72 (4.0)	65 (4.1)	7 (3.4)	$p = 0.82$
Malaria positive, *n* (%)	99/1429 (6.9)	89/1264 (7.0)	10/165 (6.1)	$p = 0.76$
HIV positive, *n* (%)	22/229 (9.6)	15/188 (8.0)	7/41 (17.1)	$p = 0.13$
Fully immunized, *n* (%)	1770/1792 (98.8)	1575/1591 (99.0)	195/201 (97.0)	$p = 0.04$
Malnourished, *n* (%):				
Underweight	469/1615 (29.0)	398/1435 (27.7)	71/180 (39.4)	$P \leq 0.001$
Wasting	344/1318 (26.1)	296/1173 (25.2)	48/145 (33.1)	$p = 0.05$
Stunting	564/1544 (36.5)	493/1371 (36.0)	71/173 (41.0)	$p = 0.22$
Comorbidities, *n* (%)				
Anemia	20 (1.1)	17 (1.1)	3 (1.5)	$p = 0.86$
Asthma	31 (1.7)	27 (1.7)	4 (2.0)	$p = 1.00$
Cancer	28 (1.6)	24 (1.5)	4 (2.0)	$p = 0.83$
Cerebral palsy	85 (4.7)	74 (4.6)	11 (5.4)	$p = 0.74$
Congenital anomalies	11 (0.6)	10 (0.6)	1 (0.5)	$p = 1.00$
Congenital heart disease	173 (9.6)	142 (8.9)	31 (15.3)	$p = 0.01$
Downs syndrome	13 (0.7)	11 (0.7)	2 (1.0)	$p = 0.97$
Hydrocephalus	21 (1.2)	18 (1.1)	3 (1.5)	$p = 0.93$
Seizure disorder	41 (2.3)	39 (2.4)	2 (1.0)	$p = 0.29$
Sickle cell anemia	110 (6.1)	108 (6.8)	2 (1.0)	$P < 0.001$
Tuberculosis	25 (1.4)	17 (1.1)	8 (3.9)	$P < 0.001$
Other	73 (4.0)	63 (3.9)	10 (4.9)	$p = 0.65$
≥1 comorbidity, *n* (%)	585 (32.4)	506 (31.6)	79 (38.9)	$p = 0.04$

IQR, interquartile range; HIV, Human Immunodeficiency Virus.

but was limited to weight-for-age *z*-scores for children under 120 months, weight-for-height *z*-scores for children between 65 and 120 cm, and height-for-age *z*-scores for children between 24 and 228 months. For the first logistic regression model, wasting was used to represent malnutrition as it was determined to be the most clinically significant form of malnutrition for this cohort.

Potential confounding factors in the relationship between delayed presentation and mortality were identified *a priori* based on clinical knowledge and a literature review, which were severity of disease (measured by the Lambaréné Organ Dysfunction Score, LODS, **Figure 3**), age, patient comorbidities, and malnutrition (1, 13, 14, 24–32). Patient age was considered because there are age-associated differences in clinical presentations of sepsis that could potentially influence time to presentation to care (1, 28), and age is a well-known predictive factor in pediatric sepsis mortality (24, 29). Comorbidities among patients in the cohort were also considered in the analysis because they have been found to influence pediatric sepsis mortality (13, 14). Malnutrition was considered a standalone comorbidity in analysis, as it is significantly associated with pediatric sepsis mortality (30–32) and could affect time to presentation to care.

The association between SES and delayed presentation to definitive care was also explored. Potential confounders in this relationship were maternal literacy and patient region of origin in Tanzania, also identified *a priori* based on a literature review (33, 34). Maternal literacy represented parental education level, which is related to SES and could also impact caregiver care-seeking behavior (33). Region of origin was considered because children may have had to travel long distances to reach MNH for definitive care, and because Tanzania's many regions differ in average SES (34).

TABLE 2 | Descriptive statistics for the full cohort and a comparison of socioeconomic characteristics by mortality outcome.

Characteristic	Total $N = 1803$	Survivors ($n = 1,600$)	Non-survivors ($n = 203$)	*P*-value
Maternal literacy, *n* (%)	1694/1798 (94.2)	1507/1595 (94.5)	187 (92.1)	$p = 0.23$
Maternal education level, *n* (%)				
No formal school	87 (4.8)	74 (4.6)	13 (6.4)	$p = 0.35$
Primary school	870 (48.3)	740 (46.3)	130 (64.0)	$P < 0.001$
Secondary school	434 (24.1)	390 (24.4)	44 (21.7)	$p = 0.45$
University/advanced degree	388 (21.5)	376 (23.5)	12 (5.9)	$P < 0.001$
Unknown	24 (1.3)	20 (1.3)	4 (2.0)	$p = 0.60$
No. of children <18 years in household, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	$p = 0.58$
No. <5 years, median (IQR)	1 (1–2)	1 (1–2)	1(1–2)	$p = 0.36$
Electricity in home, *n* (%)	1399/1796 (77.9)	1253/1596 (78.5)	146/200 (73.0)	$p = 0.04$
Toilet in home, *n* (%)	1099 (61.0)	993 (62.1)	106 (52.2)	$p = 0.01$
Improved water source, *n* (%)	1715 (95.1)	1521 (95.1)	194 (95.6)	$p = 0.89$
Private tap	505 (28.0)	475 (29.7)	30 (14.8)	$P < 0.001$
Public tap or standpipe	1065 (59.1)	915 (57.2)	150 (73.9)	$P < 0.001$
Tube well or borehole	227 (12.6)	201 (12.6)	26 (12.8)	$p = 1.00$
Protected spring	7 (0.4)	6 (0.4)	1 (0.5)	$p = 1.00$

No., number; IQR, interquartile range.

Proxies for SES were collected for this cohort and an ownership score (range: 0–3) was generated based on the reported presence of three variables: household electricity, in-home flush/pour toilet, and access to an improved water source. An improved water source is defined by the WHO as sources that are "protected from outside contamination, particularly fecal matter" (35).

The first logistic regression model generated unadjusted and adjusted odds ratios (OR) and respective 95% confidence intervals (95% CI) for the relationship between delayed presentation and mortality. The second logistic regression model explored the association between the SES of the participants, using the ownership score, and delayed presentation to care, generating unadjusted and adjusted ORs and respective 95% CIs.

Ethics Approval Statement

This study was carried out in accordance with the recommendations and approval of the Institutional Review Boards and Committees on Human Research at Muhimbili University of Health and Allied Sciences (Ref. No. 2016-03-30/AEC/Vol.X/201) and the University of California, San Francisco (IRB # 16-18977, Ref. No. 161295). Written, informed consent from all guardians and assent from subjects when appropriate was obtained in accordance with the Declaration of Helsinki.

RESULTS

Baseline Characteristics: Demographics

Overall, there was an in-hospital mortality rate of 11.3%, with 1,600 survivors and 203 non-survivors. The median age of children enrolled in the study was 25 months (IQR 13–54 months) with 77.3% ($n = 1,394$) of the children under 5 years of age (**Table 1**). Of the study population with outcome data, 1,394 patients (77.3%) were from the Dar es Salaam region of Tanzania.

Out of the patients tested, 6.9% ($n = 99/1,429$) were positive for malaria and 9.6% ($n = 22/229$) were HIV-positive. Based on WHO child anthropometry guidelines (23), 29.0% ($n = 469/1,615$) of patients were underweight, 26.1% ($n = 344/1,318$) had wasting, and 36.5% ($n = 564/1,544$) had stunting. Malnutrition was the most common comorbidity in the cohort, followed by congenital heart disease ($n = 173$, 9.6%) and sickle cell anemia ($n = 110$, 6.1%) (**Table 1**).

There were key differences noted in several baseline demographic characteristics between survivors and non-survivors (**Table 1**). Non-survivors were of a younger median age (17.1 months, IQR: 7.7–37.0) upon presentation, compared to survivors (25.8 months, IQR: 13.8–54.6) ($p < 0.001$). At the time of arrival to the hospital, more of the non-survivors were underweight ($n = 71/180$, 39.4%), compared to the survivors ($n = 398/1,435$, 27.7%) ($p \leq 0.001$). Similarly, more non-survivors had wasting ($n = 48/145$, 33.1%), compared to survivors ($n = 296/1,173$, 25.2%) ($p = 0.05$). More of the non-survivors had at least one significant comorbidity ($n = 79$, 38.9%), compared to the survivors ($n = 506$, 31.6%) ($p = 0.04$).

Baseline Characteristics: SES

The highest level of education reached by the patients' mothers differed; while 376 (23.5%) of the survivors' mothers held a university of other advanced degree, this was true for only 12 of the non-survivors (5.9%) ($p < 0.001$) (**Table 2**). When guardians were asked if their homes had electricity, less guardians of non-survivors answered affirmatively ($n = 146/200$, $n = 73.0\%$), compared to the guardians of the survivors ($n = 1,253/1,596$, 78.5%) ($p = 0.04$). Congruently, fewer non-survivors had a

TABLE 3 | Descriptive statistics for the full cohort and a comparison of pre-arrival characteristics and illness severity measures by mortality outcome.

Characteristic	Total $N = 1803$	Survivors ($n = 1,600$)	Non-survivors ($n = 203$)	*P*-value
Fever duration, *n* (%)				
≤48 h	800 (44.4)	739 (46.2)	61 (30.0)	$P \leq 0.001$
>48 h	704 (39.0)	614 (38.4)	90 (44.3)	$p = 0.12$
Unknown	299 (16.6)	247 (15.4)	52 (25.6)	$p = 0.00$
Antibiotics pre-arrival, *n* (%)	352/833 (42.3)	269/675 (39.9)	83/158 (52.5)	$p = 0.01$
Referred by hospital or clinic, *n* (%):	836/1081 (77.3)	678/1598 (42.4)	158/203 (77.8)	$P < 0.001$
Transportation method, *n* (%)				
Ambulance	517 (28.7)	380 (23.8)	137 (67.5)	$P < 0.001$
Bus	783 (43.4)	739 (46.2)	44 (21.7)	$P < 0.001$
Private car	369 (20.5)	353 (22.1)	16 (7.9)	$P < 0.001$
Taxi	50 (2.8)	48 (3.0)	2 (1.0)	$p = 0.16$
Walked	55 (3.1)	54 (3.4)	1 (0.5)	$p = 0.04$
Other	23 (1.3)	20 (1.3)	3 (1.5)	$p = 1.00$
Unknown	7 (0.4)	7 (0.4)	0	$p = 0.73$
SIRS criteria *n* (%)				
Abnormal respiratory rate	1614 (89.5)	1420 (88.8)	194 (95.6)	$p = 0.00$
Abnormal heart rate	1001 (55.5)	878 (54.9)	123 (60.6)	$p = 0.13$
Ill appearing, in distress, not responsive	1115 (61.8)	950 (59.4)	165 (81.3)	$P < 0.001$
LODS, *n* (%)				
0	893 (49.5)	823 (51.4)	70 (34.5)	$P < 0.001$
1	717 (39.8)	629 (39.3)	88 (43.3)	$p = 0.30$
2	171 (9.5)	140 (8.8)	31 (15.3)	$P \leq 0.01$
3	22 (1.2)	8 (0.5)	14 (6.9)	$P < 0.001$
AVPU scale, *n* (%)				
Alert	1616 (89.6)	1479 (92.4)	137 (67.5)	$P < 0.001$
Responds to verbal	30 (1.7)	22 (1.4)	8 (3.9)	$p = 0.02$
Responds to pain	112 (6.2)	65 (4.1)	47 (23.2)	$P < 0.001$
Unresponsive	45 (2.5)	34 (2.1)	11 (5.4)	$p = 0.01$

SIRS, systemic inflammatory response syndrome; LODS, Lambaréné Organ Dysfunction Score; AVPU, Alert-Verbal-Painful-Unresponsive.

flush/pour toilet in their homes ($n = 106$, 52.2%), compared to survivors ($n = 993$, 62.1%) ($p = 0.01$).

Baseline Characteristics: Hospital Pre-arrival and Illness Severity

The hospital pre-arrival baseline characteristics revealed that 42.4% percent ($n = 678/1,598$) of the cohort received antibiotics before presentation to MNH, and 77.3% ($n = 836/1,081$) had been referred by another hospital or clinic (**Table 3**).

Survivors and non-survivors differed in fever duration, with non-survivors having more delayed presentation to definitive care than the survivors ($p \leq 0.001$) (**Table 3**). More of the non-survivors received antibiotics before arriving ($n = 83/158$, 52.5%), compared to survivors ($n = 269/675$, 39.9%) ($p = 0.01$), and more non-survivors were referred to MNH by another clinic or hospital ($n = 158/203$, 77.8%), compared to survivors ($n = 678/1,598$, 42.4%) ($p < 0.001$).

Survivors and non-survivors differed in SIRS criteria met upon arrival, with a larger proportion of non-survivors presenting with abnormal respiratory rates ($n = 194$, 95.6%) compared to survivors ($n = 1420$, 88.8%) ($p \leq 0.00$) (**Table 3**). Additionally, more non-survivors arrived appearing ill, in distress, or non-responsive ($n = 165$, 81.3%), compared to survivors ($n = 950$, 59.4%) ($p < 0.001$). Respiratory rates were higher among non-survivors for all age groups, compared to survivors of the same age groups (28 days−1 year: $p < 0.001$; 2–5 years: $p < 0.001$, 6–12 years: $p < 0.001$, 13–14 years: $p \leq 0.00$) (**Figure 4**). Heart rates were significantly higher for non-survivors among all age groups except 2–5 years (28 days−1 year: $p = 0.02$; 2–5 years: $p = 0.25$; 6–12 years: $p = 0.01$; 13–14 years: $p = 0.01$) (**Figure 5**).

The LOD scores of survivors and non-survivors (range: 0–3) also differed significantly, with significantly less non-survivors scoring a 0 ($n = 823$, 51.4%) compared to survivors ($n = 70$, 34.5%) ($p < 0.001$), indicating greater severity of illness among non-survivors at the time of presentation. Congruently, as indicated by the Alert-Verbal-Painful-Unresponsive (AVPU) categorization, fewer non-survivors were alert upon their arrival to MNH ($n = 137$, 67.5%), compared to non-survivors ($n = 1,479$, 92.4%) ($p < 0.001$) (**Table 3**).

Lambaréné Organ Dysfunction Score (LODS) (25-27)
The patient receives 1 point for each of the following: - Blantyre-Coma Score ≤ 2 - Deep Breathing: Indicative of respiratory stress, acidosis - Prostration: Depending on age of patient, not being able to breastfeed, sit, stand, or walk independently

FIGURE 3 | LODS criteria.

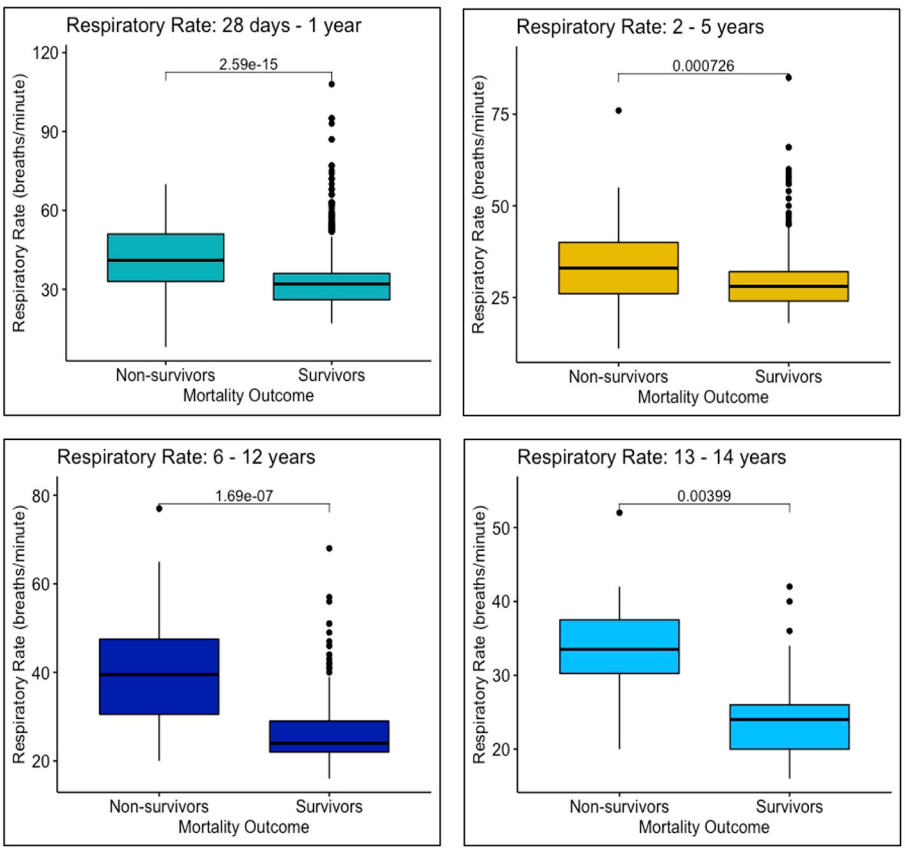

FIGURE 4 | Respiratory rates upon arrival to MNH of survivors and non-survivors in each age group: 28 days−1 year, 2–5 years, 6–12 years, and 13–14 years.

Logistic Regression Models

The children who had delayed presentation to definitive care had an unadjusted OR for mortality of 1.75 (95% CI: 1.19–2.61) and an adjusted OR for mortality of 1.85 (95% CI: 1.17–3.00) compared to children who did not have delayed presentation to care (**Table 4**). The ownership variable was not significantly associated with delayed presentation after adjusting for maternal literacy and Tanzanian region of origin classification (**Table 5**). Comparing households with 3/3 ownership variables to those with 0/3, there was an unadjusted OR for delayed presentation of 0.43 (95% CI: 0.19–0.86) and an adjusted OR of 0.60 (95% CI: 0.26–1.27).

DISCUSSION

Key Findings

Out of the children enrolled in this study with outcome data, 11% did not survive to hospital discharge. Approximately half of the

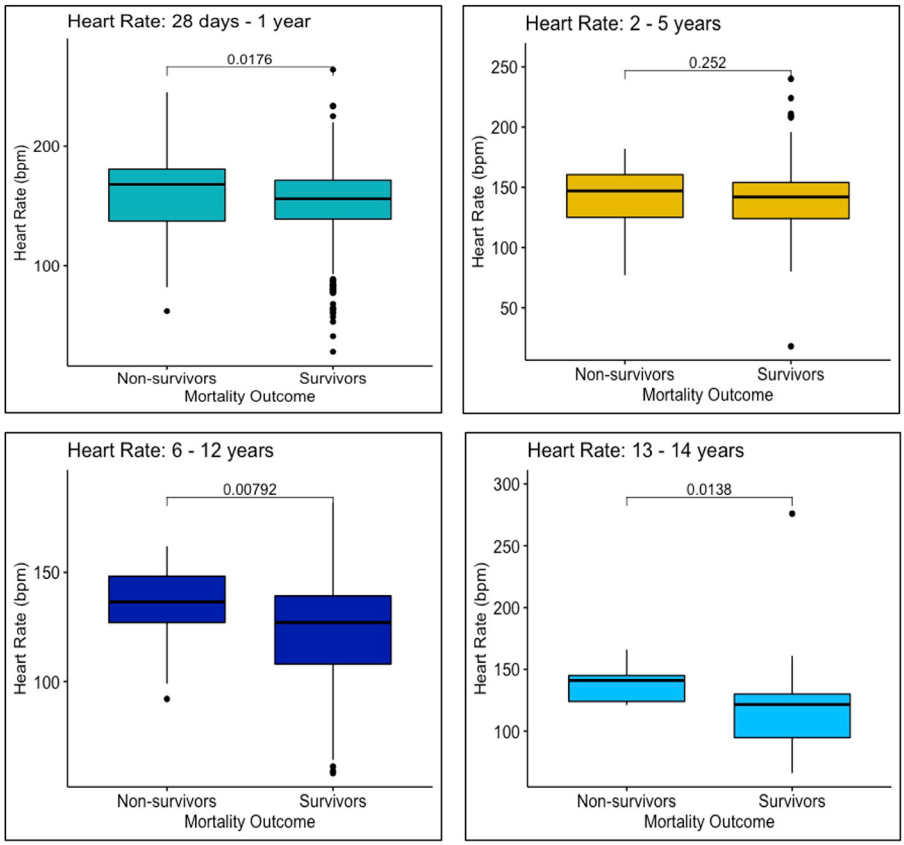

FIGURE 5 | Heart rates upon arrival to MNH of survivors and non-survivors in each age group: 28 days−1 year, 2–5 years, 6–12 years, and 13–14 years.

patients with available fever duration data presented to definitive care at MNH after the 48 h cut-off, and delayed presentation to definitive care was more common in non-survivors compared to survivors. A significantly larger proportion of non-survivors fulfilled certain SIRS, LODS, and AVPU criteria, three measures of illness severity, and non-survivors presented with more abnormal respiratory and heart rates than survivors. A logistic regression model confirmed that the children with delayed presentation to definitive care, compared to children who did not have delayed presentation, had 1.85 the odds of dying (CI: 1.17–3.00), after controlling for potential confounders. SES, measured by number of ownership variables, was not independently associated with delayed presentation.

Interpretation of Findings

The 11% mortality among children with sepsis at MNH is consistent with other published pediatric sepsis cohort studies. A study that took place in Mbarara, Uganda with children ages 6 months to 5 years with a suspected or proven infection and a lower severity of illness at the time of presentation observed a 5% probability of inhospital mortality (36). Mortality in the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study, a global point prevalence study of severe sepsis, was 25%, but included subjects that met at least two SIRS criteria *and* had dysfunction of the cardiovascular system or two other organs, or acute respiratory distress syndrome (6). Most similar to the MNH cohort was the Fluid Expansion as Supportive Therapy (FEAST) study cohort from sites in Uganda, Kenya, and Tanzania, which observed a 7.3–10.6% mortality (depending on the treatment arm) within 48 h in non-malnourished children ages 60 days−12 years with severe febrile illness (37).

Notably, a study conducted in 2020 in the newly established pediatric intensive care unit at MNH, observed that 14% of pediatric deaths were from septicemia (38). This study concluded that the quality of intensive care for children "achieved the minimum acceptable standards" and would benefit from improving pediatric critical care training, hospital infrastructure, emergency equipment, and treatment protocols (38), which suggests that improvements could be made in reducing pediatric sepsis mortality at MNH.

Delayed presentation was a significant risk factor for mortality in this cohort, emphasizing the importance of timely presentation to definitive care at MNH for pediatric sepsis patients. MNH has noted many delays in its referral system, attributed to either patient caregiver behavior or delays from referral hospitals (38). Because more of the children who were referred to MNH from other lower-level facilities died, delays in sepsis recognition

TABLE 4 | Adjusted and unadjusted odds ratios and 95% confidence intervals for mortality and its association with delayed presentation.

Variable	Unadjusted odds ratio	Unadjusted confidence interval	Adjusted odds ratio	Adjusted confidence interval
Delayed presentation	1.75	1.19–2.61	1.85	1.17–3.00
Age (years)	0.95	0.90–1.00	0.72	0.61–0.82
Malnourished (wasting)	1.46	1.00–2.10	1.41	0.90–2.16
≥1 comorbidity	1.38	1.02–1.86	1.69	1.10–2.57
Severity of Illness				
LODS 0	Ref		Ref	
LODS 1	1.64	1.18–2.29	1.47	0.95–2.29
LODS 2	2.60	1.63–4.09	1.90	0.97–3.57
LODS 3	20.58	8.52–53.10	9.07	2.05–40.17

LODS, Lambaréné Organ Dysfunction Score; Ref, reference group; Comorbidities included anemia, asthma, cancer, cerebral palsy, congenital anomalies, congenital heart disease, diabetes, Down syndrome, Human Immunodeficiency Virus (HIV), hydrocephalus, renal disease, seizure disorders, sickle cell anemia, tuberculosis, and other significant comorbidities.

TABLE 5 | Adjusted and unadjusted odds ratios and 95% confidence intervals for delayed presentation given number of ownership variables as a measure of SES.

Variable	Unadjusted odds ratio	Unadjusted confidence interval	Adjusted odds ratio	Adjusted confidence interval
SES (total no. ownership variables)				
0	Ref			
1	0.61	0.27–1.28	0.72	0.31–1.53
2	0.48	0.21–0.98	0.64	0.27–1.37
3	0.43	0.19–0.86	0.6	0.26–1.27
Maternal Literacy	0.64	0.38–1.03	0.81	0.48–1.35
Region of origin				
Dar es Salaam	Ref			
Neighboring	1.61	1.17–2.23	1.42	1.01–2.03
Mid-distance	1.55	0.96–2.58	1.38	0.84–2.33
Far	1.53	0.88–2.77	1.34	0.76–2.47

SES, socioeconomic status; No., number; Ownership variables, in-home flush/pour toilet, household electricity, and access to an improved water source; Ref, reference group; Neighboring regions: Pwani, Mjini Magharibi, Unguja, Pemba, Tanga, and Morogoro; Mid-distance regions: Arusha, Dodoma, Iringa, Kilimanjaro, Lindi, Manyara, Mtwara, and Ruvuma; Far regions: Mbeya, Mwanza, Mara, Njombe, Kagera, Katavi, Kigoma, Geita, Rukwa, Singida, Shinyanga, Simiyu, and Tabora.

and referral at these facilities may be a contributor. A next step could be increasing education of providers at all levels of care, especially among primary providers, on pediatric sepsis recognition, timely initiation of appropriate treatment within the constraints of available resources, and sepsis cases that warrant referral. This increased provider education would be especially important in regions far from Dar es Salaam, where MNH is located. Such an intervention could be cost-effective, and a dedicated study designed to determine cost-effectiveness would be informative.

Because minimizing delays can be lifesaving for septic children, another potential intervention could be an educational program directed at caregivers teaching early warning signs and symptoms of sepsis. Parental education has been shown to be a successful tool for preventing progression to severe illness for certain pediatric conditions, for example, extreme hyperbilirubinemia in newborns, as well as sepsis (33, 39). A pediatric sepsis educational campaign in Tanzania could be expanded to street billboards, public service announcements, or other methods of information dispersion, but would have to be carefully structured to ensure emergency departments do not become overburdened with children with non-emergent illnesses.

Implementation of an emergency transportation system may also improve mortality outcomes in Tanzania, however, this would be a challenge due to resource limitations. There are currently no ambulatory services provided by the government in Tanzania (40–42). Transportation is sometimes offered for inter-facility transfer and referral, but the ambulances are not staffed by certified health personnel with standardized training (40, 43). Other available ambulances are run by private companies (43), which are inaccessible to most. The implementation of boda-boda ambulances in Tanzania has been suggested as a more affordable solution (44), and there has been success in retention of emergency first aid skills from training programs offered to police and taxi drivers in sub-Saharan Africa (40). A temporary regional pilot program may be able to demonstrate the cost-effectiveness of these life-saving services.

Children who lived in remote regions of Tanzania were less likely to be represented in this study than expected based

on population distribution, indicating that they received care elsewhere, were never referred, died before referral or during transportation, or experienced another barrier to reaching MNH. Because MNH is the only public hospital in the country with pediatric critical care, this implies that there may be septic children from more distant regions of Tanzania who are attending hospitals without clinicians trained in acute pediatric care. Increasing the availability of pediatric subspeciality care, such as emergency medicine and intensive care, at regional hospitals throughout the country would likely save lives. Future cohort studies on pediatric sepsis in Tanzania should include hospitals or clinics throughout the country to compare outcomes in septic children across institutions, with and without pediatric emergency or critical care.

SES, as represented by the combined ownership variable, was not associated with delayed presentation in this cohort, which ran contrary to an El Salvadorian study in which children from families with <$2,000 in annual income had a 14-fold increased risk of dying from sepsis (16). Maternal illiteracy, another commonly used proxy for SES, was also significantly associated with delayed presentation to care in this study (16). These findings were not consistent with our results, however, which could be due to the usage of ownership variables as a proxy for SES. Further studies are needed to elucidate which, if any, factors are viable proxies for SES and important in the relationship between SES and timely access to care for septic children in resource-limited settings.

Limitations

The strengths of this study include its large sample size and 12 month duration, which captured seasonal variation in pediatric sepsis admissions and outcomes at MNH. This contribution to the limited regional data may help increase awareness of pediatric sepsis in East Africa, as well as aid local health workers in risk-stratifying cases for prioritization and resource allocation.

However, this study did have its limitations. For example, non-survivors arrived to MNH with a higher illness severity than survivors, as demonstrated by number of SIRS criteria met, LOD scores, and AVPU categorizations at the time of presentation; however, due to a lack of blood pressure monitoring and biochemical laboratory data, it was not possible to definitively state whether children were in septic shock or multiorgan failure upon presentation. Therefore, heart rates and respiratory rates of survivors and non-survivors were analyzed as clinical indicators of shock (**Figures 4**, **5**).

Another limitation of this study is the significantly larger proportion of non-survivors than survivors with unknown fever durations that could not be classified as delayed or on-time. To ensure the patients lost to follow-up were not significantly different from those who had outcome data, baseline characteristics between these groups were compared and no significant differences were found.

The usage of ownership variables as a measure of SES introduced a limitation to this study, as ownership is just one representation of SES out of many and does not consider other validated measurements, such as income, occupation, and education. A South African study found that ownership of a phone, car, and in-home flush toilet were viable SES measures as they predicted child malnutrition (45), but these findings were not replicated by this study. It is possible that SES was simply not associated with delayed presentation for this cohort, or that these specific ownership variables were not suitable proxies for SES in this setting and context. It is also possible that higher SES was associated with referral or the ability to reach MNH from other regions, because of costs associated with travel and taking time off work for parents or guardians. This would have resulted in underrepresentation of lower-SES families from other Tanzanian regions. Further studies are needed to clarify the relationship between SES and delayed presentation to definitive care for sepsis.

For this cohort, 228 patients were lost to follow-up. Chi-square tests and Wilcoxon rank-sum tests were run to assess significant differences between the full cohort ($n = 2{,}031$) and only those with outcome data ($n = 1{,}803$), but none were found, indicating that loss to follow-up most likely did not impact the results of this study (**Supplemental Table 1**).

CONCLUSION

Delayed presentation to definitive care was an independent risk factor for mortality in this cohort, emphasizing the importance of timely presentation to care for pediatric sepsis. In Tanzania, this may be a challenge for families that live in regions of the country distant from Dar es Salaam. Potential interventions include more efficient referral networks and emergency transportation systems to MNH, as well as carefully structured educational programs for pediatric sepsis recognition directed at caregivers. Additional clinics or hospitals with pediatric emergency and critical care may also reduce pediatric sepsis mortality in Tanzania.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Boards and Committees on Human Research at Muhimbili University of Health and Allied Sciences (Ref. No. 2016-03-30/AEC/Vol.X/201) and the University of California, San Francisco (IRB # 16-18977, Ref. No. 161295). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TK, HS, BM, and MM: conception and design of the work. TK, HS, and BM: data acquisition. AS: data analysis and first draft of the manuscript. AS, TK, and BM: data interpretation. AS, TK, MM, and BM: manuscript revision and editing. AS, TK, HS, MM, BM, and TR:

final approval of the version to be published work and agreement to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.764163/full#supplementary-material

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ORIGINAL RESEARCH
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Intravenous Metoclopramide to Improve the Success Rate of Blind Bedside Post-pyloric Placement of Feeding Tube in Critically Ill Children: A Randomized, Double-Blind, Placebo-Controlled Study

*Sirima Ketsuwan[1], Pornthep Tanpowpong[2], Nichanan Ruangwattanapaisarn[3], Supatra Phaopant[4], Nattanicha Suppalarkbunlue[5], Chula Kooanantkul[6], Nattachai Anantasit[1] and Jarin Vaewpanich[1]**

[1] Division of Pediatric Critical Care Medicine, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [2] Division of Gastroenterology, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [3] Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [4] Department of Nursing, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [5] Clinical Pharmacy Department, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [6] Super Kids Center, Vejthani Hospital, Bangkok, Thailand

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***Correspondence:**
Jarin Vaewpanich
jarivaew@yahoo.com

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Objective: Impaired gastric emptying is a common cause of delayed feeding in critically ill children. Post-pyloric feeding may help improve feeding intolerance and nutritional status and, hence, contribute to a better outcome. However, post-pyloric feeding tube insertion is usually delayed due to a technical difficulty. Therefore, prokinetic agents have been used to facilitate blind bedside post-pyloric feeding tube insertion. Metoclopramide is a potent prokinetic agent that has also been used to improve motility in adults and children admitted to intensive care units. The objective of this study was to determine the efficacy of intravenous metoclopramide in promoting the success rate of blind bedside post-pyloric feeding tube placement in critically ill children.

Design: The design of this study is randomized, double blind, placebo controlled.

Setting: The setting of the study is a single-center pediatric intensive care unit.

Patients: Children aged 1 month−18 years admitted to the pediatric intensive care unit with severe illness or feeding intolerance were enrolled in this study.

Intervention: Patients were randomly selected to receive intravenous metoclopramide or 0.9% normal saline solution (the placebo) prior to the tube insertion. The study outcome was the success rate of post-pyloric feeding tube placement confirmed by an abdominal radiography 6–8 h after the insertion.

Measurements and Main Results: We found that patients receiving metoclopramide had a higher success rate (37/42, 88%) of post-pyloric feeding tube placement than the placebo (28/40, 70%) ($p = 0.04$). Patients who received sedative drug or narcotic agent showed a tendency of higher success rate ($p = 0.08$).

Conclusion: Intravenous metoclopramide improves the success rate of blind bedside post-pyloric placement of feeding tube in critically ill children.

Trial Registration: Thai Clinical Trial Registry TCTR20190821002. Registered 15th August 2019.

Keywords: post-pyloric feeding, metoclopramide, blind bedside placement, nasojejunal feeding, critically ill children

INTRODUCTION

Malnutrition is a common problem in critically ill patients causing increased morbidity and mortality (1, 2), and enteral feeding is the preferred route of nutritional support to improve nutritional status for most critically ill patients with an adequate gastrointestinal function (1, 3). However, some children cannot tolerate intragastric feeding due to delayed gastric emptying, impaired motility, or carry a higher risk of aspiration or severe gastroesophageal reflux, which can cause feeding postponement. Therefore, post-pyloric feeding may be preferred for patients at high risk for aspiration and feeding intolerance (4, 5). Previously, fluoroscopic and endoscopic procedures were used in the post-pyloric tube placement, but the procedures are costly, increase radiation exposure, and require a transfer of patient to the interventional radiology or endoscopy suites (6–8).

Blind bedside post-pyloric feeding tube placement has been shown to be safe and feasible for early enteral feeding in critically ill patients (5, 9). Some studies have suggested a benefit of using a motility agent in the placement, but a definitive study, such as an RCT, has not been completed (10, 11). Metoclopramide, a prokinetic agent, works by blocking dopaminergic receptor and increasing gastric motility. It is used to treat nausea and vomiting in several conditions such as post-surgery, gastroesophageal reflux, and chemotherapy-induced vomiting (12). Studies in adults demonstrated promising results when using metoclopramide to improve a success rate of tube insertion (13, 14), but data in children are limited. Therefore, we aimed to determine whether intravenous metoclopramide improved the success rate of blind bedside post-pyloric placement of feeding tube in critically ill children in a prospective, randomized, double-blind, placebo-controlled fashion.

MATERIALS AND METHODS

Study Design

We conducted a prospective, randomized, double-blind, placebo-controlled study in the Pediatric Intensive Care Unit (PICU) at a tertiary care teaching hospital. The study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, and written informed consent was obtained from each patient or their legal guardians. This trial study was registered at the Thai Clinical Trial Registry (TCTR20190821002).

Patients

Patients admitted to the PICU between December 2018 and January 2020 with the following inclusion criteria were included: critically ill, aged 1 month to 18 years, required enteral nutrition, and having severe illness or feeding intolerance. Patients having a major abdominal surgery, a known history of malrotation, an active upper gastrointestinal bleeding, severe coagulopathy, or allergic to metoclopramide were excluded. The decision on commencing the enteral feeding was made by the on-service attending physician.

In **Figure 1**, eligible patients who fulfilled the inclusion criteria were randomly allocated by a computer-generated block-of-four randomization and assigned to receive either intravenous metoclopramide (the metoclopramide group) or 0.9% normal saline solution (the placebo group) of similar physical appearance. Clinicians who treated the patients and an investigator (SK) who inserted the feeding tube were not aware of the allocation. All the randomization, the allocation, and the medication preparation were the responsibility of a pharmacist.

Intervention

Patients in the metoclopramide group received 0.1 mg/kg of metoclopramide intravenously 30 min before the feeding tube insertion, and in the placebo group, 0.9% normal saline solution was given. The tube used was radiopaque unweighted silicone tube without wire stylet (Fortune Medical Instrument, Taiwan). The length of the nasointestinal tube before insertion was measured following the method of a previous study (15). The measurement started from the nose to one ear and then to the mid-point between the xiphisternum and the umbilicus to obtain the length for tube position in the stomach. Then, the measurement was continued to the right iliac crest to get a final length for insertion. When the measurement was done, the tube was lubricated with sterile gel and inserted from the nostril to the stomach in a supine position, with the head tilted at 30° elevation. The position of the inserted tube was confirmed by injecting air into the stomach. Then, the patient was turned to his/her right side down onto the bed, and the tube was pushed down to the pre-measured length with a corkscrew technique and fixed onto the patient's nose. The patient remained on the same position for at least 3 h after the insertion. All steps of feeding tube insertion were performed only once by one experienced physician.

Data Collection and the Study Outcome

Demographic characteristics, primary diagnosis, and indication admitted to the PICU, disease severity, Pediatric Risk of Mortality III (PRISM III), and Pediatric Logistic Organ Dysfunction (PELOD) scores, medications, and potential adverse events from the medication including extrapyramidal side effects, life-threatening arrhythmia, or drug allergy were recorded. Besides, adverse events from the tube insertion including epistaxis, vomiting, and bowel perforation were also recorded. An abdominal radiograph was done to evaluate the feeding tube position at 6 to 8 h after the insertion, and the position

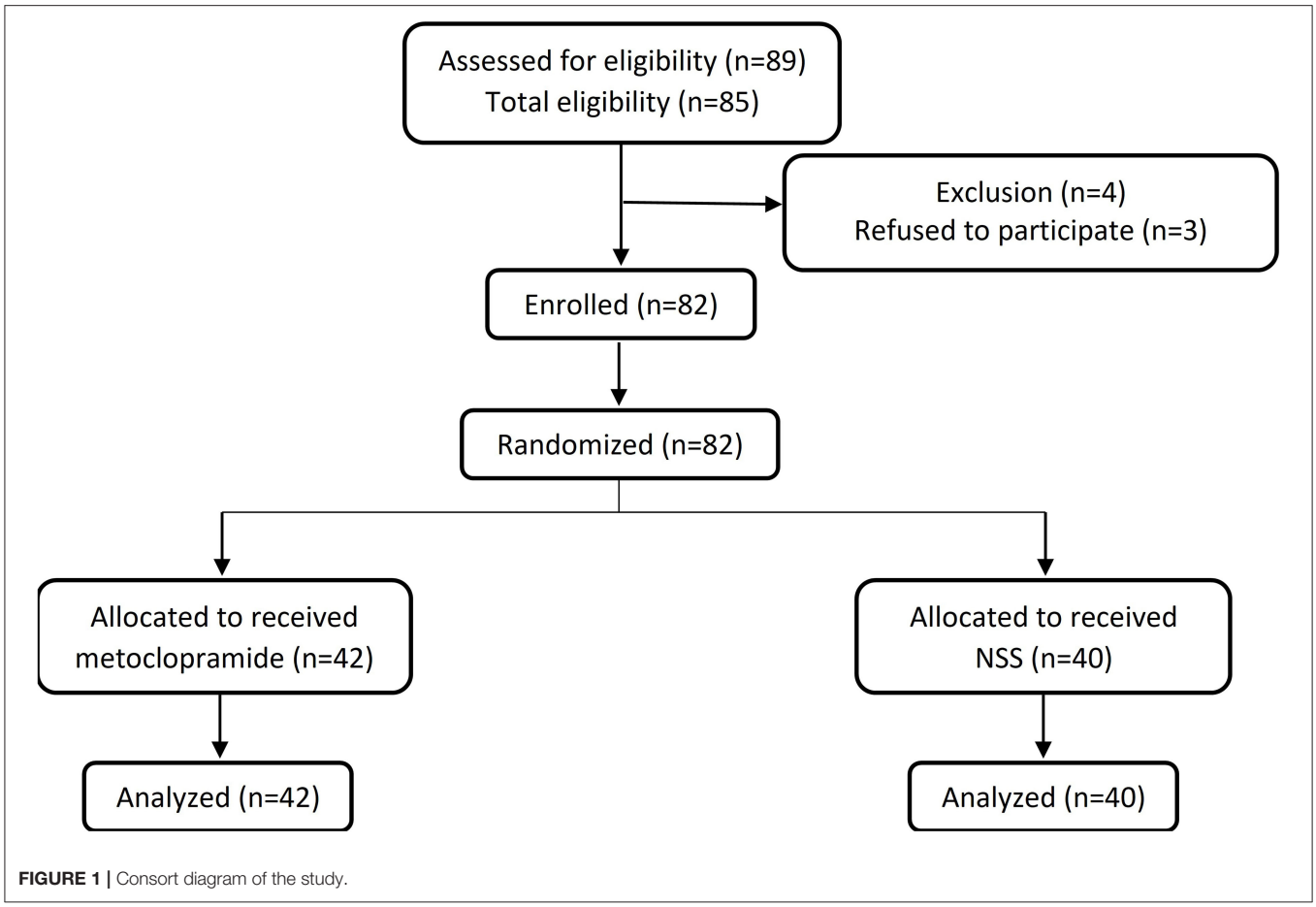

FIGURE 1 | Consort diagram of the study.

was confirmed by a pediatric radiologist who was also blinded to this study. The study outcome was a successful placement of feeding tube into the post-pyloric area (duodenum and proximal jejunum).

Statistical Analysis

The sample size was calculated by the Power and Sample size Calculation Program version 3.1.2 using type I error of 0.05 and power of 80%. Based on previous studies, 82 patients were required to show an increased success rate from 40 to 81% using prokinetic agent administration (16, 17).

The demographic data were analyzed by independent sample *t*-test or Mann–Whitney *U*-test. Position of the feeding tube was compared between groups using Chi-square test. Bivariate analysis was performed to study the impact of sedative and inotropic drugs. The effective size of metoclopramide was calculated by using odds ratio. The data were analyzed using SPSS program version 24.

RESULTS

Eighty-two patients (42 in the metoclopramide group and 40 in the placebo group) were enrolled in the study. The demographic data of the patients are presented in **Table 1**. There were no significant differences of baseline characteristics, mechanical ventilation, and drug administered between the two groups. In addition, the PICU length of stay, the total hospital stay, the PRISM III, and the PELOD were not significantly different (**Table 2**).

The mean insertion time was 9.5 ± 3.6 min. The metoclopramide group had a higher success rate of post-pyloric feeding tube insertion than the placebo group [88 vs. 70%, odds ratio 3.2 (95% CI: 1.0, 10.0), $p = 0.04$, **Table 3**]. Patients who received sedative drug or narcotic agent were more likely to have a successful tube insertion ($p = 0.08$, **Table 4**). Other factors, such as the use of inotropic drugs, PRISM III score ≥10, demonstrated no statistical significance. No serious adverse events related to the medication or tube placement were encountered.

DISCUSSION

To our knowledge, this is the first randomized, double-blind, placebo-controlled trial demonstrating that the intravenous metoclopramide before feeding tube insertion could improve the success rate of blind bedside post-pyloric tube placement in critically ill children. As a selective dopamine-2 receptor antagonist and a 5-hydroxytryptamine receptor 4 agonist (18),

TABLE 1 | Demographic and clinical characteristics of the metoclopramide and the placebo groups.

Characteristics	Metoclopramide ($N = 42$)	Placebo ($N = 40$)	*p* value
Males; n (%)	21 (50)	23 (58)	0.50
Age [months]; median (IQR)	21 (5, 116)	17 (3, 55)	0.48
Body weight; median (IQR)	11 (6, 21)	10.5 (5, 16)	0.56
Primary diagnosis; n (%)			0.27
Neurological	10.0 (24)	7 (18)	
Cardiovascular system	7 (17)	8 (20)	
Respiratory system	18 (43)	17 (43)	
Gastrointestinal system	3 (7)	0 (0)	
Others	4 (9)	8 (19)	
Respiratory support; n (%)			0.10
Low flow oxygen cannula	3 (7)	2 (5)	
HHHFNC[a]	15 (36)	6 (15)	
CPAP[b]/BIPAP[c]	1 (2)	1 (3)	
Mechanical ventilator	23 (55)	31 (77)	
Mechanical ventilator day (days); median (IQR)	11 (3, 21)	14 (6, 28)	0.10
Procedure was done in PICU; n (%)	34 (81)	31 (78)	0.70
Procedural time; median (IQR)	10 (7, 10)	10 (7, 10)	0.82
Feeding; n (%)			0.20
Absolute nil per os	1 (2)	4 (10)	
Partial feeding	41 (98)	36 (90)	
Feeding intolerance or severe reflux	14 (33)	11 (28)	0.57
Use of inotrope; n (%)	15 (36)	11 (28)	0.42
Use of Muscle relaxant; n (%)	6 (14)	6 (15)	0.93
Use of sedative drug; n (%)			
Continuous drip	20 (48)	18 (45)	0.81
Intermittent dose	20 (48)	26 (65)	0.11

[a] *Heated humidified high-flow nasal cannula.*
[b] *Continuous positive airway pressure.*
[c] *Bilevel positive airway pressure.*

TABLE 2 | Severity, mortality, length of pediatric intensive care unit (PICU) stay, and length of hospital stay.

Characteristics	Metoclopramide ($N = 42$)	Placebo ($N = 40$)	*p* value
PRISM[a]; mean (SD)	8 (7)	8 (6)	0.71
PELOD[b]; mean (SD)	5 (4)	5 (4)	0.41
28-day mortality; n (%)	8 (19)	8 (20)	0.91
Length of PICU stay (days); median (IQR)	11 (5, 21)	12 (6, 26)	0.22
Length of hospital stay (days); median (IQR)	24 (13, 42)	30 (21, 55)	0.14

[a] *Pediatric Risk of Mortality III score.*
[b] *Pediatric Logistic Organ Dysfunction score.*

TABLE 3 | Success rate of post-pyloric feeding tube placement compared between the metoclopramide and the placebo groups.

Feeding tube position	Metoclopramide ($n = 42$)	Placebo ($n = 40$)	*p*-Value
Post-pyloric[a]: n (%)	37 (88)	28 (70)	0.04
• D1[b]: n (%)	4 (9)	4 (10)	
• D2[c]: n (%)	10 (24)	7 (18)	
• D3[d]: n (%)	4 (9)	2 (5)	
• D4[e]: n (%)	5 (12)	1 (2)	
• Proximal jejunum[f]: n (%)	14 (33)	14 (35)	

[a] *Reaching the duodenal bulb and beyond.*
[b] *Reaching the duodenal bulb to the first portion of the duodenum.*
[c] *Reaching the first portion of the duodenum to the second portion of the duodenum.*
[d] *Reaching the second portion of the duodenum to the third portion of the duodenum.*
[e] *Reaching the third portion of the duodenum to the fourth portion of the duodenum.*
[f] *Reaching the proximal jejunum or beyond.*

TABLE 4 | Factors influencing the success rate of post-pyloric position of feeding tube.

Parameter	Gastric position ($n = 17$)	Post-pyloric position ($n = 65$)	*p*-Value
Sedative drug or narcotic agent	9 (53%)	49 (75%)	0.08
Inotropic use	3 (18%)	11 (17%)	>0.99
PRISM III[a] $\geq$ 10	7 (41%)	26 (40%)	0.93

[a] *Pediatric Risk of Mortality III score.*

metoclopramide helps promote gastric emptying and enhances cholinergic-induced peristaltic contractility of the stomach. Metoclopramide has been used to improve peristalsis and facilitate post-pyloric tube placement (10, 19, 20). A randomized controlled study in adults showed the increased success rate of post-pyloric tube placement of 55% in the metoclopramide group compared with 27.3% in the placebo group (13). Nevertheless, a systematic review of four studies demonstrated that metoclopramide did not improve the chance of success (RR 0.82; 95% CI 0.61, 1.10) (21). However, the study on this regard in children is scarce.

Our study showing 88% success rate of blind bedside post-pyloric tube placement in the metoclopramide group, compared with 70% in the placebo group, supports the use of metoclopramide in pediatric post-pyloric tube placement. While a previous study reported successful tube placement of 38% among the non-intervention standard group (22), our study demonstrated a higher success rate; the increase in the success rate may be contributed by the experienced tube placement operator (9). Some studies mentioned about the training years of physicians being the variable associated with successful feeding tube placement (11, 15); therefore, the tube placement in this study was performed by one single clinician to limit this confounder. There were no significant differences in the advancement through the small intestine (**Table 3**), which may be due to small sample size, anatomical variation of the small bowel, and different clinical settings, e.g., degree of dysmotility.

Different techniques have been used for post pyloric feeding tube placement in pediatric patients including an electromagnetic guidance technique (22) and an insufflation air technique (23). However, the electromagnetic guidance carries a high cost and

a need of specialized equipment, and the air insufflation may cause abdominal discomfort. Blind bedside post-pyloric tube placement is an alternative technique, which is considered safe, inexpensive, and effective (24). We considered the technique time-efficient as the mean insertion time was 9.5 ± 3.6 min, which was similar to a previous study (25).

Most PICU patients require sedative drug or narcotic agent. In our study, we found that both the sedative drug and the narcotic agent may enhance the success rate of tube placement ($p = 0.08$). Hence, we hypothesized that the cooperation and comfort of the patient during tube placement is crucial to the increase of success rate.

Theoretically, based on the pharmacokinetic property of intravenous metoclopramide having an average elimination half-life of 4.9 h (26), a duration of 6–8 h to perform plain abdominal radiography was applied in the present study. Furthermore, this duration was also used for the migration of feeding tube along with the bowel peristalsis. However, studies in adult patients have found that a much longer observation time of 24 to 72 h was applied after feeding tube insertion (13, 27, 28). In pediatric patients, they had less energy reserve than the adults, and the standard practice guideline also recommends early enteral feeding as soon as possible (1).

Adverse effects from intravenous metoclopramide are arrhythmias and extrapyramidal side effects (13, 26), but none was reported in our study. Additionally, the adverse events associated with nasointestinal tube insertion (such as misplacement, epistaxis, duodenal perforation, pain, or vomiting) were reported in previous studies (13, 25, 29); we did not observe any of these events in our study.

Our study had some limitations: abdominal radiography was not performed immediately after the procedure as we wanted to wait for the maximal effect of intravenous metoclopramide on bowel peristalsis. Therefore, we are not fully able to clarify whether the tube was placed in the proper location due to the original placement or the ongoing peristalsis facilitated by the metoclopramide. However, this study has some strong points of view, which are the randomized controlled fashion and the feeding tube insertion performed by one single operator. Besides, the relatively small sample size from a single tertiary center may limit the generalizability. Further multicenter studies in various acuity settings may lead to an increase in generalizability of the aforementioned findings.

CONCLUSION

Intravenous metoclopramide can improve the success rate of blind bedside post-pyloric placement of feeding tube in critically ill children.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Asst. Prof. Chusak Okascharoen, Office of The Committee for Research, Faculty of Medicine Ramathibodi Hospital, Mahidol University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JV, SK, and PT contributed to conception and design of the study. NR, SP, and NS organized the database. CK performed the statistical analysis. JV and SK wrote the first draft of the manuscript. NA wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Management of Pediatric Septic Shock and Acute Respiratory Distress Syndrome in Thailand: A Survey of Pediatricians

Pasita Puttiteerachot[1], *Nattachai Anantasit*[1]*, *Chanapai Chaiyakulsil*[2], *Jarin Vaewpanich*[1], *Rojjanee Lertburian*[1] and *Marut Chantra*[1]

[1] Division of Pediatric Critical Care, Department of Pediatric, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [2] Division of Pediatric Critical Care, Department of Pediatrics, Faculty of Medicine, Thammasat University Hospital, Thammasat University, Bangkok, Thailand

Introduction: Pediatric septic shock and acute respiratory distress syndrome (pARDS) are major causes of morbidity and mortality in pediatric intensive care units (PICUs). While standardized guidelines for sepsis and pARDS are published regularly, their implementation and adherence to guidelines are different in resource-rich and resource-limited countries. The purpose of this study was to conduct a survey to ascertain variation in current clinician-reported practice in pediatric septic shock and acute respiratory distress syndrome, and the clinician skills in a variety of hospital settings throughout Thailand.

Methods: We conducted an electronic survey in pediatricians throughout the country between August 2020 and February 2021 using multiple choice questions and clinical case scenarios based on the 2017 American College of Critical Care Medicine's Consensus guideline for pediatric and neonatal septic shock and the 2015 Pediatric Acute Lung Injury Consensus Conference.

Results: The survey elicited responses from 255 pediatricians (125 general pediatricians, 38 pulmonologists, 27 cardiologists, 32 intensivists, and 33 other subspecialists), with 54.5% of the respondents having <5 years of PICU experience. Among the six sepsis scenarios, 72.5 and 78.4% of the respondents had good adherence to the guidelines for managing fluid refractory shock and sedation for intubation, respectively. The ICU physicians reported greater adherence during more complex shock. In ARDS scenarios, 80.8% of the respondents reported having difficulty diagnosing ARDS mimic conditions and used lesser PEEP than the recommendation. Acceptance of permissive hypercapnia and mild hypoxemia was accepted by 62.4 and 49.4% of respondents, respectively. The ICU physicians preferred decremental PEEP titration, whereas general pediatricians preferred incremental PEEP titration.

Conclusion: This survey variation could be the result of resource constraints, knowledge gaps, or ambiguous guidelines. Understanding the perspective and rationale for variation in pediatricians' practices is critical for successful guideline implementation.

Keywords: septic shock, acute respiratory distress syndrome, survey, pediatrician, Thailand

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***Correspondence:**
Nattachai Anantasit
nattachai032@hotmail.com

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INTRODUCTION

Pediatric septic shock and pediatric acute respiratory distress syndrome (pARDS) are the leading causes of morbidity and mortality in pediatric intensive care units (PICUs) worldwide. Mortality rates range from 4 to 50% in sepsis (1–5) and 10 to 33% in pARDS (6), depending on the severity of the illness, risk factors, and geographic location. A recent multicenter Asian study found that pediatric septic shock had a mortality rate of 19.2% (7), while pARDS had a mortality rate of 30.3% (8). The American College of Critical Care Medicine (ACCM) (9) and the Pediatric Acute Lung Injury Consensus conference group (PALLIC) (10) had regularly published guidelines and recommendations for sepsis and pARDS to standardize patient care and improve outcomes. Adherence to these guidelines had been shown to reduce the mortality in pediatric septic shock from 38 to 8%; however, only 30% of the resuscitation practice adheres to standards (11). The lung-protective ventilation strategy such that of low tidal volume ventilation had been shown to reduce mortality in patients with ARDS (12). However, in an observational study, 25% of pediatric patients were ventilated with >10 ml/kg of expiratory tidal volumes (13). The guidelines were implemented and adhered throughout the world. Thailand, one of the developing country in Southeast Asia, is divided into 76 provinces and a capital city. Our country's population is predicted to be 66 million, with over 13 million children. Due to the shortage of pediatric ICU physicians in our country, other specialists and general pediatricians manage the majority of critical care in PICU, which might result in a greater variation in the management and less adherence to guidelines.

Thus, we decided to conduct this self-reported survey to describe pediatricians' knowledge in the management of pediatric septic shock and pARDS. The objectives of this study were to evaluate pediatricians' knowledge compared to guidelines and assess practice variation among ICU and non-ICU physicians as well as the capability of physician skills across various types of hospitals.

METHODS

Study Design

We developed a cross-sectional, self-administered survey to assess pediatricians' stated septic shock and pARDS practice patterns. Pediatricians with at least 1 year of experience working in pediatric intensive care units were eligible, whose worked in the tertiary care hospitals or higher. Currently, there are approximately 51 PICUs, comprises of 31 tertiary care hospitals, twelve university hospitals, and eight private hospitals. Over the last three decades, pediatric pulmonologists, pediatric cardiologists, and some general pediatricians have been tasked with the responsibility of caring for critically ill children in the PICU. For example, they were able to perform tracheal intubation and manage the ventilator settings, as well as administer fluid resuscitation and inotropic therapy due to the unavailability of pediatric intensivists. There were no respiratory therapists, clinical pharmacists, or nutritionists in our country. However, critically ill children now faced more challenges than in the past. Since 2015, the Thai Society of Pediatric Respiratory and Critical Care Medicine has established a pediatric critical care fellowship training program (TPRC). At the time of writing, Thailand has 32 pediatric intensivists, with the majority of them based in Bangkok (capital city of Thailand). The TPRC hosts two academic conferences, six interhospital critical care conferences, and 2–3 ventilatory management workshops each year to ensure that both ICU and non-ICU physicians have adequate critical care knowledge. In addition, in 2018, the TPRC issued the evidence-based guideline for the management of Thai pediatric sepsis and septic shock. In our country, pediatric intensivists, pulmonologists, and cardiologists were the majority of pediatricians who cared for critically ill children in the PICU and were considered to be the ICU physicians. Nevertheless, in some hospitals with PICU, there were no available ICU physicians, therefore all the critically ill children in those hospitals would be taken care of by the general pediatricians or other pediatric subspecialties. Thus, in this study, we divided the enrolled pediatricians into two categories: the ICU physicians (pediatric intensivists, pulmonologists, and cardiologists) and the non-ICU physicians.

Survey Development

The survey questionnaire was developed in accordance with the 2014 American College of Critical Care Medicine consensus guideline for pediatric and neonatal septic shock (9) and the 2015 Pediatric acute lung injury consensus conference (10), to assess current practices and knowledge among Thai pediatricians. The authors drafted the questionnaire following a thorough review of the literature and had it reviewed by four pediatric intensivists for clarity, consistency, objectivity, content validity, and completion time. The questionnaire was modified and finalized based on the feedback following a pilot survey of 15 pediatricians from our center who were not the participants of this study.

The final survey included three domains: (I) demographic data of physicians and hospitals, (II) clinical skills, and (III) six clinical case scenarios for sepsis and six clinical case scenarios for pARDS, each of which assessed a different component of the guidelines for the diagnosis and management. The questionnaire for each clinical scenario included questions regarding fluid-refractory shock, sedation for intubation, catecholamine-resistant shock, normotensive shock with increased systemic vascular resistance (SVR), hypotensive shock with decreased SVR, and refractory vasoplegic shock, shown in **Table 1**. The questionnaires for pARDS included questions about diagnosis, ventilator strategies in mild ARDS, optimal positive end-expiratory pressure (PEEP) in severe ARDS, lung protective strategies, PEEP titration, and recruitment maneuver, shown in **Table 2**. **Tables 1**, **2** were the case scenarios that represent in each objective of pediatric septic shock and pARDS. To avoid misinterpretation, all advanced hemodynamic parameter reference ranges were clearly stated. Each scenario had multiple-choice answers, and adequate knowledge was defined as the appropriate answer in accordance with the ACCM and PALICC guideline. For example, the first case scenario with a fluid-refractory shock patient, the proper response would be norepinephrine or epinephrine infusion. This study

TABLE 1 | Description of the six scenarios of pediatric septic shock.

Scenario 1: A 2-year-old boy, known case of acute lymphoblastic leukemia, who received an induction phase of chemotherapy, presents with septic shock. He receives 40 ml/kg of isotonic crystalloid solution and appropriate antibiotic. Body temperature 39.5°C, HR 170/min, RR 30/min, capillary refill 2 sec, BP 80/30 mmHg., SpO_2 98% (O_2 cannula 2 LPM), warm extremities, Lungs: fine crepitation both lungs, mild distress, mild chest retraction. Initial arterial lactate 4 mmol/L. Which of the following is the next step of appropriate management?
Scenario 2: As information above, he develops respiratory failure and requires intubation. Which of the following is the sedation of choice?
Scenario 3: As information above, his HR is 150/min, BP 80/55 mmHg while receiving 0.2 mcg/kg/min of norepinephrine and 0.1 mcg/kg/min of epinephrine. His lactate and $ScvO_2$ are 5 mmol/L and 75%, respectively. Non-invasive monitoring shows adequate preload, normal cardiac index, and LVEF of 60%. Which of the following is the next management?
Scenario 4: A previously healthy 8-year-old girl was admitted to the PICU for septic shock. She received a total of 60 ml/kg of fluid resuscitation through an internal jugular venous catheter and appropriate antibiotics. Epinephrine was titrated up to 0.2 mcg/kg/min. At PICU: Body temperature 39°C, HR 170/min, RR 40/min, capillary refill is 4 s, ABP 100/70 mmHg, Cold extremities, good peripheral pulse. Hb 12 g/dL, $ScvO_2$ 60%, Lactate 5 mmol/L. Ultrasound shows adequate preload without pericardial nor pleural effusion. Which of the following is the appropriate inotrope/vasopressor?
Scenario 5: A 6-year-old boy, BW 20 kg, presents with severe pyelonephritis and septic shock. He received a total of 60 ml/kg of fluid and epinephrine was titrated to 0.3 mcg/kg/min. Body temperature 39.5°C, HR 170/min, RR 45/min, capillary refill 5 s, ABP 48/32 (39) mmHg, cold extremities, weak central pulse. CVP 13 cmH_2O, lactate 10 mmol/L, $ScvO_2$ 60%, Hb 11 g/dL. Urine output was 0.2 cc/kg/hr. Bedside ultrasound reveals LVEF of 55%, distended IVC, and diffused B-line from lung ultrasound. Non-invasive monitoring shows CI 8.3L/min/m^2, SVRI 507 dyns/sq.mm/m^2 (normal range 1000–2000 dyns/sq.mm/m^2). Which of the following is the most appropriate management?
Scenario 6: A 1-year-old boy, BW 8 kg, known case of biliary atresia presents with spontaneous bacterial peritonitis and septic shock. He received a total of 60 ml/kg of NSS and norepinephrine was titrated to 0.2 mcg/kg/min. At PICU: Body temperature 39°C, HR 160/min, RR 50/min, capillary refill is 1 s, ABP 70/35 (45) mmHg, warm extremities, and bounding peripheral pulses. Non-invasive hemodynamic monitoring (USCOM) shows CI 7.9 L/min/m2, SVRI 717 dyns/sq.mm/m2 (normal range 800–1200 dyns/sq.mm/m2), SV 15 ml (normal range 1.5-2.25 ml/kg). What is your next step of management?

TABLE 2 | Description of the six scenarios of pediatric acute respiratory distress syndrome.

Scenario 1: A 1-month-old boy, previously healthy with no postnatal complication, presents with 3 days of URI symptoms and later develops respiratory failure. He is intubated and ventilated in a pressure control mode PC 10 PEEP 5 FiO_2 0.6 (SpO_2 85%). ABG shows pH 7.38, PCO_2 42 mmHg, PaO_2 50 mmHg, Oxygenation index = 8, $ScvO_2$ 90%. Physical examination reveals fine crepitation both lungs without cardiac murmur. CXR shows pulmonary congestion. Do you diagnose this patient with pediatric ARDS?
Scenario 2: A 1-year-old boy presents with pneumonia and respiratory failure. He is on high flow nasal cannula with FiO_2 of 0.5. ABG shows pH 7.35, PCO_2 38 mmHg, PO_2 105 mmHg, HCO_3 19 mmol/L. He is diagnosed with pediatric ARDS. He is intubated and sedated. Which of the following is the initial ventilator setting?
Scenario 3: An 11-year-old girl, known case SLE, was admitted to the PICU with pulmonary hemorrhage. She is intubated and ventilated in a pressure control mode PC 16 above PEEP 6 FiO_2 0.6 (SpO_2 88%) Pmean 14. ABG shows pH 7.35, PCO_2 35 mmHg, PO_2 50 mmHg, HCO_3 19 mmol/L. Which of the following is your management on ventilator setting?
Scenario 4: Which of the following are the lung protective strategies for severe pARDS?
Scenario 5: A 5-year-old boy visits a general hospital with a diagnosis of community-acquired pneumonia. He was intubated and ventilated with a pressure control mode, pressure above PEEP 20, PEEP 5, RR 30 (Pmean 16), TV 5 ml/kg. His SpO_2 is 85%, FiO_2 was increased to 1.0 to maintain SpO2 90–92%. His hemodynamic parameters are stable. Initial ABG shows: pH 7.294 PaO_2 60 mmHg (FiO_2 1.0) -> oxygenation index 26, $PaCO_2$ 34.5 mmHg HCO_3 16.7 mmol/L. His diagnosis was pediatric ARDS. He was referred to your hospital. Which of the following is the next step on ventilator management?
Scenario 6: Do you plan to do the lung recruitment maneuver in moderate to severe ARDS patient? What is your method of lung recruitment maneuver?

was approved by the institutional review board (IRB). Online informed consent was obtained prior to enrollment. Respondents were voluntary and anonymous.

Distribution of Surveys

Our country had 31 tertiary-level hospitals, 12 university-level hospitals, and eight private hospitals with pediatric intensive care units. The survey was distributed via electronic mail to all registered general pediatricians, pediatric intensivists, pulmonologists, and cardiologists working in these hospitals, and was followed up with 2 monthly email reminders. Participants provided their consent and the information was kept confidential. Participants were asked to electronically sign the informed consent before answering the survey. Data were collected automatically using an electronic survey engine (Google Form). After we received responses from the participants, we rechecked that the responses were not duplicates. Initially, we received a low response rate. Therefore, we attempted to announce on several national academic conferences and social media platforms such as Line and Facebook during the study period. The survey was opened between August 2020 and February 2021.

Statistical Analyses

Statistical analyses were performed using SPSS software (version 23, SPSS, Inc., Chicago, Illinois, USA). Descriptive variables were analyzed as absolute frequencies, percentages, means, and standard deviations. Comparisons of categorical variables across different groups were assessed using a Chi-square test or Fisher's exact test and we used a Student *t*-test for continuous variables. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

A total of 255 pediatricians responded to the survey. The demographic and baseline characteristics were illustrated in

Table 3. The majority (74.5%) were females, and general pediatricians (49%). Almost all responders had spent <10 years in the PICU (86.7%). There were 118 (46.3), 97 (38), 86 (33.7), and 197 (77.2%) respondents who have experience in using video laryngoscope, laryngeal mask airway, non-invasive hemodynamic monitoring, and ultrasound-guided vascular access, respectively. Furthermore, there were only 65 (25.5%) respondents who have experience in the initiation of an extracorporeal membrane oxygenator.

Practices for Sepsis Management

Overall, 185 (72.5), 200 (78.4), 115 (45.1), 143 (56.1), 142 (55.7), and 192 (75.3%) of the respondents demonstrated adequate knowledge of pediatric septic shock management in each clinical scenario (**Figure 1**). Almost three-quarters of the respondents indicated that norepinephrine should be the first inotrope/vasopressor of choice in fluid-refractory shock with wide pulse pressure. The most frequently prescribed sedative medications for intubation were a combination of fentanyl and midazolam (49.8%), while 21.6 % of respondents chose etomidate in combination with other sedative medications. Approximately 45.1% of the respondents prescribed corticosteroids in patients with catecholamine-resistant shock, while only 4.7% conducted random cortisol levels prior to initiating corticosteroids. Around half of the respondents (46.3% for milrinone and 9.8% for dobutamine) prescribed vasodilator medications to patients who were in normotensive shock with high SVR. Over half of the respondents would add norepinephrine in hypotensive shock with low SVR patients, while 12.9 and 7.1%, respectively, would increase epinephrine and dopamine to high doses. In refractory vasoplegic shock, the majority of respondents (49.8%) would increase norepinephrine and 25.5% would add terlipressin as the vasopressor.

Practices for PARDS Management

A total of 206 (80.8%) of respondents misdiagnosed the patient in scenario 1 with pARDS rather than total anomalous pulmonary venous return with obstruction which was the ARDS mimic conditions (**Figure 1**). The majority of the respondents followed the Pediatric Acute Lung Injury Consensus conference group (PALLIC), which preferred using the pressure-controlled mode, 5–8 ml/kg of tidal volume, 5–7 cmH_2O of positive end-expiratory pressure (PEEP), and limited the plateau pressure to less than or equal to 28 cmH_2O in mild pARDS patients. Only 14.1% of respondents reported using an adequate PEEP of 10–15 cmH_2O, while the majority reported using PEEP less than the recommendation in patients with severe pARDS. The permissive hypercapnia with mild acidosis (pH 7.15–7.30) was accepted as the optimal strategy for 50.2% of the respondents. Surprisingly, 49.4% preferred a pH range between 7.30 and 7.40. Mild hypoxemia with a target SpO_2 of 88–92% was tolerated by 62.4% of respondents, while 5.9% desired a target SpO_2 of >95%. In the case of persistent hypoxemia with low PEEP (case scenario 5), 74.9% of respondents considered increasing PEEP, whereas 21.6% switched to high-frequency oscillatory ventilation. Almost all respondents reported performing the lung recruitment maneuvers on patients with moderate to severe pARDS. Three-quarters of ICU physicians preferred decremental PEEP titration, while half of the non-ICU physicians preferred incremental PEEP titration.

TABLE 3 | Demographic data and baseline characteristics of participants.

Characteristics	Participants ($n = 255$)
Female, *n* (%)	190 (74.5)
Age, mean (SD)	35.7 (6.9)
Pediatric subspecialties, *n* (%)	
General pediatrician	125 (49)
Pulmonologist	38 (14.9)
Cardiologist	27 (10.6)
Intensivist	32 (12.5)
Other subspecialists	33 (12.9)
Years of PICU experience, *n* (%)	
<5	139 (54.5)
5–10	72 (28.2)
>10	44 (17.3)
Workplace, *n* (%)	
Tertiary hospital	139 (54.5)
Medical school	78 (31.6)
Private hospital	38 (14.9)
Type of PICU, *n* (%)	
Mixed PICU	158 (61.9)
Medical PICU	82 (32.2)
Adult mixed ICU	11 (4.3)
Cardiac PICU	4 (1.6)

PICU, pediatric intensive care unit.

Comparing Results From ICU Physicians to Non-ICU Physicians

We analyzed the percentage of an appropriate answers in each scenario comparing ICU and non-ICU physicians. ICU physicians had a significantly higher percentage of an appropriate answers in normotensive shock with high SVR, hypotensive shock with low SVR, and in refractory vasoplegic shock than non-ICU physicians (75.3 vs. 44.3%, $p < 0.001$, 76.3 vs. 43%, $p < 0.001$, and 92.8 vs. 64.6%, $p < 0.001$, respectively) [**Figure 2**]. However, when a subgroup of 97 ICU physicians were analyzed, the intensivists were more likely to have the appropriate answers than the cardiologists and the pulmonologists (100 vs. 89.5 vs. 88.9% $p = 0.13$, respectively). ICU physicians demonstrated significantly greater comprehension of optimal PEEP in severe ARDS and PEEP titration than non-ICU physicians (19.6 vs. 10.8%, p 0.05 and 83.5 vs. 69.6%, p 0.01, respectively) [**Figure 2**].

DISCUSSION

Our study demonstrated a significant level of heterogeneity in the clinical practices among Thai pediatricians, as well as some discrepancies with ACCM and PALLIC guidelines. The choice of first-line inotrope or vasopressor for warm shock was unclear until the 2014 update version of the ACCM, which favored the use of norepinephrine in warm shock (9).

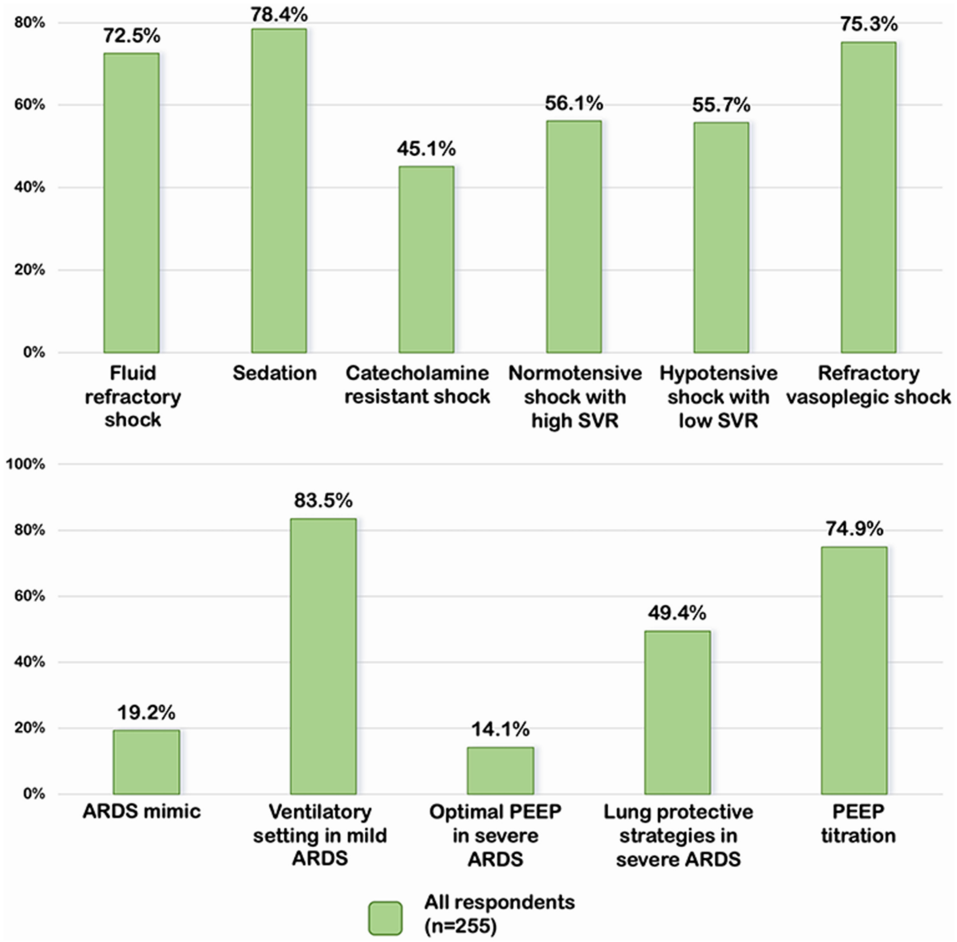

FIGURE 1 | Percentage of appropriate answers on septic shock and pARDS in all respondents. SVR, systemic vascular resistance; PEEP, positive end expiratory pressure; ARDS, acute respiratory distress syndrome.

According to our survey, the majority of Thai pediatricians chose norepinephrine as a vasopressor of choice, followed by 11.4% who preferred epinephrine. These results corresponded with the previous survey published in 2019 (14), which demonstrated that 60% of pediatric intensivists preferred norepinephrine and 25% chose epinephrine.

The current pediatric sepsis guideline highlighted the hemodynamic effects of sedative and analgesic drugs in vulnerable patients with shock. The preemptive use of ketamine and atropine is considered the best regimen to promote cardiovascular integrity by augmenting SVR and protects against bradycardia (15, 16). Even though 71.8% of hospitals in our survey had ketamine available, only one-fourth of Thai pediatricians use this combination. The fact that general pediatricians are unfamiliar with the use of ketamine may have contributed to this finding.

The role of corticosteroids in catecholamine-resistant shock has been widely debated in both the adult and pediatric literature. Adjunctive corticosteroid hastened the resolution of shock but only demonstrated controversial evidence regarding mortality benefits (17–19). ACCM recommended hydrocortisone therapy in shock despite epinephrine or norepinephrine infusion without clear definition (9). Consequently, physicians providing care are left to make individual decisions at the bedside, resulting in a significant practice variation. Our survey showed that 45.1% of the respondents prescribed hydrocortisone in patients with fluid refractory shock who required one high dose of the vasoactive agent. This was consistent with a previous survey which reported that 50% of physicians prescribed hydrocortisone for patients requiring one high dose vasoactive agent and 91.4% of physicians would prescribe hydrocortisone for patients requiring two or more vasoactive agents (20).

Case scenarios in more complex shock types were created to measure respondents' interpretation and implementation of advanced non-invasive monitoring to patient management. ICU physicians showed more consistent adherence to the guidelines than the non-ICU physicians since management beyond catecholamine-resistant shock requires advanced hemodynamic monitoring and medications. Resource-limited hospitals and unacquaintance to more complex shock for non-ICU physicians might restrict their management practices. In pARDS, we found that Thai pediatricians have quite good adherence to

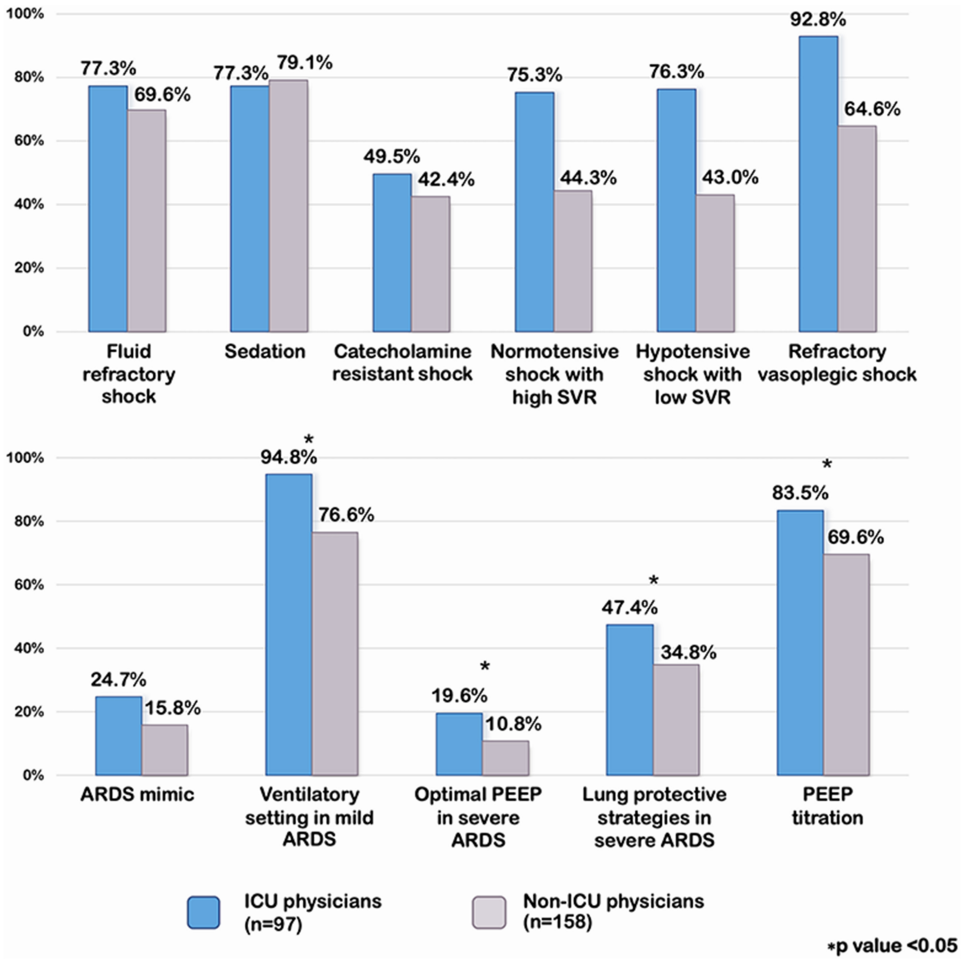

FIGURE 2 | Percentage of appropriate answers on septic shock and pARDS compared ICU and non-ICU physicians. SVR, systemic vascular resistance; PEEP, positive end expiratory pressure; ARDS, acute respiratory distress syndrome.

low tidal volumes ventilation with only 1.2% reported using high tidal volumes (>10 mL/kg). These results corresponded with the previous self-reported surveys in North America and Europe, which showed that most of the pediatric intensivists used tidal volumes between 5 and 8 mL/kg, and none of them reported using high tidal volumes (>10 mL/kg) (21). However, they differed from the actual practices in a cross-sectional observational study (PALIVE) taking place in the same population, which reported that ∼25% of patients were ventilated with exhaled tidal volumes of >10 mL/kg (13). This highlighted the gap between theoretical knowledge and routine practices. Adequate positive end-expiratory pressure (PEEP) is essential to prevent repetitive opening and closing of the alveoli during the respiratory cycle, which may lead to further ventilator-induced lung injury and is associated with lower mortality. Observational studies in both adults and children showed that many patients with ARDS received lower PEEP than the recommendation (22, 23). We discovered similar results, with just 14.1% of severe ARDS patients receiving optimal PEEP, most of the respondents reported not to use PEEP above 10 cmH_2O. A retrospective study in 1,134 patients with pARDS illustrated that 26.6% of patients were managed with lower PEEP relative to the amount of FIO_2 recommended by the ARDSNet protocol. Patients managed with lower PEEP significantly experienced higher mortality than those who were managed with PEEP levels in line with or higher than recommended by the protocol (23). Pediatricians were hesitant to increase PEEP in response to hypoxemia, preferring to increase FiO_2 instead (13, 23). The reasons were likely multifactorial and might be related to concerns about high PEEP levels in infants and neonates with low chest wall elastance, concerns about cardiopulmonary interactions, or a perception that high FiO_2 is not harmful (23–25).

A recruitment maneuver is a sustained increase in airway pressure to open collapsed alveoli, followed by sufficient PEEP to keep the lungs open (26). PALLIC guideline recommended careful recruitment maneuvers in the attempt to improve severe oxygenation failure (10). A variety of approaches have been used, including decremental PEEP titration, incremental PEEP titration, sustained inflation with CPAP, intermittent sigh breaths, and others. However, evidence is lacking that one

approach is superior to the others, and the choice is determined by individual practice (27, 28). Our study discovered that ICU physicians favored decremental PEEP titration, whereas non-ICU physicians preferred incremental PEEP titration, which might be attributed to the gradual rise of pressure is better tolerated from a hemodynamic standpoint for non-ICU physicians.

Permissive hypercapnia is a ventilation strategy that allows an unphysiologically high partial pressure of carbon dioxide (PCO_2) to permit lung-protective ventilation with low tidal volumes. Nearly half of the respondents aimed for relatively normal arterial blood gas, highlighting Thai pediatricians' misconceptions about permissive hypercapnia and mild hypoxemia.

Our study had some strengths. Opportunities for critical care training in resource-limited setting are scarce. Our country is a developing country with a scarcity of specialty physicians, infrastructure, and medical equipment. We conducted the first survey of Thai pediatricians regarding their current practices and understanding related pediatric septic shock and pARDS. Our country is a developing country with a scarcity of specialty physicians, infrastructure, and medical equipment. This survey gathered replies from individuals with a variety of professional titles, years of experience, and hospital kinds, ranging from general hospitals to medical schools. In 2018, Thailand adopted a clinical practice guideline for pediatric sepsis and septic shock. Our findings indicated that the majority of participants demonstrated enough knowledge regarding sepsis management. On the other hand, the majority of participants provided an inadequate answer to criticism about pARDS and sophisticated pediatric septic shock management. The survey's findings imply that the local guideline may help improve management adherence. A previous study revealed that critical care is frequently regarded inappropriate and of minor importance than primary care efforts, particularly in resource-limited settings (29). This study may be the first step toward gaining a better understanding of the knowledge, self-reported practice, and skills of local pediatricians caring for children with sepsis and ARDS. Although following international guidelines can improve patient outcomes, there will be some knowledge gaps among pediatricians in developing countries. These knowledge gaps could be reduced by increasing the hands-on workshops and frequently updated conference meetings. In addition, local guidelines for sepsis and pARDS management for non-ICU physicians should be developed, and pediatric critical care fellowship training programs should be promoted as part of national policy to improve quality of care.

Our study may have some limitations. First, it was unclear overall target population since we did not know the exact total number of pediatricians who have been practicing in PICU. Although our study collected from 255 pediatricians, these participants cannot be considered definitively representative of all nations. It was unclear overall target population and an inability to quantify response rates owing to the survey's distribution *via* social media. Our survey, on the other hand, was distributed to all tertiary and university-based hospitals with a pediatric intensive care unit. Second, there was high proportion of pediatricians who was working in the upper level of tertiary center which might limit generalizability. There was also the possibility of selection bias, since pediatricians interested in critical care medicine may be more likely to respond to our questionnaire. Nevertheless, this study could explain the actual practice and perception to manage pediatric septic shock and pARDS patients. Last, the management in a self-reported survey may not accurately reflect real-life practices at the bedside, despite our best efforts to construct scenarios to best suit actual practices.

CONCLUSION

This survey added more confirmation on the variability of current self-reported pediatric septic shock and pARDS management practices, as well as knowledge gaps and lack of adherence to guidelines. The variation might be due to resource constraints, unacquaintance to critically ill children, lower grading of pediatric evidence compared to adults, and unclear recommendations of current guidelines. Caring for critically ill children had been increasingly difficult in recent years, highlighting the necessity of pediatric critical care physicians in treating these patients. We emphasized the need for continuous education and training in pediatric intensive care medicine in order to improve the quality of care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PP and NA: contributed to the design of the study, data collection, data analysis, and manuscript drafting. JV, RL, and MC: contributed to the design of the study. PP, NA, and CC: contributed to the initial draft of the manuscript. NA: critically revised it for important intellectual content. All authors gave final approval of the version to be published.

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METHODS
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Global PARITY: Study Design for a Multi-Centered, International Point Prevalence Study to Estimate the Burden of Pediatric Acute Critical Illness in Resource-Limited Settings

Qalab Abbas[1†], Adrian Holloway[2†], Paula Caporal[3,4], Eliana López-Barón[5], Asya Agulnik[6], Kenneth E. Remy[7,8], John A. Appiah[9], Jonah Attebery[10], Ericka L. Fink[11], Jan Hau Lee[12,13], Shubhada Hooli[14], Niranjan Kissoon[15], Erika Miller[2], Srinivas Murthy[15], Fiona Muttalib[15], Katie Nielsen[16], Maria Puerto-Torres[6], Karla Rodrigues[17], Firas Sakaan[6], Adriana Teixeira Rodrigues[17], Erica A. Tabor[18], Amelie von Saint Andre-von Arnim[16], Matthew O. Wiens[19,20,21], William Blackwelder[22], David He[23], Teresa B. Kortz[24,25‡] and Adnan T. Bhutta[2,26‡] on Behalf of the PALISI Global Health Subgroup the Global PARITY Investigators*

[1] Department of Pediatrics and Child Health, Aga Khan University Karachi, Karachi, Pakistan, [2] Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Maryland Baltimore, Baltimore, MD, United States, [3] Hospital Interzonal Especializado en Pediatría "Sor María Ludovica", La Plata, Argentina, [4] Red Colaborativa Pediátrica de Latinoamérica (LARed Network), Buenos Aires, Argentina, [5] Hospital Pablo Tobón Uribe, Unidad de Cuidado Crítico Pediátrico, Medellín, Colombia, [6] Department of Global Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, TN, United States, [7] Division of Critical Care Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, United States, [8] Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University Hospitals of Cleveland and Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, United States, [9] Pediatric Intensive Care Unit, Komfo Anokye Teaching Hospital, Kumasi, Ghana, [10] Department of Pediatrics, Section of Pediatric Critical Care, University of Colorado, Aurora, CO, United States, [11] Division of Pediatric Critical Care Medicine, Department of Critical Care Medicine, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, United States, [12] Children's Intensive Care Unit, KK Women's and Children's Hospital, Singapore, Singapore, [13] SingHealth Duke-NUS Global Health Institute, Singapore, Singapore, [14] Division of Pediatric Critical Care, Department of Pediatrics, BC Children's Hospital, The University of British Columbia, Vancouver, BC, Canada, [15] Department of Pediatrics, Section of Pediatric Emergency Medicine, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States, [16] Division of Pediatric Critical Care, Department of Pediatrics, University of Washington, Seattle Children's, Seattle, WA, United States, [17] Department of Pediatrics, Hospital das Clínicas da UFMG/EBSERH, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [18] Pennsylvania State University, State College, PA, United States, [19] Center for Child Health at BC Children's Hospital, The University of British Columbia, Vancouver, BC, Canada, [20] Department of Pediatrics, Mbarara University of Science and Technology, Mbarara, Uganda, [21] Department of Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada, [22] Department of Epidemiology and Public Health, University of Maryland, Baltimore, MD, United States, [23] Analytical Solutions Group, Inc., North Potomac, MD, United States, [24] Division of Critical Care, Department of Pediatrics, University of California, San Francisco, San Francisco, CA, United States, [25] Institute for Global Health Sciences, University of California, San Francisco, San Francisco, CA, United States, [26] Center for Vaccine Development and Global Health, University of Maryland, Baltimore, MD, United States

Background: The burden of pediatric critical illness and resource utilization by children with critical illness in resource limited settings (RLS) are largely unknown. Without specific data that captures key aspects of critical illness, disease presentation, and resource utilization for pediatric populations in RLS, development of a contextual framework for appropriate, evidence-based interventions to guide allocation of limited but available resources is challenging. We present this methods paper which describes our efforts to determine the prevalence, etiology, hospital outcomes, and resource utilization associated with pediatric acute, critical illness in RLS globally.

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Suresh Kumar, Postgraduate Institute of Medical Education & Research, India

***Correspondence:**
Adnan T. Bhutta
abhutta@som.umaryland.edu

†These authors have contributed equally to this work and share first authorship
‡These authors have contributed equally to this work and share senior authorship

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Methods: We will conduct a prospective, observational, multicenter, multinational point prevalence study in sixty-one participating RLS hospitals from North, Central and South America, Africa, Middle East and South Asia with four sampling time points over a 12-month period. Children aged 29 days to 14 years evaluated for acute illness or injury in an emergency department) or directly admitted to an inpatient unit will be enrolled and followed for hospital outcomes and resource utilization for the first seven days of hospitalization. The primary outcome will be prevalence of acute critical illness, which Global PARITY has defined as death within 48 hours of presentation to the hospital, including ED mortality; or admission/transfer to an HDU or ICU; or transfer to another institution for a higher level-of-care; or receiving critical care-level interventions (vasopressor infusion, invasive mechanical ventilation, non-invasive mechanical ventilation) regardless of location in the hospital, among children presenting to the hospital. Secondary outcomes include etiology of critical illness, in-hospital mortality, cause of death, resource utilization, length of hospital stay, and change in neurocognitive status. Data will be managed via REDCap, aggregated, and analyzed across sites.

Discussion: This study is expected to address the current gap in understanding of the burden, etiology, resource utilization and outcomes associated with pediatric acute and critical illness in RLS. These data are crucial to inform future research and clinical management decisions and to improve global pediatric hospital outcomes.

Keywords: pediatric critical illness, acute pediatric care, critical care, outcome, low-and lower-middle-income countries, resource utilization, low resource setting

INTRODUCTION

Over 80 percent of the annual 6.4 million global deaths in children less than 14 years of age occur in low- and middle-income countries (LMICs) with limited resources (1). These deaths are predominantly a result of acute illnesses – sepsis, pneumonia, and trauma – that can be successfully managed with basic, intensive care interventions, such as fluid resuscitation, ventilator support, and transfusion of blood products. Unfortunately, though pediatric acute critical illnesses are the leading causes of death and disability for children outside of the neonatal period globally, acute and critical care services are not universally available in resource-limited settings (RLS) (2–7). A lack of acute and critical care resources is directly associated with worse outcomes, including increased mortality, in children (6–12). Furthermore, this global disparity not only exists with respect to available resources, but also in the availability of data. The true burden and incidence of pediatric acute critical illness is unknown (2, 3, 7, 13–17). Without specific data that captures etiology of acute critical illness and resource utilization in RLS, we cannot develop a contextual framework for appropriate, evidence-based interventions, or appropriately allocate limited but available resources in RLS.

Point prevalence studies are a valuable study design to prospectively gather individual-level data, determine disease prevalence, and measure variability in outcomes and resource utilization across many geographic regions and healthcare settings. Recently, there have been several global point prevalence studies to determine the prevalence of specific pediatric acute critical illnesses: the Pediatric Acute Lung Injury Ventilation (PALIVE) and Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) studies estimated the prevalence of acute pediatric lung injury (10, 15) the International Survey of Critically Ill Children with Acute Neurological Insults (PANGEA) estimated the prevalence of new neurologic injury due to a variety of etiologies (6); and the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study estimated the prevalence of severe pediatric sepsis (18). While each of these studies contributed significant knowledge about specific critical illnesses, they failed to capture the true global burden of disease and resource utilization within and across LMICs. These studies also required Pediatric Intensive Care Unit (PICU) admission as an inclusion criterion, limiting participation to hospitals with intensive care units. This likely resulted in an underestimation of disease prevalence and mortality in RLS where critical illness is often managed outside of formal intensive care units (2). Additionally, there is significant overlap between illnesses (e.g., pneumonia is a frequent cause of sepsis) and resources required (e.g., mechanical ventilation may be required to support trauma and septic patients) to treat pediatric acute critical illness; therefore, a narrow, disease-specific focus fails to capture both the burden of acute critical illness overall nor does it provide a realistic estimate of resource required to deliver critical care to these patients.

For these reasons the true burden of and outcomes associated with pediatric acute critical illness in RLS have not been

previously characterized. As a result, the overall health impact of pediatric acute critical illness in RLS is not known. To better understand the burden of pediatric acute critical illness and associated resource utilization in RLS, we propose the **P**ediatric **A**cute c**R**itical **I**llness point prevalence s**T**ud**Y**; Global PARITY. The overarching objectives of the study are to 1) engage the global pediatric critical care community to establish baseline frequencies and outcomes of common conditions leading to morbidity and mortality of children in RLS, 2) inform a prospective research agenda to challenge the status quo and discover breakthroughs in care to improve pediatric outcomes globally, and 3) measure the burden of pediatric acute critical illness in RLS. Addressing these data gaps are a crucial first to set future clinical research, health delivery, and resource allocation priorities for RLS globally.

METHODS

Study Design and Setting

A prospective, observational, multicenter, multinational point prevalence study will be conducted in resource-limited hospitals in North, Central, and South America, Africa, the Middle East, and South Asia over four sampling time periods to capture seasonal variation. The specific aims of this study are to determine 1) the etiology and prevalence of pediatric acute critical illness among children presenting to participating hospitals in RLS; 2) measure hospital outcomes (mortality, length of stay) in children with acute critical illness in RLS; 3) determine hospital resource utilization by children with acute critical illness; and 4) determine the current resources available to provide acute critical care across RLS.

RLS are characterized by a lack of funds to cover health care costs, resulting in: limited access to medication, equipment, supplies, and devices; less-developed infrastructure; and fewer or less-trained personnel. Resource limitations at each site will be assessed by a separate Hospital Resource Survey (7). Eligible sites will: self-identify as a RLS; be an acute care hospital; provide emergency and inpatient care to a general population of children with acute illnesses (i.e., not a specialty hospital); have a reliable internet connection or cellular service for uploading data; have a member of the local research team who can communicate in and understand English; have an established Institutional Review Board (IRB) or ethical approval process; have previous experience with clinical research and data collection; have the ability to support or apply for support for study-related costs. Hospitals will be recruited via established relationships from the Global Health subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators' (PALISI) Research Network (www.palisiglobalhealth.org), the St. Jude Global Critical Care Program (www.stjude.org/global), and the Red Colaborativa Pediátrica de Latinoamérica (LARed Network). At time of this manuscript, 61 sites from 27countries in 8 regions have committed to participation (**Table 1**, **Figure 1**). The study is coordinated by the Department of Pediatrics at the University of Maryland and has been deemed exempt by the University of Maryland Institutional Review Board (IRB, HP-00086107).

All children presenting to the Emergency Department (ED), or equivalent acute hospital receiving unit, or who are directly admitted to a participating site hospital will be screened during a 24-h period on four separate days within four epochs over a 12-month period for inclusion and exclusion criteria. Inclusion criteria will include children aged 29 days to 14 years of age evaluated in the ED for an acute illness or injury or directly admitted to an inpatient unit. Children who are evaluated in the ED and discharged home after evaluation, who die in the ED, or are evaluated and transferred to a higher level of care will be included. This number will serve as the total population (denominator) to calculate the prevalence.

Children presenting for a scheduled follow-up visit, vaccinations, suture removal (or other non-acute complaint), children with a corrected gestational age less than 42 weeks, and children who present to the ED and are pronounced dead on arrival will be excluded. Neonates and infants up to 28 days will not be included in this study as the etiology of critical illness and resource requirements to manage neonates and young infants differs significantly from that of older children. Since the upper age limit of what defines a pediatric patient varies by site and region, 14 years was chosen as the upper limit of age, as patients 14 years and younger are generally considered to be children regardless of setting. All children meeting inclusion criteria and no exclusion criteria

TABLE 1 | Participating sites by country and global PARITY-designated region.

Country	Number of participating sites	Global PARITY region
Argentina	5	Spanish-speaking South America
Barbados	1	North America/Caribbean/Central America
Bolivia	1	Spanish-speaking South America
Brazil	1	Portuguese-speaking South America
Colombia	12	Spanish-speaking South America
Ethiopia	2	West Africa/Ethiopia
Ghana	8	West Africa/Ethiopia
Guatemala	1	North America/Caribbean/Central America
Haiti	1	Francophone Countries
India	2	Middle East/India/Pakistan
Indonesia	1	Southeast Asia
Kenya	1	East/Central Africa
Lebanon	1	Middle East/India/Pakistan
Malaysia	1	Southeast Asia
Mali	1	Francophone Countries
Mexico	2	North America/Caribbean/Central America
Mongolia	1	Southeast Asia
Nigeria	3	West Africa/Ethiopia
Pakistan	3	Middle East/India/Pakistan
Paraguay	1	Spanish-speaking South America
Peru	2	Spanish-speaking South America
Rwanda	3	East/Central Africa
Tanzania	1	East/Central Africa
Thailand	1	Southeast Asia
Turkey	1	Middle East/India/Pakistan
Uganda	2	East/Central Africa
Uruguay	2	Spanish-speaking South America

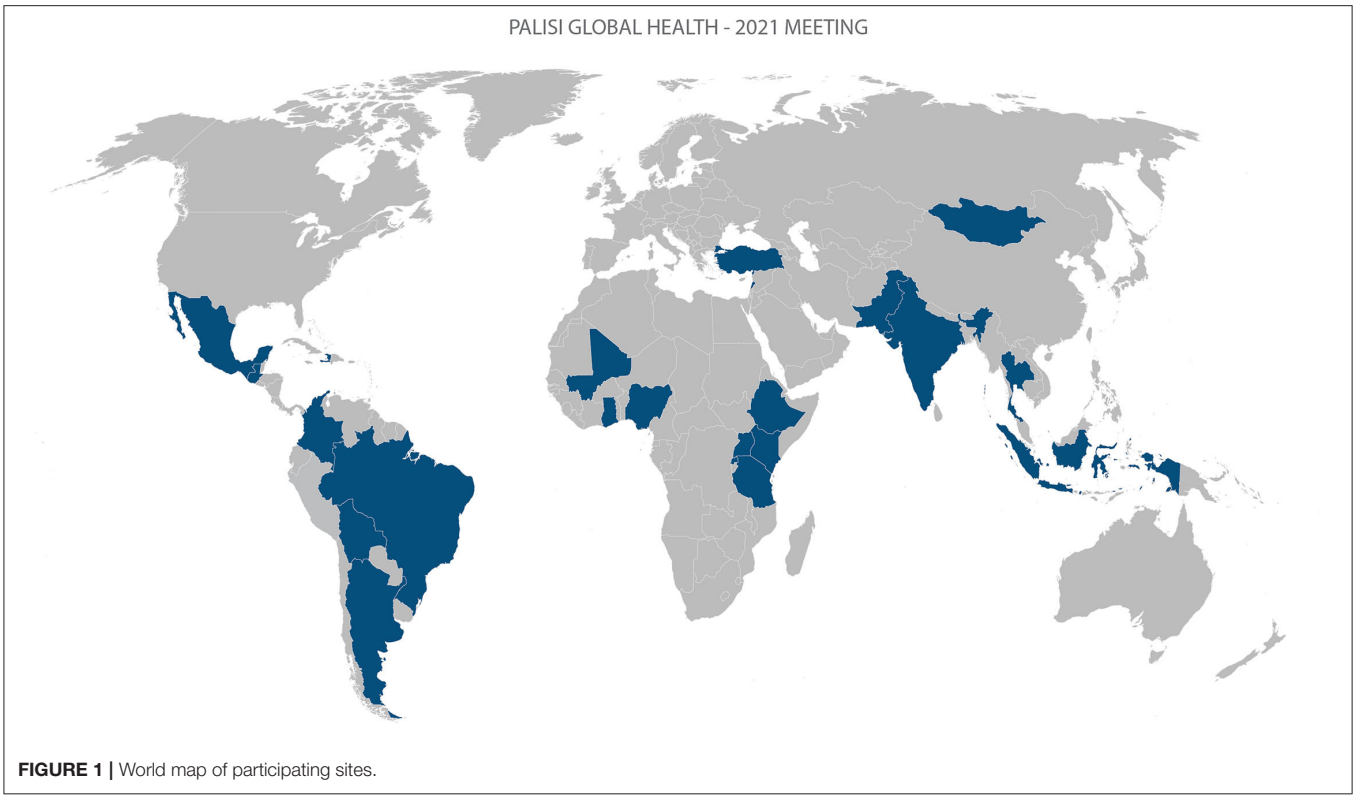

FIGURE 1 | World map of participating sites.

will be enrolled. Due to the IRB exempt status, consent is not required.

Patients who are admitted to the hospital (e.g., general pediatric ward, high dependency unit [HDU], or intensive care unit [ICU]) either directly or through the ED will be followed daily for up to 7 days to determine daily resource utilization. Admitted patients will also be followed until the time of discharge, death, transfer or hospital day 30, whichever occurs first, to determine hospital outcomes. These admitted patients will be the numerator to calculate the overall prevalence of hospitalizations.

Data Collection and Management

All data will be collected and managed via REDCap (Research Electronic Data Capture); a secure, web-based application and electronic data capture tool hosted at the University of Maryland (19, 20). No patient-identifying data will be collected. Prior to data collection, a pilot will be conducted at each site to identify challenges in data acquisition and to test study procedures. Study data will be collected using a hospital resource survey, an initial intake survey, a daily resource utilization survey (to be completed daily from the day of presentation up to hospital day seven), and a final outcomes survey (see **Supplementary Material**). The hospital resource survey is an adapted version of a previously published (7) survey that aims to assess aspects of resource availability, the presence of a basic research infrastructure including ethical and/or IRB approval mechanisms, and the availability of a local site principal investigator (PI). The following data will be collected from the medical record, per exempt status of the IRB, during the study: hospital characteristics including average number of patient encounters and admissions, types of inpatient units, available human resources, available infrastructure including healthcare devices, medications and laboratory resources; patient characteristics including severity of illness, anthropometrics (weight, height, mid-upper arm circumference), comorbidities (HIV status, congenital heart disease, malnutrition), presenting vital signs, routine laboratory test results, imaging results, and the Pediatric Overall Performance Category (POPC) (5) prior to the current illness; hospital resource utilization including use of blood transfusion, fluid bolus, vasoactive agents, non-invasive positive pressure ventilation, oxygen, mechanical ventilation, ICU admission, and antibiotic administration; and outcomes including discharge home, transfer to a higher level of care within the hospital, transfer to another hospital, death, final hospital diagnosis, length of stay, cause of death (if applicable), and the POPC at the time of discharge. For the selected case report forms, see supplements entitled 1) Initial Intake Survey, 2) Daily Assessment Survey, 3) Final Outcomes Survey.

Outcomes

The primary outcome of interest is prevalence of pediatric acute critical illness, defined as death within 48 h of presentation to the hospital, including ED mortality; or admission/transfer to an HDU or ICU; or transfer to another institution for a higher level-of-care; or receiving critical care-level interventions (vasopressor infusion, invasive mechanical ventilation, non-invasive mechanical ventilation) regardless of location in the

hospital. Secondary outcomes include etiology of critical illness, in-hospital mortality, cause of death, resource utilization, length of hospital stay, and change in neurocognitive status from premorbid state from admission to discharge POPC.

Statistical Analysis

Data will be analyzed on all subjects who meet inclusion criteria. Descriptive analyses will summarize population-level information. Regression modeling will be used to explore risk factors associated with critical illness (primary outcome), in-hospital mortality, resource utilization, length of hospital stay, and change in neurocognitive status from baseline (secondary outcomes). These analyses will include adjustments for clustering (facility-level, region-level), time-varying variables, and time-invariant variables. Variables will be chosen for evaluation in multivariable models based on their empirical significance in the literature (age, sex, severity of illness, HIV status, anemia, malnutrition) and their performance in univariable models.

Secondary Analyses

Owing to the international and collaborative nature inherent to this study, investigators participating in this study were able to submit proposals for secondary analysis. Proposals for secondary analysis were requested from participating site investigators to query the data generated by Global PARITY to address important questions and gaps not addressed by primary and secondary outcomes of the study. The proposals were reviewed by the Scientific Committee of the Global Health Subgroup; and, a total of 15 proposals were accepted. The list of approved secondary analyses are listed in **Table 2**.

DISCUSSION

Global PARITY will address the current gap in knowledge regarding the burden of pediatric acute critical illness and hospital resource utilization in RLS. In contrast to previous point prevalence studies estimating the prevalence of specific pediatric critical illnesses (e.g., ARDS, sepsis), Global PARITY aims to measure the burden of all pediatric acute critical illness. Additionally, by expanding the definition of critical illness to include PICU admission, intensive care-level resource utilization, and/or early hospital mortality, the Global PARITY definition is more inclusive and likely to capture critical illness managed in hospitals without formal intensive care units. To our knowledge, this is the first global pediatric point prevalence study to include settings without formal intensive care services and aimed at measuring the prevalence of pediatric critical illness as one entity instead of separate, individual diagnoses.

There are some anticipated limitations to our study. Our study shares limitations common to all point prevalence studies, including inability to account for prehospital mortality or resource utilization. This may result in an underestimation of disease prevalence and resource requirements, especially in those that have a fulminant course or in patients who lack quick access to a hospital setting. Likewise, while the Global PARITY definition of acute critical illness is more inclusive than prior global pediatric point prevalence studies, it has not been previously studied or validated. It is possible that this definition may over or underestimate the true burden of critical illness. However, similar definitions have been used in other

TABLE 2 | Global parity secondary analyses.

Lead investigators	Location	Topic or Theme
1. Asya Agulnik	Global	Burden of critical illness in cancer compared to other patients
2. Enkhtur Sh, Solongo.O, Dulamragchaa.Ch	Mongolia	Epidemiology and outcomes for pediatric acute respiratory distress, sepsis and sepsis-like diseases
3. Shubhada Hooli, Christian Umuhoza	Global	Prediction modeling and scoring systems for mortality in critical illlness
4. Kandamaran Krishnamurthy, Seetharaman Hariharan	Caribbean	Ways to improve education with ethical dilemmas especially when futility reached
5. Onah Stanley et al.	Nigeria	Metabolic derangements and pathogen specific diseases
6.Sofia Esposto et al.	Global	Time to antibiotics in pneumonia
7. Fiona Muttalib	Global	Association between resource availability at the sites and resource utilization/outcomes
8. Teresa Kortz	Global	Predictive success of existing clinical scores developed for RMICs at identifying children at risk of death
9. John Appiah, Adrian Holloway	Global	Blood transfusion delivery in sepsis and influence on patient outcomes
10. Ariet Figueroa et al.	Global	Early measurement of Age adjusted Shock Index to predict outcomes in non-trauma pediatric patients
11. Madiha Raees, Ericka Fink	Global	Epidemiology, resource use, and outcomes of children with neurocritical illness
12. Sofia Esposto et al.	Global	Characteristics of patients and the factors that determine the onset of empiric antibiotic therapy in sepsis
13. Sebastián González-Dambrauskas et al.	Latin America Caribbean	Outcomes and resources between two geographical different locations
14. Tigist Bacha Heye	Global	Presentation, Epidemiology, and Outcomes in Sepsis
15. Kenneth Remy, Tex Kissoon	Global	PP of sepsis, the presence of adequate antimicrobials, factors leading toward increased sepsis burden, and understand comparative mortality associated with certain available supportive therapies in each LMIC for patients with sepsis.

multicenter studies (19, 21) in RLS, and we expect to capture the majority of critical illness and associated hospital resource utilization in these patients. Further, while we tried our best to recruit centers from a wide range of countries and regions, we know that there can be disparities within countries based on region, socioeconomic status and type of healthcare facility (such as public vs. private). Thus, our study is still susceptible to selection bias and participating centers may not fully represent the epidemiology of pediatric acute critical illness or resource utilization patterns in a given country or region. Additionally, while we broadened eligible site criteria to include hospitals with or without a formal intensive care unit, the current site requirements (English language, resources, internet connectivity, available Principal Investigator) may still be too burdensome for some sites in RLS to participate. As a result, our study may underestimate the true impact of pediatric acute critical illness, as non-participating sites are likely more resource-limited than those able to meet study criteria. To address this limitation, we are applying for pilot funds to help defer study-related costs at participating sites. We also plan to further explore the reasons site non-participation in future studies. Regardless of these limitations, the results of our study will be the starting point for a generation of urgently need new research and interventional studies.

Global PARITY represents a unique opportunity to engage pediatric clinicians across the world. Only with a large, concerted effort can we, as a global pediatric community, start to understand the spectrum of acute critical illness and its association with childhood morbidity and mortality across resource-variable settings. The results of Global PARITY will inform a prospective, inclusive, global research agenda that includes children around the world, regardless of local resource availability. The data from this study will challenge the status quo and move us toward achieving the long-term goal to develop a body of evidence to support basic, universal, cost-effective critical care interventions appropriate for all settings, especially those with resource limitations. The implementation of such interventions could then be used for targeted capacity-building across resource-limited settings and has the potential to significantly reduce childhood morbidity and mortality due to acute critical illness globally.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors participated in the development, writing, and editing of the manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Pediatric Critical Care in Resource Limited Settings—Lessening the Gap Through Ongoing Collaboration, Advancement in Research and Technological Innovations

Ashley Bjorklund[1,2*†], *Tina Slusher*[1,2†], *Louise Tina Day*[3], *Mariya Mukhtar Yola*[4], *Clark Sleeth*[5], *Andrew Kiragu*[1,2,6], *Arianna Shirk*[7], *Kristina Krohn*[2,8] *and Robert Opoka*[9]

[1] *Department of Pediatrics, Hennepin Healthcare, Minneapolis, MN, United States,* [2] *Global Pediatric Program, Division of Pediatric Critical Care, Department of Pediatrics, University of Minnesota, Minneapolis, MN, United States,* [3] *Maternal and Newborn Health Group, Department of Infectious Disease Epidemiology, London School Hygiene and Tropical Medicine, London, United Kingdom,* [4] *Department of Pediatrics, National Hospital Abuja, Abuja, Nigeria,* [5] *Department of Pediatrics, Tenwek Hospital, Bomet, Kenya,* [6] *Childrens Hospital of Minnesota, Minneapolis, MN, United States,* [7] *Department of Pediatrics, Africa Inland Church Kijabe Hospital, Kijabe, Kenya,* [8] *Department of Internal Medicine, University of Minnesota, Minneapolis, MN, United States,* [9] *Department of Pediatrics, Makerere University, Kampala, Uganda*

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Yves Ouellette, Mayo Clinic, United States

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***Correspondence:**
Ashley Bjorklund
bals0064@umn.edu

† These authors have contributed equally to this work and share first authorship

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Pediatric critical care has continued to advance since our last article, *"Pediatric Critical Care in Resource-Limited Settings—Overview and Lessons Learned"* was written just 3 years ago. In that article, we reviewed the history, current state, and gaps in level of care between low- and middle-income countries (LMICs) and high-income countries (HICs). In this article, we have highlighted recent advancements in pediatric critical care in LMICs in the areas of research, training and education, and technology. We acknowledge how the COVID-19 pandemic has contributed to increasing the speed of some developments. We discuss the advancements, some lessons learned, as well as the ongoing gaps that need to be addressed in the coming decade. Continued understanding of the importance of equitable sustainable partnerships in the bidirectional exchange of knowledge and collaboration in all advancement efforts (research, technology, etc.) remains essential to guide all of us to new frontiers in pediatric critical care.

Keywords: pediatric critical care, low and middle income countries, telemedicine, simulation, device innovation, virtual platforms, medical education, global health

INTRODUCTION

Three years have passed since our article *"Pediatric Critical Care in Resource-Limited Settings—Overview and Lessons Learned"* was published (1). That article reviewed the history of pediatric critical care (PCC), discussed recent advances in PCC, as well as highlighting the expanding gap in the level of care available in pediatric intensive care units (PICUs) in high income countries (HICs) vs. low-and-middle income countries (LMICs). An overview of PCC in LMICs was discussed in regard to the current state of *staff* (properly trained and compensated medical staff), *stuff* (appropriate medical equipment), *space* (clean environment to treat patients), and *systems* (infrastructure and logistical organization to provide the services) with an emphasis on the lessons that have been learned and opportunities that remain in advancing PCC in resource-limited settings

(1). Since its' publication, the field of PCC medicine has continued to advance rapidly through the use of quality improvement initiatives, advanced training programs with an emphasis on readiness and simulation, clinical research, and ongoing advanced technology development (i.e., non-invasive monitoring devices, extracorporeal support) and big data.

In this current update article, we discuss selected areas in which PCC has continued to advance in LMICs with aim of highlighting important advancements that have been made while emphasizing areas amendable to future growth. To focus the discussion and build on the prior review, we will highlight three areas of significant developments–research, training, and technology. The discussion will highlight lessons learned, as well as on the horizon innovations and opportunities for further engagement. Underscoring all these advances, and the momentum to propel them forward, has been a renewed understanding of the importance of equitable and sustainable partnerships in place of colonialism and paternalistic endeavors. It is important to point out that the authors' experiences are mixed (some based in primarily LMICs, others based primarily in HICs) thus this review is written from the mixed perspective of researchers/clinicians who have worked in LMIC-HIC partnerships over the past several decades.

Additionally, while the COVID-19 pandemic has created many challenges in healthcare, the alternative routes needed to accomplish research, training, and provision of care to larger populations in resource constricted situations has brought with it new innovations that have the potential to have a sustainable positive impact on PCC in these settings. In some ways the world became smaller with rapid transition to virtual meetings and trainings, creating a platform for rapid dissemination of knowledge. The possibility of HICs having a shortage of oxygen and lifesaving equipment, such as ventilators, sparked an interest in and support for bioengineers and medical device developers in HICs to focus energy inventing alternative low-cost options for costly technology. This is not mentioned to lessen the distressing impact of the pandemic, but rather to emphasize that with focused, motivated, supported effort, seemingly impossible hurdles can be overcome, and disparities lessened.

Abbreviations: ACES, academic competencies series; AAP, American academy of pediatrics; bCPAP, bubble continuous positive airway pressure; CPAP, continuous positive airway pressure; EMR, electronic medical records; TAT, emergency triage, assessment, and treatment; HBB, helping babies breathe; FDA, federal drug administration; FOAMed, free open access medical education; HICs, high income countries; LMICs, low- and middle-income countries; NHA, national hospital abuja; NIH, national institutes of health; NICST, networking for improving critical care systems and training; PALISI, pediatric acute lung injury and sepsis investigators; PCC, pediatric critical care; PICUs, pediatric intensive care units; PALS, pediatric acute life support; PAN, pediatric association of nigeria; PEARLS, pediatric educational adaptations for resource limited settings; PECC-K, pediatric emergency and critical care-kenya; SUGAR, simulation use away rotations; USAID, simulation use for global away rotations, united states agency for international development for international development; WHO, world health organization.

RESEARCH

Role of Research in Advancing PCC in LMICs

Clinical research has an essential role in the advancement of PCC. Understanding how our therapeutic choices impact clinical outcomes provides a framework for future study, guides therapies and informs protocol development. The importance of clinical research has been understood and supported financially by large institutions throughout HICs for decades, however the support for such research in LMICs has lagged. As noted in *Challenges and Priorities for Pediatric Critical Care Clinician-Researchers in Low and Middle Income Countries*, an article published in 2017 and written by authors from the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) research network (2), more data on both clinical care outcomes and treatment in LMICs is needed. Local research is essential in advancing critical care in LMICs, as outcomes from clinical research performed in HICs often do not translate directly to LMICs. The infrastructure, supplies and funding needed to conduct research in LMICs has often been prohibitive. In addition, the ethical concerns of research in vulnerable populations with variable availability of local institutional review boards has been another area requiring thoughtful discernment and attention to detail.

Despite these barriers, there have been considerable advances in research in LMICs over the last decade, notably an increase in: (1) Support for and engagement in research pertinent to PCC based therapies and outcomes specifically for children in LMICs; (2) Recognition of the importance of the research agenda being directed by LMIC clinician researchers; and (3) Support for research efforts directed by LMIC researchers in their own environment. These advances all have their unique but monumental impact on the expansion of pertinent research in these settings. It is beyond the scope of this article to review all the important LMIC led studies; however, we have chosen to discuss a few examples to highlight the advancing research agenda in LMICs and the variety of ways it impacts the delivery of PCC.

Clinical Research Advancement Impact

One notable example of the impact of research in guiding and advancing PCC in LMICs was the "FEAST" trial (3). This trial was conducted in Uganda, Kenya and Tanzania and enrolled over 3,000 children with severe infection and impaired perfusion (3). The researchers found increased mortality with the administration of fluid boluses in this pediatric population (3) in contrast to findings of smaller studies in pediatric patients with sepsis in HICs, which supported the use of rapid, aggressive fluid resuscitation—and were informing the surviving sepsis guidelines already being rapidly rolled out in many countries. While there is ongoing discussion regarding differences in the study population, methods, and reasons for differing outcomes, giving some pause to widespread adoption of a "fluid restrictive" protocol, the trial results clearly changed guidelines for fluid therapy in septic children in Africa where fluid use is now much more judicious. Moreover, these results influenced resuscitation and sepsis guidelines in HICs, including the widely accepted Pediatric Advanced Life Support (PALS) guidelines and other

protocols, which now encourage a more cautious approach to fluids in septic shock (4, 5).

Research in LMICs affirming the benefit of interventions recommended for children in HICs has also advanced PCC. As an example, while the use of intraosseous needles in acute pediatric resuscitation is widely accepted in HICs, it remains important to evaluate this practice in LMIC settings to ensure similar outcomes. A study by El-Nawawy et al., in Egypt (6), demonstrated statistically significant shorter time to vascular access, and decreased mortality in pediatric patients with sepsis with an intraosseous line vs. intravenous catheter. This in-country research helps to validate this practice and increase widespread acceptance in all settings.

Yet another area of advancement in clinical research in LMICs is the investigation of therapies employed in LMICs that may not be commonly used in HIC settings. Without clinical research on these therapies, the standard of practicing evidence-based medicine is difficult to achieve. One area now being studied, is the use of "bubble" continuous positive airway pressure (bCPAP) in children beyond the neonatal period. BCPAP is a low-cost respiratory support being utilized worldwide for neonates with respiratory distress with proven efficacy (7, 8). However, because older children in HIC have access to ventilator derived continuous positive airway pressure (CPAP) or mechanical ventilation, bCPAP is not used and not studied in HICs. In LMICs, as pediatric appropriate ventilators are often not available, bCPAP has been utilized to fill a gap. A variety of well-designed studies have recently looked at outcomes of children supported with bCPAP in LMICs (9–11). These studies have yielded variable results, from improved survival to increased complications. This highlights (1) the advancements seen in research in LMICs with a technology that has been used for many years now being evaluated for efficacy and (2) the need for additional robust clinical trials to assist in determining which patients would benefit from this support in this specific setting.

Finally, surfactant has long been established as a lifesaving therapy in neonatal respiratory distress syndrome, traditionally requiring intubation and mechanical ventilation. Over the past decade, clinician-researchers have explored innovative ways of delivering surfactant in the preterm infant. This research has allowed for expanded use of surfactant with results demonstrating the efficacy of two alternative methods of delivery, using a nasogastric tube or laryngeal mask airway, when intubation and/or ventilation is not feasible (12, 13). For a costly therapy like surfactant, knowing that the alternative, feasible methods of delivery are efficacious is essential to good stewardship of resources in all settings.

Networking and Research Agenda

Over the past decade, increased networking and partnership between researchers in LMICs and HICs has had a positive impact on PCC research worldwide. Both strive to improve critical care through research for the most disadvantaged patients. The PALISI network is a United States based group known for their large and impactful PCC studies with over 150 high impact publications and 30 active research studies (14). PALISI has expanded to include a Global Health Subgroup designed to focus on the global burden of pediatric critical illness and support investigators dedicated to advancing the care of critically ill children throughout the world. Investigators from around the globe who seek to collaborate with communities caring for critically ill children limited by geography, resources, or social constraints, work together on projects with a research agenda guided by partner institutions in LMICs. Their multi-county survey of PICUs provided the most comprehensive overview and understanding of the currently available resources and infrastructure for PCC across the globe (15). This study highlights how having a large network can more rapidly accomplish the goals needed to improve care and advance research.

Another successful example of partnership and collaboration advancing critical care research in LMICs is the Networking for Improving Critical Care Systems and Training (NICST) in Sri Lanka. NICST has trained over 4,500 nurses and doctors in acute and critical care skills. Beyond the clinical training this "collaborative of clinicians, researchers, and educational experts linked through continuous audit is designed to improve patient outcomes" (16). NICST research focuses on improving quality and access of acute and critical care services by combining "clinical medicine with health informatics, epidemiological and social science, along with health systems and improvement science" (17, 18).

Other large collaborations which have had substantial impact include the Essential Emergency and Critical Care (EECC) Collaborators and the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS). The EECC is a group of critical care providers from around the globe that worked together to provide recommendations for essential emergency and critical care requirements for care across all ages in all locations as stated in their consensus statement article published in BMJ global health in 2021 (19). The WFPICCS is a leading organization advocating for care of critically ill children across the globe that combines national societies into an international network. In addition to the examples listed above some other prominent programs include societies of critical care in India, Cuba, Argentina, Iran, Egypt, and Brazil.

Research Training and Financial Support

The importance of training and funding on research advancement cannot be overstated—with the right resources, LMIC researchers are building sustainable research capacity to progress the field of PCC medicine. Training programs for researchers in LMICs have increased over the past decade. The Academic Competencies Series (ACES) course is one example of training that is now available. This program enrolls early-career researchers registered at universities in Ethiopia, Zimbabwe, Malawi, and South Africa in a year-long training course that equips the them with the necessary skills to become productive researchers (20). Similarly, the National Institutes of Health (NIH) and the Gates Foundation have provided training specifically geared to build capacity of researchers in LMICs.

Funding has historically been a barrier for researchers in LMICs. There has been some increase in funding mechanisms and grant opportunities for studies designed to PCC in LMICs

and financially support the researchers and support staff needed to conduct these studies. Some examples include the grants offered through the Thrasher Research Fund, the Doris Duke Research Fellowship, Fogarty Funding (NIH), Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries (NIH), U.S. Agency for International Development (USAID), and Gates Foundation.

Research: Lessons Learned and Where We Go From Here

While we highlight the advancements in research, many lessons have been learned along the way. "Well intended" research projects have "gone wrong" by either (1) not ensuring the research agenda is on point with the research needed, or (2) pulling important scarce resources for research (nurses, supplies administrative time, equipment, etc.) that negatively impact overall function of the system. The balance of these priorities is essential to consider when planning a research agenda.

Our shared experience has demonstrated that research partnerships work best when built on a solid ethical framework, coupled with "mutual respect and benefit, trust, good communication, and clear partner roles and expectations" as described in *Successful Global Research Partnerships: What makes them work?* (21) The goals of any research conducted must first and foremost provide benefit to the population being studied and be driven predominately by the stated needs of the LMIC partner. Additionally, representation in the whole research cycle must be equitable including the opportunity for the LMIC partners to be principal investigators, first and senior authors, and present their work in national and international meetings. Depending on each researcher's starting point, whether from a LMIC or HIC, moving into key leadership positions in research requires training and time. Mentorship into these leadership roles should be the goal and outcome as soon as possible in these relationships, with the recognition that mentorship must be bidirectional.

Understanding challenges to all aspects of conducting research—such as implementing study protocols, consent, development of standard operating procedures, budgets, data collection and entry, and database maintenance is essential. This is key for all research, but especially to modify HIC practices to fit in resource constrained settings. Additionally, grant office support should include the researcher and the research, as well as administrative staff to avoid overstretching already limited resources. Partnerships ensure context-specific ethical issues are addressed for all settings.

Other vital aspects include engaging the regulatory bodies of all countries involved in the research. Some studies have demonstrated or highlighted challenges that can arise when ethical issues related to research in a vulnerable population and other local regulations are not adequately addressed prior to the study starting (22–24). Multinational studies may have different regulations for each country which can create challenges in satisfying all involved agencies [i.e., investigational review boards, clinical trials.gov, agencies regulating drugs and devices such as the Federal Drug Administration (FDA) or the equivalent LMIC agency; rules and regulations regarding importation of supplies and equipment necessary for the research].

As modeled by successful LMIC researchers such as Professor Philippa Musoke *(Makerere University, Kampala, Uganda), Executive Director for the Makerere University-Johns Hopkins University Research Collaboration (MU-JHU), Kampala and* Associate Professor Nadia Sam-Agudu *(University of Maryland School of Medicine, Baltimore, MD, USA)*, *Senior Technical Advisor, Pediatric HIV, Institute of Human Virology, and International Senior Technical Advisor, Pediatric and Adolescent HIV, Institute of Human Virology Nigeria* both of whose publications span a wide range of research topics including but not limited to HIV and education (21, 25–28), providing equitable instruction/education for all team members in the details necessary to conduct successful and ethical research is essential. This must include fostering and role-modeling open regular communication with the entire team and following good research practice protocols including data integrity evaluation and study protocol adherence. Unforeseen circumstances may arise (power outages, supply shortage, broken equipment) and it is important to quickly recognize when a study protocol needs to be modified or additional training needs to be provided to ensure accurate data collection and results. These two exemplary researchers are among many others who have demonstrated lifelong achievement in research that should be looked to as a model for junior researchers.

Despite the numerous granting agencies willingness to fund LMIC-led projects, it remains difficult to find grants that are appropriate for funding some well-designed and pertinent studies. Developing resources and experts to guide the process of finding funding for important projects, writing grants that score well, and executing grants remain a challenge for both HIC and LMIC researchers.

TRAINING

Role of Training in Advancing PCC in LMICs

Specialty specific training is essential for provision of quality PCC. While PCC physician training is important, multidisciplinary training is even more critical. Well-trained nurses form the backbone of every PICU in the world. Training can be delivered in multiple different ways but having training include nurses and providers together increases the learning for all, as trainees learn from each other's different perspectives. Education must be guided by the learner, with some learning best through case-based presentations, others with hands on and simulated experiences and still others learning best through a more formal curriculum which encompasses the use of lectures and independent reading (books, online, etc.). All these methods can be effective if they meet the learner where they are and build sequentially on their knowledge, experience, and current practices.

Training Standards and Guidelines

The recently published *Standards for improving the quality of care for children and young adolescents in health facilities* from

the World Health Organization (WHO) creates a framework that PCC training programs can utilize to determine their educational goals. Training relevant to pediatric intensive care is captured by 24 quality measures (**Table 1**) (29), relating to eight quality standards and specify that the frequency of in-service refresher training is ideally at least once every 12 months. The breadth of recommended training covers the wide range of skills, knowledge and attitudes needed for multidisciplinary PCC health professionals to be competent, motivated, and empathetic (Standard 7). *Evidence-based practices (Standard 1) training relevant to PCC health workers is specified across a continuum of critical care: triage, assessment, emergency treatment, monitoring, supportive care, infection prevention, unnecessary interventions. Illness management training for conditions that may require pediatric intensive care are specified: Injuries, neglect, violence, surgical conditions and the common LMIC co-morbidity of malnutrition.* These standards provide an outline of goals and objectives for comprehensive PCC training.

Simulation Based Medical Training

Healthcare simulation is an area of fast growth in HICs with much advancement in fidelity over the course of the last decade. Simulation based medical education has allowed all levels of learners to acquire skills needed to perform high-risk procedures and has improved teamwork and comfort in high-risk, low volume clinical situations. Simulation technology and educational strategies are being increasingly adapted to low-resource settings (30). Simulation can be "hands on" (31), virtual reality (32, 33), or screen based (34). Organizations producing mannequins "not-for-profit" have helped advance "hands-on" simulation in LMICs in the last 10 years, as have trainings designed specifically for PCC in low resources settings (35).

The mannequin-based simulation training course, Helping Babies Breathe (HBB), which utilizes a low-fidelity, low-cost mannequin and equipment is a prime example of a high yield training which has assisted in training multidisciplinary healthcare workers in neonatal resuscitation techniques and priorities for LMICs. This training reinforces important concepts and has the essential fidelity. Utilized supplies allow for participants to demonstrate bag-valve-mask use with appropriate mouth/nose seal, feel a pulse on the umbilical cord, or hear the apical heart beat—the essential skills that the course wants to teach (36). Taking this one step further, this low-cost training equipment (including a bag-mask and penguin suction) is high-quality, re-usable equipment designed for actual patient care.

Standardized emergency and pediatric critical care curricula that can be adapted for use in LMIC settings provide comprehensive training. These trainings are often designed for the "non-intensivist" and are readily deployable and consistent. Successful examples include the Pediatric Basic Assessment and Support Intensive Care (BASIC) course, Pediatric Fundamentals of Critical Care Study (PFCCS) and Emergency Triage, Assessment, and Treatment plus (ETAT) course. BASICS was created by pediatric intensive care leaders from WFPICCS and has courses geared toward nurses and non-intensive care physicians. BASICS has shown success in building local critical care capacity through a "train the trainer" model in high, middle and low income countries. PFCCS was developed by pediatric critical care leaders from the Society of Critical Care Medicine and can be administered through traditional live, in person course or online. The course has been successfully run internationally by 30 institutions; however, the course must be administered by trained, certified instructors (rather than train the trainer) and the cost can be prohibitive (37). ETAT is a comprehensive training for healthcare workers practicing pediatric emergency care in low resource settings that is available for free online or with in person courses (offering hands-on or screen based simulation options). Recently the "Pediatric ETAT guidelines" have been updated (38). The materials are based on the WHO pediatric care guidelines and the training has been successfully implemented in many eastern African countries and is expanding (39).

Finally, other low-tech examples of teaching procedural skills, in addition to facilitating low-cost adaptations for commonly needed pediatric procedures, is provided for free, on the open-access web-based *Simulation Use for Global Away Rotations* (SUGAR) platform. Short videos are available under the *Procedural Education for Adaptation to Resource-Limited Settings* (PEARLS) tab, which review procedures and how they can be practiced for use in resource limited settings (40). These procedures and scenarios can then be practiced with mannequins and low-cost "task trainers".

Improved internet and smart phone availability in many LMIC settings, that was unimaginable a decade ago, has made it possible to utilize relevant open-access distance learning training courses already developed for the PCC setting. The COVID-19 pandemic has illustrated the importance of the ability to rapidly update materials for emerging situations. An example of this being the rapidly developed, and quickly distributed, WHO Severe Acute Respiratory Infection Training materials (41, 42). Mobile phones apps of contextualized guidelines increase access to information when needed for decision support (43, 44). Innovative refresher low-dose high frequency training using mobile virtual reality simulation has been successfully piloted in LMIC for neonatal resuscitation including the recently released Essential Newborn Care Now (45, 46).

Specialty Training Programs

Formal specialty training programs such as PCC fellowships for physicians and dedicated pathways to train nurses and other healthcare providers have been limited in resource constrained settings. In a recent survey, by the PALISI Global Health Subgroup, Muttalib et al., reported that less than half of the 238 hospitals representing 60 countries had subspecialty acute care training (PCC or pediatric emergency medicine) (15). Pediatric acute care fellowship training designed for physicians in LMICs are increasing in number, though not nearly fast enough to meet the needs of populations they serve.

There are different models that can be utilized for establishing subspecialty training in LMIC. South Africa, Egypt and India, have developed programs in an LMIC context, therefore modeling new programs based on their model is one way

TABLE 1 | Pediatric critical care relevant training measures in the "Standards for improving the quality of care for children and young adolescents in health facilities" document (24).

Standard	WHO SSNB standard	Quality statement		Quality measure	Type
1	Evidence-based practices and management of illness	1.1	All children are triaged and promptly assessed for emergency and priority signs to determine whether they require resuscitation and receive appropriate care according to WHO guidelines.	Proportion of all professional health staff who care for children in a health facilitywho received training or refresher courses in emergency triage, assessment and treatment or pediatric emergency care during the past 12 months.	Process/ output
		1.7	All children at risk for acute malnutrition and anemia are correctly assessed and classified and receive appropriate care according to WHO guidelines.	The professional staff at the health facility who care for children receive training and regular refresher sessions in assessment, identification, appropriate management and follow-up of children with acute malnutrition at least once every 12 months	Input
		1.11	All children are screened for evidence of maltreatment, including neglect and violence, and receive appropriate care.	The health facility staff receive training and refresher sessions on screening, preventing, protecting and managing children with evidence of maltreatment, including neglect and violence	Input
		1.12	All children with surgical conditions are screened for surgical emergencies and injuries and receive appropriate surgical care.	Health professionals receive in-service training and refresher sessions in appropriate care of child injuries, trauma and other common pediatric surgical conditions at least once every 12 months	Input
		1.13	All sick children, especially those who are most seriously ill, are adequately monitored, reassessed periodically and receive supportive care according to WHO guidelines.	Health professionals receive in-service training and regular refresher sessions on patient monitoring and supportive care at least once every 12 months	Input
		1.14	All children receive care with standard precautions to prevent health care-associated infections.	Health professionals who care for children receive training in standard infection prevention and control at least once every 12 months	Input
		1.15	All children are protected from unnecessary or harmful practices during their care	Health care staff in the facility receive in-service training and regular refresher sessions on harmful practices and unnecessary interventions at least once every 12 months	Input
2	Actionable Health Information Systems	2.1	Every child has a complete, accurate, standardized, up-to-date medical record, which is accessible throughout their care, on discharge and on follow-up.	The health facility staff receive training and refresher sessions at least once every 12 months on the use of standardized medical records, including birth and death registration, and classification of conditions and diseases in accordance with the ICD	Input
		2.3	Every health facility has a mechanism for collecting, analyzing and providing feedback on the services provided and the perception of children and their families of the care received.	Health facility staff (clinical and non-clinical) receive training or orientation in customer service and provision of child- and family-centered care at least once every 12 months.	Input
4	Effective Communication and Meaningful participation	4.1	All children and their carers are given information about the child's illness and care effectively, so that they understand and cope with the condition and the necessary treatment	Health care staff receive training and regular mentoring or refresher training at least every 12 months in fully explaining a condition to children and their carers, giving "bad news" and supporting children and parents in coping with the information given.	Input
		4.1	All children and their carers are given information about the child's illness and care effectively, so that they understand and cope with the condition and the necessary treatment	Proportion of health care staff, by cadre and social professionals who received proper continuous training in communication and counseling	Process/ output
		4.3	All children and their carers are enabled to participate actively in the child's care, in decision-making, in exercising the right to informed consent and in making choices, in accordance with their evolving capacity.	Staff who care for children receive orientation or training in patient-centered care and legal and medical ethical principles of autonomy, informed consent, confidentiality and privacy at least once every 12 months	Input
5	Respect, Protection and fulfillment of children's rights	5.1	All children have the right to access health care services, with no discrimination of any kind	The health facility staff receive training and periodic refresher courses on nondiscrimination practices, promoting equity and cultural competence	Input
		5.3	All children and their carers are treated with respect and dignity, and their right to privacy and confidentiality is respected.	Health facility staff are trained in providing care with respect for dignity and for maintaining confidentiality during the care of children and have received refresher training at least once in the past 12 months	Input

(Continued)

TABLE 1 | Continued

Standard	WHO SSNB standard	Quality statement		Quality measure	Type
		5.3	All children and their carers are treated with respect and dignity, and their right to privacy and confidentiality is respected.	Proportion of health facility health care providers who have attended training or received orientation in respecting and protecting the dignity of children and their carers.	Process/ output
		5.4	All children are protected from any violation of their human rights, physical or mental violence, injury, abuse, neglect or any other form of maltreatment	The health facility staff receive training and orientation in identifying, assessing and providing care and support for victims of any form of maltreatment and on child protection procedures	Input
6	Educational, emotional and psychological support.	6.1	All children are allowed to be with their carers, and the role of carers is recognized and supported at all times during care, including rooming-in during the child's hospitalization	The health facility staff receive training and regular mentoring or refresher training in children's rights, including the right not be separated from their parents, and also in parents' rights and responsibilities	Input
		6.3	Every child is assessed routinely for pain or symptoms of distress and receives appropriate management according to WHO guidelines.	The health staff receive training and regular refresher courses in assessing, preventing and controlling children's pain at least once every 12 months	Process/ output
		6.3	Every child is assessed routinely for pain or symptoms of distress and receives appropriate management according to WHO guidelines.	Proportion of staff who have received training or refresher training in children's pain management and palliative care within the past 12 months	Process/ output
7	Competent, motivated, empathetic, multidisciplinary human resources	7.1	All children and their families have access at all times to sufficient health professionals and support staff for routine care and management of childhood illnesses.	Proportion of nurses who care for children admitted to the facility who have had pediatric training or in-service medical education in child care	Process/ output
		7.2	Health professionals and support staff have the appropriate skills to fulfill the health, psychological, developmental, communication and cultural needs of children.	Health professionals and staff who care for children in the health facility receive in-service training and supportive supervision with regard to the legal entitlements and rights of children in relation to health care.	Input
		7.2	Health professionals and support staff have the appropriate skills to fulfill the health, psychological, developmental, communication and cultural needs of children.	Proportion of health professionals who care for children who received in-service training and/or refresher sessions within the past 12 months	Process/ output
		7.3	Every health facility has managerial leadership that collectively develops, implements and monitors appropriate policies and legal entitlements that foster an environment for continuous quality improvement	Proportion of staff members who gave positive feedback about internal policies and activities for continuous quality improvement, including on-the-job training and personal mentoring	Outcome
8	Essential physical resources for SSNB available	8.2	Child-friendly water, sanitation, hand hygiene and waste disposal facilities are easily accessible, functional, reliable, safe and sufficient to meet the needs of children, their carers and staff.	Proportion of health facility health professionals and support staff who received training or mentoring in sanitation, hand hygiene and infection prevention and control in the past 6 months.	Process/ output
		8.4	Adequate stocks of child-friendly medicines and medical supplies are available for the routine care and management of acute and chronic childhood illnesses and conditions	Proportion of health professionals who provide child health services who have received training in appropriate child medication.	Process/ output

forward. For example, Professor Andrew Argent and his team runs the "African Pediatric Fellowship Program" (47) out of the University of Cape Town with training based at the Red Cross War Memorial Children's Hospital. The fellowship offers different training options including a 2-year master's program or a 1 year post graduate diploma—both aimed at allowing practicing physicians to develop skills specific to management and advancement of care for critically ill children. A program in India similarly offers a 1 or 2 year clinically focused training option, in addition to more formal 3 year training (48). Additionally, there are increasing established nurse led academic initiatives with post graduate nursing diplomas in child nursing, critical care nursing, and a Master of Nursing in child nursing—again all aimed at decreasing under 5 mortality through improved critical care for children (49). They have established programs from this model in Kenya, Malawi, Nigeria, and Zambia as well. Additionally, in many LMICs, critical care is provided by anesthesiologists. Opportunities for combined pediatric critical care and anesthesiology training should be considered.

Finally, another notable example of a training model is the Pediatric Emergency and Critical Care-Kenya (PECC-Kenya) Fellowship training program. This two-year fellowship in Pediatric Emergency and Critical Care is customized for

pediatricians from Sub-Saharan Africa, with training occurring at University of Nairobi/Kenyatta National Hospital and at A.I.C. Kijabe Hospital in rural Kenya. This fellowship uses the model of a collaborative effort between established national universities and a partner institution in the USA, bringing together national and international faculty to train the fellows. Without fellowship training programs such as this, physicians pursuing formal specialty training in PCC would often travel to HICs to train. Removing physicians for training out of country, burdens countries already struggling with critically low numbers of healthcare providers and even lower numbers of critical care providers—a concept referred to as "brain-drain." Collaborative training programs that are less formal than PECC-Kenya, such as the Haitian Pediatric Critical Care Collaborative, with training occurring at Saint Damien's Pediatric Hospital on the outskirts of Port-au-Prince, Haiti, utilize a similar model of national and international faculty training local physicians to specialize in PCC through a combination of virtual and local training. The establishment of formalized fellowship programs, such as local programs described in Egypt, South Africa, and India as well as collaborative programs such as PECC-Kenya are advancing training in the field of pediatric critical care in LMICs in a sustainable manner.

As we previously highlighted in the last article, without trained PCC nurses it's impossible to have PCC. Much of that training has been on-the-job training but there are increasing efforts to provide more formalized training for nurses and other allied health professional in PCC. One of the stated objectives of WFPICCS is to "promote multidisciplinary collaboration between Pediatric Intensive and Critical Care specialists by supporting education and professional developments of all health professional involved in Pediatric Intensive (and Critical) Care" which they accomplish through lectures focused on nursing (38). One example of a short course specifically focused on nursing sick children is a 16 week course being offered through the University of Cape Town in South Africa (50). The school of Post Basic Nursing at the University Of Abuja Teaching Hospital also offers a 1 year program on Intensive Care Nursing. Longer more in depth courses are needed but these offerings are a start. Encouraging educational opportunities which include not only physicians but also nurses, and allied health professionals, is essential if we are to continue to advance care globally.

Training: Lessons Learned and Where We Go From Here

While there are a variety of available PCC trainings, the importance of contextualization is essential for the training to be effective (51). "Off the shelf" short courses developed in HIC contexts will result in little sustained behavior change if local adaptation is overlooked (52). When collaborations with HICs are established for LMIC training, a participatory needs assessment is an effective way to invite mutual identification of learning needs, epidemiology, work environments, equipment, infrastructure and team composition (53). Inter-professional team-based learning, is most likely to overcome the systems barriers to transfer into the workplace (52). Partnering for curricula adaptation will enable training faculty and maximize sustainability (52). An excellent example of a partnership encompassing international HIC guidelines with local adaptations is the ETAT course which has resulted in improved outcomes in LMICs (54). There remains the challenge of measuring the impact of these trainings in regard to sustained changes in care patterns and improved outcomes in LMIC (52, 55).

Typically, PCCs short courses focus more on skills/doing (psychomotor) and knowledge/thinking (cognitive) domains of learning with less emphasis on the affective domain of attitudes/values. Including even short learning activities that connect to learners' values/attitudes can be a powerful learning experience e.g., "Start with a story" at the opening of the neonatal Helping Babies Breathe course (35). Normalizing these activities is also important to improve the support for health providers with emotional fatigue and burnout before they leave the PCC workforce.

Reviewing collaborative training partnerships with a decolonizing lens is vital. Long-term relationships, cultural humility and shared planning with genuine listening to expert PCC colleagues in LMIC is only the beginning of that journey (56). Barriers to international travel for PCC training opportunities disproportionately affected health care providers from LMIC including funding and visa regulations (57). During the COVID-19 pandemic, inequitable vaccine availability, as well as nation-specific travel regulations, have further hampered calls for bidirectional training opportunities and affected training collaboration exactly at the time health workers in both HIC and LMIC settings need it the most.

VIRTUAL TECHNOLOGY, COLLABORATION AND RESOURCE SHARING

Role of Virtual Technology, Collaboration, and Resource Sharing in Advancing PCC in LMICs

It has long been realized that sharing information and knowledge is essential to advancement of PCC. Over the last decade, the advancement in technology has made the ability to collaborate and share resources much easier. Worldwide there has been significant improvement in internet access and platforms have been created to easily interact across the globe.

Telemedicine

A major challenge in the provision of critical services has been the lack of adequate numbers of intensive care physicians. This is particularly concerning in LMICs. In HIC's the absence of intensive care coverage in remote areas where an intensivist is absent has been managed in part through the employment of telemedicine and other virtual platforms (58–60). Telemedicine is essentially the delivery of care to critically ill patients by critical care providers located remotely to fill gaps in healthcare services (58–61). This important critical care innovation offers an

opportunity for the provision of critical care services even in the most remote parts of our world.

ICU telemedicine providers employ the use of electronic medical records (EMRs) in combination with audiovisual tools to assist caregivers at the bedside with patient care, clinical monitoring, and the development and implementation of care plans (60). Since its rollout, the growth of telemedicine as a modality of care delivery has evolved and encompasses care across multiple electronic platforms and clinical settings (59, 60). A variety of models of telemedicine have been in use from a centralized, single remote center providing care to multiple other locations (59, 60), to a remotely located intensivist virtually reviewing individual patients using an audio-visual connection either via computer or mobile device (59, 60).

Cellular and satellite technology has been used to assist in the provision of critical care in disaster settings (59). An example of the successful use of Tele-Pediatric Intensive care came from its' use in war torn Syria where a volunteer core of physicians provided consultation to medical directors in field hospitals regarding multiple management decisions such as mechanical ventilation settings, vasoactive medications, resuscitation, and intravenous fluid management (62). When high-definition video failed due to limited internet connectivity they quickly resorted to text, voice, and photo-based interactions such Facebook™ messenger and Skype™ to facilitate communication (63).

Unfortunately, traditional telemedicine services can be cost prohibitive for remote needs in both HIC and LMICs, which has presented widespread implementation (59–61, 64). Low-cost innovations for telemedicine are on the horizon. One example, utilized in Kenya, is a mobile application (app) called "Daktari Popote" (Doctor Anywhere)- which gives users access to medical specialists for a consultation. The app allows users to upload photos and x-rays, as well as receive prescriptions. Development of these app based virtual care platforms enable patients increased access to care (65). Similar applications and telemedicine consultative services have been developed and utilized by Medicin Sans Frontieres and Enlace Hispanico Americano de Salud (Hispano American Health Link) (EHAS), as well as other international collaborative groups. Best practices for use of these applications are still being developed (66, 67).

The covid pandemic has revolutionized telemedicine on a global scale. It has also been an opportunity for the promotion and validation of telemedicine technologies (61, 68). By necessity, clinical care had to adapt to the pandemic-related shutdowns of clinics and limitations of access to hospital services. Globally, healthcare systems have had to adapt to this new paradigm. The employment of platforms such as Zoom™, Cisco WebEx™, Microsoft Teams, Google Meet™, GoToMeeting™ and apps such as WhatsApp™ and FaceTime™ among others have enabled critical care professionals to fairly seamlessly share information and collaborate in patient care. Caveats remain, as these easy-to-use platforms are not designed specifically for sharing personal health information and they need to be equipped with a manner to protect patient information. There is password protected and Health Insurance Portability and Accountability Act (HIPAA) compliant versions that should be utilized as feasible and attention needs to be paid to where information is being broadcast or discussed (just as with in person care). Of course, having an appropriately trained PCC physician at the bedside is still the best practice care plan, however, the ability to reach areas with no access to such a resource is a huge advancement for PCC during times of resource constraint or in areas that have limited care provider availability.

Virtual Conferences

While virtual platforms for clinical care have advanced rapidly, the virtual education opportunities are even more expansive. Online learning opportunities have been expanding over the last decade, but with the pandemic even more virtual options have been created. The ability to participate in virtual conferences has meant that major impediments to clinicians from LMICs participating in international medical society meetings, such as the cost associated with travel abroad, the ability to leave heavy patient care responsibilities, and travel restrictions, have been eliminated. Time zone constraints can be overcome through creating recorded "on-demand" resources. Costs of virtual attendance, however, need to be adjusted to enable those in LMICs to attend.

One example of how virtual platforms can quickly impact knowledge dissemination occurred during the early days of the pandemic. One of the authors (AK) participated in a number of weekly Zoom calls set up by a tertiary care center in Kenya to share information with clinicians around the country about COVID. These Zoom sessions featured speakers from Kenya as well as other countries in Africa, China, the US, and Europe. They were attended by hundreds of clinicians across Kenya, from remote district hospitals to larger referral centers, and had a significant impact in preparing Kenyan clinicians for managing patients and protecting themselves from infection.

Similar collaborations between American Academy of Pediatrics (AAP) and The Pediatric Association of Nigeria (PAN) via the ECHO platform (a telemedicine/teleconferencing like technology) facilitated virtual learning to hundreds of healthcare workers on the topic of COVID-19 in children, with speakers and case presentations from Nigeria and various parts of the world (69). Additionally, the International COVID-19 PICU Collaborative, a voluntary collaboration was formed with hundreds of pediatric critical care medicine and infectious disease providers from around the world to share best practices and real time information across the globe. This group met via virtual platform on a weekly basis to rapidly share best practices and real-time information while sharing characteristics of the pediatric patients they were seeing in the early pandemic. The rapid formation of these global collaborations demonstrate how virtual platforms can bring educational resources rapidly together in real-time.

Online Learning—Sharing Knowledge and Resources

Over the past decade, opportunities to share PCC educational materials and global health educational materials online have increased dramatically, again with rapid advancement during the COVID-19 pandemic. Some schools have created entire online PICU curricula (70), while others have utilized online education to augment PICU residents' understanding of certain topics (e.g.,

mechanical ventilation) (71). Others created online global health educational resources designed to be widely shared and used in various settings. Courses ranged from pre-travel education (and simulation as discussed in training above) to prepare American residents for working abroad to free PICU critical care cases with open access, and online continuing medical education for critical care nurses (72–74). During the COVID-19 pandemic many medical education centers moved to online education for a myriad of topics, including video conferences (75), joint online training and projects between global health partners in more than one physical location (76).

An excellent example of an established online resource for sharing clinical education is OPENPediatrics (www.openpediatrics.org) which was developed by Boston Children's Hospital (77). This site offers access to peer-reviewed content, including accredited and non-accredited courses, expert lectures and demonstrations, interactive device simulators, protocols and medical calculators. Additionally, the Twitter hashtag for Free Open Access Medical Education (78) (#FOAMed) has been widely used to rapidly disseminate medical information to medical practitioners around the world, particularly emergency medicine physicians, including to physicians in low resourced settings (78) however, this remains controversial due to concerns about maintaining quality (79). MedTwitter, in particular #PedsICU, has been used to rapidly share PICU relevant information around the world during the COVID-19 Pandemic (80).

Virtual Technology Online Education, and Educational Collaboration and Resource Sharing: Lessons Learned and Where We Go From Here

Technology in many ways has made the world a much smaller place. Collaboration in patient management and in medical training and education can literally happen in real time across the globe and across multiple time zones. Challenges remain in the use of telemedicine including developing ways to protect patient information, increasing the availability of computer and mobile technology in LMICs, and ensuring adequate internet and cellular service connectivity.

While access to online educational material is an opportunity to expand available information, which aspects of pediatric intensive care can be taught well-online remains to be elucidated. Studies of medical trainees' knowledge, attitudes, and practices comparing in-person to online training are currently being done (81), and will continue to be studied for years to come. Once again, the applicability of the material to the setting in which one is practicing or the resources available in that setting make some topics less ideal for "non-individualized" virtual/online education. Continued development of these resources by clinicians in LMICs is essential to broadening the applicability of this method of education.

ON THE HORIZON DEVELOPMENTS

As excited as we are about the advancements that have taken place over the past decade, there are other "on the horizon" developments that have the potential to significantly advance PCC in LMICs even further over the coming decade. As we conclude this article, we have highlighted a few of the advancements that we believe will have a large impact in the coming years.

Electronic Medical Records

With the advancement in telemedicine and virtual training/education platforms, a push for development of electronic medical records becomes more salient. EMR is a technology that becomes increasingly important in critical care as the share of multidisciplinary, medically complex, and chronic conditions increase. In addition to the commonly recognized benefits, such as the ability to track labs, images, and other information across time and improved legibility, other benefits include the facilitation of telemedicine (virtual private networks), tele-radiology, and research and quality improvement initiatives.

However, like any other infrastructure, EMRs come at a cost. There is a cost to initial investment and training, server infrastructure and maintenance, backup electrical systems due to lack of reliable electricity, and ongoing costs of feature implementation as needs evolve. Unfortunately, while many EMR vendors with a presence in LMICs are well-equipped to provide a system adequate for outpatient and basic inpatient care, most have never implemented features that are required for critical care, such as flowsheets, drip records, ventilator flowsheets, computerized order entry that can deal with complex medication scheduling, and basic order error checking, etc. In that case, these features must be implemented, which can take significant time and effort, or else parallel systems are created, which reduces efficiency.

Other less obvious challenges not commonly present in HICs blunt some of the promise of EMRs. For instance, patients may deliberately register under different names each time they are admitted, to avoid paying outstanding bills—making it so that you can no longer take advantage of historical data in the system. Poor internet access in satellite centers of care makes it difficult to implement a synchronized record. Computer literacy amongst staff, including ancillary clerical staff that must interact with the record, is not a given, which must be considered when planning initial implementation. Once implemented, record failure can be more catastrophic than a non-electronic system.

Devices, Equipment and Supplies

Innovation in medical technology, equipment and supplies has continued to advance over the past decade. Many innovations were reviewed in our last article under "stuff," however innovations not previously highlighted include the local production of hand cleansers (82), improvised peritoneal dialysis catheters and fluids (83), filtered sunlight phototherapy (84) and improvised electrical phototherapy machines (85).

Acute respiratory failure remains one of the leading causes of death in children under 5-years old, and therefore it should be the focus of much of the research and technological developments. Examples of on the horizon equipment advancements include the recently developed "National Hospital Abuja (NHA) Bubble CPAP Model" (86) which uses a Y-connector to blend humidified oxygen and medical air, a simple graduated container as the

pressure generator, and an oxygen prong that provides the interface along with the inspiratory and expiratory limbs. An oxygen concentrator can be used with the NHA customized CPAP which decreases need for oxygen cylinders which are a valuable resource (86).

Other up and coming innovations related to respiratory support technology include, but are not limited to, the development of low-cost oxygen blenders (87, 88), humidifiers (89), and bi-level ventilators (90). Although pulse oximeters have been increasingly used and supported by companies like Lifebox^{TM} many more are needed (91) for more advanced affordable cardiac and respiratory monitoring. Most critical care units in low-resource settings are managed without the availability of blood gases or end-tidal carbon dioxide monitoring using pulse oximetry, respiratory rate, and clinical exam alone to determine how and when to change ventilator settings or wean to extubation. Untold numbers die because of limited availability of rapid accurate point-of-care testing (92).

Finally, ultrasound including point-of care ultrasound, is increasingly being used to improve the diagnosis and treatment in acute care critical illnesses and conditions like severe pneumonia and pericardial effusions (93). Unfortunately, this technology is often still outside the realm of many practioners due to both cost and availability. It is essential to continuing to focus on adaptations to these machines that will increase their accessibility in LMICs, along with training and research-based protocols so that this can become a standard part of care.

CONCLUSION

Providing high quality PCC to the global community is an ethical and moral obligation. We are well-positioned to meet this challenge if we continue to work collaboratively with our partners around the world building on our past experiences and lessons learned and advancing care through research, education and training, virtual collaboration and information sharing, and ongoing technological innovations for medical devices and supplies. If the pandemic has taught us anything it has taught us that we can rise to the occasion and modify care in a way that can be expansive and lead to new frontiers in PCC.

AUTHOR CONTRIBUTIONS

AB and TS: conceptualization, reviewing literature, drafting, writing, critically editing for important intellectual content, final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LD: reviewing literature, drafting, co-writing key section critically editing for important intellectual content, final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LD, MY, CS, AK, and KK: reviewing literature, drafting, writing, critically editing for important intellectual content, final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AS and RO: reviewing literature, critically editing for important intellectual content, final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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METHODS
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The Burden of Critical Illness in Hospitalized Children in Low- and Middle-Income Countries: Protocol for a Systematic Review and Meta-Analysis

Teresa B. Kortz[1,2], Katie R. Nielsen[3,4], Rishi P. Mediratta[5], Hailey Reeves[2], Nicole F. O'Brien[6], Jan Hau Lee[7,8], Jonah E. Attebery[9], Emaan G. Bhutta[10], Carter Biewen[1], Alvaro Coronado Munoz[11], Mary L. deAlmeida[12], Yudy Fonseca[13], Shubhada Hooli[14], Hunter Johnson[6], Niranjan Kissoon[15,16], Mara L. Leimanis-Laurens[17,18], Amanda M. McCarthy[11], Carol Pineda[19], Kenneth E. Remy[20,21], Sara C. Sanders[6], Yemisi Takwoingi[22,23], Matthew O. Wiens[24,25†] and Adnan T. Bhutta[13†] The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network on Behalf of the PALISI Global Health Subgroup*

[1] Division of Critical Care, Department of Pediatrics, University of California, San Francisco, San Francisco, CA, United States, [2] Institute for Global Health Sciences, University of California, San Francisco, San Francisco, CA, United States, [3] Division of Critical Care, Department of Pediatrics, University of Washington, Seattle, WA, United States, [4] Department of Global Health, University of Washington, Seattle, WA, United States, [5] Division of Pediatric Hospital Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, United States, [6] Division of Critical Care Medicine, Department of Pediatrics, The Ohio State University/Nationwide Children's Hospital, Columbus, OH, United States, [7] Children's Intensive Care Unit, KK Women's and Children's Hospital, Singapore, Singapore, [8] SingHealth Duke-NUS Global Health Institute, Singapore, Singapore, [9] Division of Critical Care, Department of Pediatrics, University of Colorado, Aurora, CO, United States, [10] Eberly College of Science, Pennsylvania State University, State College, PA, United States, [11] Division of Critical Care, Department of Pediatrics, University of Texas Health Science Center at Houston, Houston, TX, United States, [12] Division of Critical Care, Department of Pediatrics, Emory University, Atlanta, GA, United States, [13] Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, United States, [14] Section of Pediatric Emergency Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX, United States, [15] Children's and Women's Global Health, University of British Columbia, Vancouver, BC, Canada, [16] Department of Pediatrics and Emergency Medicine, University of British Columbia, Vancouver, BC, Canada, [17] Pediatric Critical Care Unit, Helen DeVos Children's Hospital, Grand Rapids, MI, United States, [18] Department of Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing, MI, United States, [19] Division of Critical Care, Department of Pediatrics, Baystate Medical Center, University of Massachusetts Chan Medical School, Springfield, MA, United States, [20] Division of Critical Care Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, United States, [21] Division of Pediatric Critical Care Medicine, Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH, United States, [22] Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom, [23] National Institute for Health Research Birmingham Biomedical Research Centre, University Hospitals Birmingham National Health Service Foundation Trust and University of Birmingham, Birmingham, United Kingdom, [24] Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada, [25] Mbarara University of Science and Technology, Mbarara, Uganda

Background: The majority of childhood deaths occur in low- and middle-income countries (LMICs). Many of these deaths are avoidable with basic critical care interventions. Quantifying the burden of pediatric critical illness in LMICs is essential for targeting interventions to reduce childhood mortality.

Objective: To determine the burden of hospitalization and mortality associated with acute pediatric critical illness in LMICs through a systematic review and meta-analysis of the literature.

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Yee Hui Mok,
KK Women's and Children's Hospital, Singapore
Anne-Sylvie Ramelet,
University of Lausanne, Switzerland

***Correspondence:**
Teresa B. Kortz
teresa.kortz@ucsf.edu

[†] These authors have contributed equally to this work and share senior authorship

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Data Sources and Search Strategy: We will identify eligible studies by searching MEDLINE, EMBASE, CINAHL, and LILACS using MeSH terms and keywords. Results will be limited to infants or children (ages >28 days to 12 years) hospitalized in LMICs and publications in English, Spanish, or French. Publications with non-original data (e.g., comments, editorials, letters, notes, conference materials) will be excluded.

Study Selection: We will include observational studies published since January 1, 2005, that meet all eligibility criteria and for which a full text can be located.

Data Extraction: Data extraction will include information related to study characteristics, hospital characteristics, underlying population characteristics, patient population characteristics, and outcomes.

Data Synthesis: We will extract and report data on study, hospital, and patient characteristics; outcomes; and risk of bias. We will report the causes of admission and mortality by region, country income level, and age. We will report or calculate the case fatality rate (CFR) for each diagnosis when data allow.

Conclusions: By understanding the burden of pediatric critical illness in LMICs, we can advocate for resources and inform resource allocation and investment decisions to improve the management and outcomes of children with acute pediatric critical illness in LMICs.

Keywords: critical illness, resource limited setting, pediatrics—children, child health, global health, hospitalization, low- and middle-income countries (LMIC)

INTRODUCTION

Greater than 80% of the global 6.64 million annual deaths in children and adolescents in 2017 occurred in low- and middle-income countries (LMICs) (1). Acute pediatric illnesses (e.g., sepsis, pneumonia, diarrheal disease, trauma) are the leading causes of death and disability outside of the neonatal period (1–5). The World Health Organization defines acute pediatric critical illness as "any severe problem with the airway, breathing, or circulation, or acute deterioration of conscious state; [which] includes apnea, upper airway obstruction, hypoxemia, central cyanosis, severe respiratory distress, total inability to feed, shock, severe dehydration, active bleeding requiring transfusion, unconsciousness, or seizures" (6). A significant number of children's lives could be saved with supportive critical care interventions, such as fluid resuscitation, high-flow oxygen therapy, non-invasive and invasive mechanical ventilation, and vasoactive support (7–11). Unfortunately, critical care services, defined as hospital care for children with sudden, serious reversible disease, are not universally available and are frequently lacking in LMIC settings, where disease burden, both in terms of hospitalization and mortality, is the highest (7). Furthermore, it is difficult to assess the burden of critical illness in settings without formal critical care services, where critical illness is frequently managed in emergency departments and inpatient wards.

Several recent global point prevalence studies have described the prevalence of key, individual acute pediatric critical illnesses. The Pediatric Acute Lung Injury Ventilation (PALIVE) study, conducted in 59 pediatric intensive care units (PICUs), found that 10.8% of children were diagnosed with acute lung injury (12). The Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) study reported a prevalence of pediatric acute respiratory distress syndrome of 3.2% and an associated mortality of 17% mortality in children admitted to 145 PICUs from 27 countries (13). The International Survey of Critically Ill Children with Acute Neurological Insults (PANGEA) study conducted in 107 PICUs across 23 countries found an overall prevalence of acute neurologic insult to be 16.2% and all-cause hospital mortality was 12% (14). Finally, the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study was conducted in 128 PICUs across 26 countries and demonstrated a prevalence of pediatric severe sepsis of 8.2% with a hospital mortality of 25% (15).

While each of these studies contributed significant knowledge about specific acute pediatric critical illnesses, there are limitations to the available data. The first limitation stems from the focus on a single, critical illness or insult as opposed to all pediatric critical illnesses. There is substantial overlap between illnesses (e.g., pneumonia is a frequent cause of sepsis). In addition, critical care resources support patients with many diagnoses (e.g., mechanical ventilation supports children with pneumonia, shock, or trauma), and resource availability, or lack thereof, greatly impacts patient outcomes. A narrow, illness-specific view fails to capture the burden of pediatric critical illness, which makes it difficult to prioritize resources and achieve the greatest potential impact on child mortality. The most significant limitation, however, is that current global pediatric critical illness point prevalence studies do

not reflect the prevalence of disease is LMICs. The PALIVE study was conducted exclusively in North American and European countries; (12) no low-income countries were included in the PARDIE study; (13) approximately 80% of PANGEA study sites were in North America and Europe; (14) and the SPROUT study, while it included several LMICs, did not include any countries from sub-Saharan Africa outside of South Africa (15). Each of these global point prevalence studies required PICU admission as an inclusion criterion. This drastically limited which centers and settings could participate and may have resulted in a gross underestimation of pediatric critical illness in LMICs where critical illness may be managed in sites without a formal PICU (7).

In this systematic review, we will describe the burden of hospitalizations and mortality associated with acute pediatric critical illness in LMICs including in settings that may not have a PICU or formal intensive care services. This review will contribute to our knowledge of the etiologies and prevalence of acute pediatric critical illness in settings with the highest burden of disease. This information will help guide decisions justifying resource allocation and investment as well as inform educational, policy, and research priorities to improve outcomes following acute pediatric critical illness globally.

MATERIALS AND METHODS

Objectives

The objectives of this study are to (1) determine common causes of pediatric hospital admissions (critical and non-critical) and mortality in LMICs; (2) determine the prevalence of and mortality associated with acute pediatric critical illness in LMICs; and (3) analyze the differences in common causes of critical illness by age and region.

Protocol and Registration

This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (PRISMA), is registered in the international prospective register of systematic reviews (PROSPERO #230228) and was organized and reviewed by the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) Network Global Health subgroup and PALISI Network Scientific committee (16, 17). The multinational and multidisciplinary scientific Working Group responsible for development of the systematic review protocol includes subject matter and/or methodology experts from across the globe who are members in good standing of the PALISI Global Health subgroup. The inclusion criteria are presented according to published guidelines for prevalence systematic reviews of observational studies (CoCoPop or condition, context, and population) (18).

Population

The population of interest is a general pediatric admission population admitted to a hospital in a low-, lower-middle, or middle-income country (LMIC), defined below in Section Context. The age range of interest includes post-neonatal (>28 days of age) and pre-adolescent (<13 years of age) children; studies that do not include some portion of this age range (>28 days to <13 years) will be excluded. However, studies that include this age range (>28 days to <13 years) plus either neonates and/or adolescents will be included, if it is a pediatric study population (e.g., includes study participants <18 years of age). All hospital admissions, regardless of admission disposition (high-dependency unit, PICU, ward, etc.) will be included. Studies where the available denominator represents a specific patient population and not all hospital admissions, such as emergency department patients, neonatal intensive care admissions, pediatric intensive care admissions, and neonatal populations, will be excluded. In situations when the denominator of interest does not represent the entire general pediatric admission population due to study-imposed exclusions, Working Group members will assess these texts individually and decide whether the study exclusion criteria likely resulted in a significantly different case mix (i.e., highly prevalent condition, condition highly relevant to critical illness) compared to the overall, general pediatric admission population. If so, then the text will be excluded. If not, then it will be included and assessed for bias during quality assessment.

Condition

The burden of critical illness is hospitalization or mortality due to a critical illness. Critical illness is defined as a state of ill health with vital organ system dysfunction and/or a high risk of imminent death. Studies must report the proportion of children with a specific admission diagnosis or cause of death (the numerator), such as pneumonia, human immunodeficiency virus (HIV), malaria, etc., relative to the number of general pediatric hospital admissions (the denominator) over that same period to be included. Both the numerator and denominator must represent the same patient population.

Context

Observational studies (prospective or retrospective cohorts, surveillance studies, hospital database publications, cross-sectional studies, before data from before-and-after studies, registry data, etc.) must be published since January 1, 2005, in Spanish, French, or English to be included. For studies including data collected before the year of 2000, only data from 2000 to present will be included; however, if it is not possible to extract only data after the year 2000, the study will be excluded in its entirety. Exclusion of data before the year 2000 and the publication date of January 2005 were chosen to reflect recent trends in pediatric hospitalization and mortality.

Only studies conducted in LMICs will be included. Low- and middle-income country status will be determined by the Global Burden of Disease (GBD) 2017 Socio-Demographic Index (SDI) (19). The SDI is a composite indicator that includes indices of total fertility rate for women under age 25 years, mean education for people 15 years and older, and a lag-distributed income per capita. Socio-Demographic Index represents a country's overall development status and strongly correlates with health outcomes. Studies that present aggregated data representing multiple countries (e.g., multi-center study) will be included, and we will report regional data. Publications conducted in

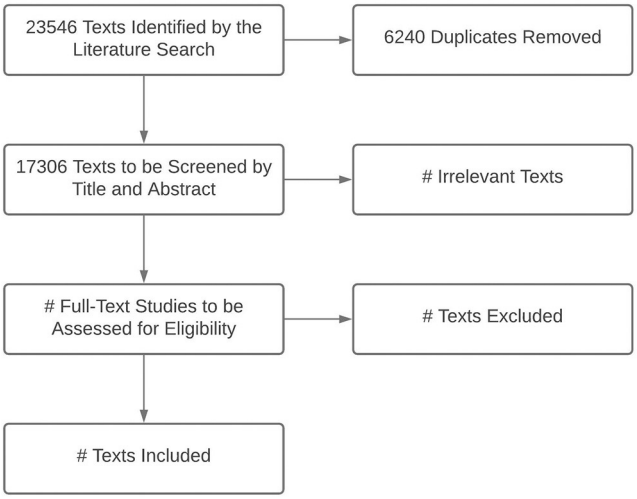

FIGURE 1 | Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) flowchart for title and abstract screening and text selection from the final search (conducted March 1, 2021).

LMICs but not representative of the setting (e.g., medical mission, foreign military hospital, disaster response efforts) will be excluded.

Abstract only publications, case studies, narrative reviews, surveys, study protocols, comments, editorials, letters, notes, conference materials, interventional trials, and texts for which we cannot locate the full text will be excluded. The search may be updated prior to publication to include more recent publications.

Data Sources and Search Strategy

A search strategy was developed among co-investigators and an academic librarian and tested for feasibility. The final search results are shown in **Figure 1**. We identified eligible studies by searching Ovid MEDLINE (1946 to February 26, 2021, with Epub Ahead of Print, In-Process, and Other Non-Indexed Citations), EMBASE.com (1974 to March 2021), CINAHL (1981 to March 2021), and LILACS (1982 to March 2021) (**Table 1**). The MEDLINE search was performed using MeSH and key words for "hospitalization," "patient admission," "patient readmission," "hospital units," "critical care," "intensive care," "mortality," and "developing countries." Countries determined to be LMICs by SDI criteria were listed individually to increase the specificity of the search. The MEDLINE strategy was adapted to search EMBASE, CINAHL, and LILACS. All results were limited to infants or children (ages 29 days to 12 years) and publication years 2005 to present. There were no language restrictions; texts in languages other than English, Spanish, or French will be manually excluded during screening. Specified publication types were excluded in MEDLINE and EMBASE (e.g., comments, editorials, letters, notes, conference materials) (**Supplementary Table 1**).

TABLE 1 | Summary of searched databases and number of texts identified by the search strategy.

Database	Dates included	Date searched	Number of texts identified
Ovid MEDLINE (R) Epub Ahead of Print In-Process and other Non-Indexed Citations Daily and Versions (R)	1946 to February 26, 2021	3/1/2021	11,240
EMBASE.com	1974 to Present (includes Medline 1966 to Present)	3/1/2021	11,403
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	1981 to Present	3/1/2021	3,878
Latin American and Caribbean Health Sciences Literature (LILACS)	1982 to Present	3/1/2021	1,453
Total			**27,974**

Study Selection and Screening Process

The titles from the search will be uploaded to and screened using Covidence (Veritas Health Innovation, Melbourne, Australia) (20). Covidence is a web-based systematic review platform designed to facilitate citation screening, full-text upload, and conflict resolution. Citations will be screened for eligibility based on title and abstract, and full text using a study-specific flowchart (**Figure 2**).

Working Group members will complete a training set of 25 citations (titles and abstracts) before initiating screening for the project. At least 5–10 true positives will be purposely included in the training set. The training set will be created by the study investigator (TK). Members of the Working Group will independently screen the titles and abstracts and then discuss and align on the final decision during a Working Group meeting.

Each title will be screened by two reviewers using the predetermined eligibility criteria. Specific Working Group Members fluent in non-English languages will be designated to review citations in Spanish (ACM, KN, TK, YF, CP) and French (ACM, HR, NO, CP). Titles that are eliminated by both reviewers will be rejected; titles accepted by both reviewers will advance to full-text screening; and titles in which a consensus is not reached will be resolved by a third member. Each full-text article will be assessed by two members of the Working Group for inclusion in the final set of articles for data extraction. At each screening and assessment phase, conflicts will be resolved by a third member of the Working Group using the conflict resolution function in Covidence.

For full texts with exclusion criteria, a reason for exclusion will be recorded (e.g., ineligible language; ineligible setting; not original research/wrong study design; ineligible population; ineligible denominator; ineligible numerator; full text not found; duplicate article). Texts identified by title and abstract screening will be excluded if the full text cannot be found

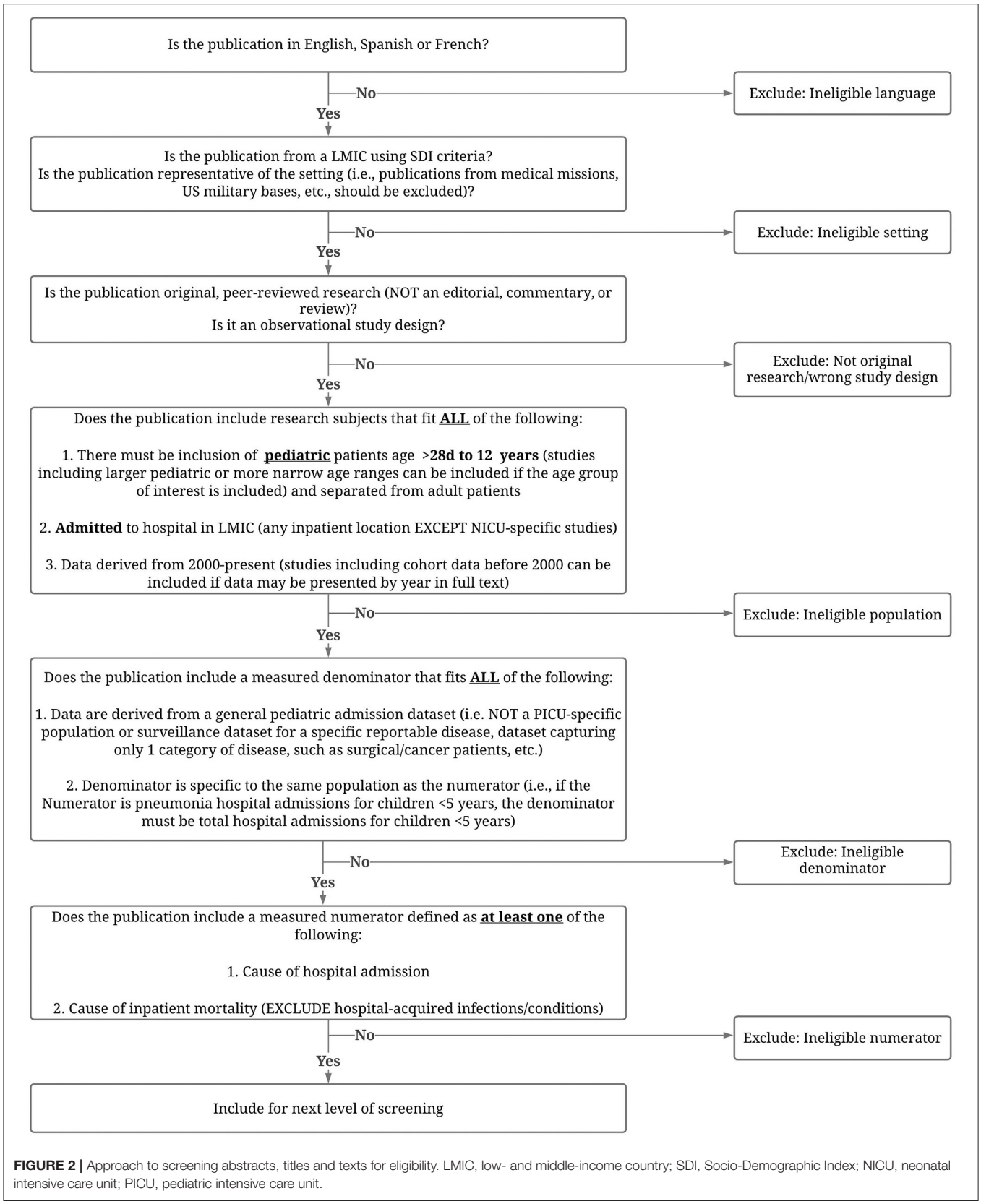

FIGURE 2 | Approach to screening abstracts, titles and texts for eligibility. LMIC, low- and middle-income country; SDI, Socio-Demographic Index; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

after the following stepwise process is completed: search of available journal article subscriptions at two or more academic institutions; a general web-based search using Google; an Interlibrary Loan request from at least two academic institutions; an article request via direct email to the corresponding author or editor. For multiple publications from one dataset, we will only include the data once (e.g., the most recent or most relevant publication). For publications with multiple years of data presented by year or groups of years (e.g., vaccine surveillance studies), we will include the most recent year(s) as this is more likely to reflect the current epidemiology of disease. Publications with data from more than one country (e.g., global prevalence studies) will be considered for inclusion if either (a) all included countries meet LMIC criteria, or (b) data from LMICs can be extracted separately from non-LMIC data. We may contact authors to stratify data by age for already published texts.

Data Extraction and Management

Data from all included full-text articles will be extracted by two, independent Working Group members and managed using REDCap, a secure, web-based application and electronic data capture tool hosted at the University of California, San Francisco (21). Data extraction conflicts will be resolved by a third member of the Working Group using the data comparison functionality in REDCap.

Data extraction will include information related to study characteristics (i.e., title, authors, year of publication, date of enrollment, urban/rural, country, language, journal, study design, sample size, inclusion/exclusion criteria, data source); hospital characteristics (public/private/faith-based, referral/district, community/academic, children's hospital, intensive care resources available, number of beds); underlying population characteristics (population served, proportion living in poverty, malaria rate, HIV rate, malnutrition rate); patient population characteristics (age, sex, presence of malnutrition, and other comorbidities); and outcomes (cause of admission, cause of death, length of stay).

Risk of Bias in Individual Studies

Two members of the Working Group will independently assess the quality of each selected article and risk of bias using an adapted version of the Quality in Prognosis Studies (QUIPS) tool (22). While this review will not assess prognostic factors for admission and/or mortality, biases relevant to prognostic factors are similar to those relevant to the assessment of causes of these outcomes. The QUIPS tool includes six domains of bias, of which the three deemed appropriate for this review are: (1) study participation; (2) study attrition; and (3) prognostic factor (i.e., cause) measurement. The fourth, outcome measurement, is not relevant as this systematic review assesses causes of admission (and where relevant, death), and the cross-sectional nature precludes a temporally linked outcome to the cause. The fifth and sixth domains, study confounding and statistical analysis, respectively, were also deemed not relevant as the data to be extracted are counts. Issues around improper analyses will be adequately captured in domains 2 (attrition) and 3 (measurement of cause). The adapted domains, key issues, and items for consideration relevant to this review are shown in **Table 2**. Risk of bias will be classified as high, moderate, or low when the relationship between the listed causes and outcome is very likely to be, may be, or unlikely to be, respectively, different for participants and eligible non-participants. Conflicts in the risk of bias assessment will be resolved by discussion or by a member of the Working Group if consensus cannot be reached. We will produce one or more summary of findings tables that will provide an overview of the evidence to make the findings accessible to readers. The tables will include summaries of the methodological quality (risk of bias), precision of summary estimates (imprecision), concerns about heterogeneity (inconsistency), applicability of the findings to our review question (indirectness), and issues with publication bias. The tables will also include any additional limitations of the evidence. We will explore the impact of the risk of bias domains in sensitivity analyses.

Data Synthesis and Analysis

We will summarize data on study (author, publication year, study country, study design, sample size, ages included, data source), hospital [catchment population, type of hospital (level, affiliation, pediatric, etc.), number of health facility and pediatric beds, and available intensive care resources] and patient (median age, prevalence of comorbidities such as malnutrition, congenital heart disease, prematurity, malignancy, malaria, and anemia) characteristics; outcomes; and risk of bias assessment using tables, graphs, and narrative summaries. Continuous outcomes will be summarized using mean and standard deviations (SDs) or medians with interquartile ranges as appropriate. Binary outcomes will be summarized using frequencies and percentages.

The primary outcomes of interest are (1) cause of hospital admission and (2) cause of in-hospital mortality. Causes of hospital admissions will be further categorized as critical (potentially life-threatening) and non-critical (unlikely to be life threatening) based on group consensus and a review of the literature. If available, data for secondary outcomes will be collected including in-hospital mortality, case fatality rate (CFR), and length of hospital stay.

We will report the causes of admission and mortality (categorized by GBD grouping) by region (Central Europe, Eastern Europe, and Central Asia; Latin America and Caribbean; North Africa and Middle East; South Asia; Southeast Asia, East Asia, Oceania; Sub-Saharan Africa), SDI country income level (low-, lower-middle, or middle-income), and age (<5 years, 5–12 years).

When possible, we will report the CFR for each cause of admission and/or cause of death. This may require calculating these estimates from individual studies when not reported directly, provided that the necessary data to perform these calculations are reported. Causes of hospital admissions will be categorized as non-critical or critical (potentially life-threatening) by the same multinational, multidisciplinary scientific Working Group compiled of experts described above. The Working Group will reach consensus as to whether the reason for admission is consistent with vital organ system

TABLE 2 | Risk of bias domains and questions adapted from the Quality in Prognosis Studies (QUIPS) criteria.

Domain	Key Issue in this Review	Items for Consideration During Assessment
Study participation	Do those subjects who are enrolled/analyzed represent the general admission population of this age group at this facility (or these facilities if multisite)?	(a) Adequate participation in the study by eligible persons (i.e., all those admitted in the target age group). (b) Description of the source population or population of interest. (c) Description of the baseline study sample. (d) Adequate description of the sampling frame and recruitment (i.e., if not a census sample, effort was made to ensure a representative sample of the admission population). (e) Adequate description of the period and place of recruitment (e.g., representative in terms of seasonality, natural fluctuations in causes based on time of day, day of week, etc.). (f) Adequate description of inclusion and exclusion criteria (i.e., any efforts in sample selection should be to make the sample more representative of the general admission population, not less).
Study attrition	Do those subjects who are enrolled represent those in whom the outcome (cause of admission, cause of death) is measured? This is especially relevant to those studies assessing both causes of admission AND causes of death.	(a) Those who are enrolled and those in whom a cause (of admission, death, etc.) was measured are the same. (b) Reasons for losses between enrollment (admission) and outcome ascertainment (cause of admission, cause of death) are provided. (c) Adequate description of participant losses. (d) There are no important differences between participants who completed the study and those who did not.
Listed causes of measurement (i.e., measurement of admission/death)	Do those subjects in whom a cause of admission/death is reported have this cause (or these causes) measured reliably?	(a) A clear definition or description of the listed causes is provided. (b) Method of the determination of causes valid and reliable. (c) The method and setting of measurement of listed causes is the same for all study participants. (d) Appropriate methods of imputation are used for missing listed causes data.

dysfunction and/or a high risk of imminent death based on a review of region-specific literature. We will explore different definitions and cut-offs for critical illness (proportion of total admissions, proportion of total mortality, CFR).

As the data allow, we will perform a meta-analysis on the proportions of causes of admission and causes of death, as well as the CFRs using random-effects models. We will conduct meta-regression, where possible, to explore predictors for all-cause and cause-specific mortality (pneumonia, sepsis, and diarrhea). Possible predictors will include SDI, facility type, and geographic region. Additionally, we will explore temporal trends in admission and mortality by age and region. We will consider subgroup analyses if we have adequate numbers of studies and/or patients within the included studies.

We will examine sources of heterogeneity, including differences in methodology, setting (urban vs. rural), region, income level, and patient populations (e.g., age, sex, prevalence of comorbidities, etc.). Statistical heterogeneity will be assessed using the variance estimates from the random effects model. It is likely that there will be significant heterogeneity between studies, and we will therefore pool results when studies are comparable. All analyses will be performed using STATA (version 16).

ANTICIPATED RESULTS

Through this systematic review, we expect to identify the most common causes of acute pediatric critical illness resulting in hospital admission and mortality in LMICs by age and region. If data are available, we will also show temporal trends in admission and mortality by age and region. We will classify causes of admission as critical or non-critical and illustrate the global prevalence of critical illness with a map. Furthermore, we anticipate identifying diagnoses with the highest CFR for each age and region and illustrating these results through a series of forest plots for all-cause mortality, cause-specific mortality (pneumonia, sepsis, diarrhea, malaria), critical illness, and hospital length of stay (data permitting).

There are several advantages to the proposed approach. First, with broad inclusion criteria, we expect to capture most if not all relevant texts. Second, by not restricting the search to exclusively pediatric intensive care populations, we will be able to calculate the prevalence of critical illness across settings, including those without a formal PICU. Third, by including both individual LMICs by name and terms such as "resource-limited," "low income," and "developing" in the search strategy, we will likely identify more texts from LMICs, which will provide a more complete assessment of the burden of critical and non-critical disease in these countries.

There are potential limitations to the proposed protocol. First, neonatal and adolescent populations are included in some pediatric studies, and the search was not designed to capture these populations. We will intentionally exclude exclusively neonatal and adolescent populations from data analyses and will not be able to draw conclusions about children <28 days or >12 years of age. Second, we will exclude disease-specific studies that do not report overall pediatric hospital admissions, which may result in an underestimation of disease prevalence. Additionally, estimates will not include disease prevalence during outbreaks, potentially underestimating the true prevalence of disease and overall required critical care capacity. Third, we will restrict

study inclusion to publications in Spanish, French, or English, and may not identify all potentially relevant texts. Fourth, we may underestimate the true burden of critical illness in LMICs by excluding emergency department or PICU population studies that lack the denominator of interest (general hospital admissions). However, without a common denominator, we cannot draw comparisons across studies. Sixth, it is possible that critical, but rare illnesses, will not be adequately represented in this systematic review as they are often categorized in the "other" category in texts. This systematic review will, however, describe the most common causes of pediatric critical illness, which is of greatest importance when the objective is to improve overall child health outcomes and inform resource allocation. Finally, we expect to include a small number of studies where the denominator does not represent the entire general pediatric admission population due to original study-imposed exclusions. The degree of bias from these texts should be minimal because only those with a similar case mix to the overall, general pediatric admission population will be included.

DISCUSSION

There is intense competition for limited resources in many LMICs and children are frequently overlooked as the global focus shifts away from infectious diseases toward non-communicable diseases, which are far more common in adult populations (23). To decrease childhood morbidity and mortality, health systems require capacity to deliver both preventative medicine and treatment, such as proven, effective therapies, like critical care (23). While dedicated PICUs are being developed in LMICs, clinician, and staff education is sub-optimal due to a lack of appreciation of the common pediatric critical illnesses.

The objective of this systematic review is to describe the most common causes of critical illnesses causing hospitalization and death in children in LMICs. This will provide much needed insight into the burden, etiology, and distribution of pediatric critical illness in LMICs, especially in settings where formal critical care services may not be currently available. Region-specific data that capture the burden of disease and outcomes for children in LMICs are essential to inform educational initiatives and training, shape advocacy and policy objectives, allocate limited resources appropriately, and implement context-appropriate, evidence-based critical care interventions for children in need. This systematic review is a crucial first step in setting future educational, advocacy, policy, research, and health delivery priorities for children with acute critical illness in LMICs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TK: substantial contributions to the conception, design of the work, drafting, and revising the work. KN, RM, HR, NOB, JL, JA, EB, CB, YF, HJ, ML-L, ACM, AMM, MLd, SH, SS, NK, KR, CP, YT, MW, and AB: substantial contributions to the conception, design of the work, and revising the work critically for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.756643/full#supplementary-material

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Family-Assisted Severity of Illness Monitoring for Hospitalized Children in Low-Resource Settings—A Two-Arm Interventional Feasibility Study

Amelie O. von Saint Andre-von Arnim[1,2], Rashmi K. Kumar[3], Jonna D. Clark[1,4], Benjamin S. Wilfond[4,5], Quynh-Uyen P. Nguyen[6], Daniel M. Mutonga[7], Jerry J. Zimmerman[1], Assaf P. Oron[8†] and Judd L. Walson[9,10†]*

[1] Division of Pediatric Critical Care, Department of Pediatrics, University of Washington and Seattle Children's, Seattle, WA, United States, [2] Department of Global Health, University of Washington, Seattle, WA, United States, [3] Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Kenya, [4] Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute, Seattle, WA, United States, [5] Divisions of Bioethics & Palliative Care and Pulmonary & Sleep Medicine, Department of Pediatrics, University of Washington, Seattle, WA, United States, [6] Department of Pediatrics, University of Washington and Seattle Children's, Seattle, WA, United States, [7] Institute of Tropical and Infectious Diseases, University of Nairobi, Nairobi, Kenya, [8] Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, United States, [9] Departments of Global Health, Epidemiology, Infectious Disease, University of Washington, Seattle, WA, United States, [10] Childhood Acute Illness and Nutrition Network, Nairobi, Kenya

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J. Mark Ansermino, University of British Columbia, Canada

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***Correspondence:**
Amelie O. von Saint Andre-von Arnim
ameliev@uw.edu

†These authors share last authorship

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Introduction: Pediatric mortality remains unacceptably high in many low-resource settings, with inpatient deaths often associated with delayed recognition of clinical deterioration. The Family-Assisted Severe Febrile Illness ThERapy (FASTER) tool has been developed for caregivers to assist in monitoring their hospitalized children and alert clinicians. This study evaluates feasibility of implementation by caregivers and clinicians.

Methods: Randomized controlled feasibility study at Kenyatta National Hospital, Kenya. Children hospitalized with acute febrile illness with caregivers at the bedside for 24 h were enrolled. Caregivers were trained using the FASTER tool. The primary outcome was the frequency of clinician reassessments between intervention (FASTER) and standard care arms. Poisson regression with random intercept for grouping by patient was used, adjusting for admission pediatric early warning score, age, gender. Secondary outcomes included survey assessments of clinician and caregiver experiences with FASTER.

Results: One hundred and fifty patient/caregiver pairs were enrolled, 139 included in the analysis, 74 in the intervention, 65 in the control arm. Patients' median age was 0.9 (range 0.2–10) and 1.1 years (range 0.2–12) in intervention vs. control arms. The most common diagnoses were pneumonia (80[58%]), meningitis (58[38%]) and malaria (34 [24%]). 134 (96%) caregivers were patients' mothers. Clinician visits/hour increased with patients' illness severity in both arms, but without difference in frequency between arms (point estimate for difference −0.9%, $p = 0.97$). Of the 16 deaths, 8 (four/arm) occurred within 2 days of enrollment. Forty clinicians were surveyed, 33 (82%) reporting that FASTER could improve outcomes of very sick children in low-resource settings; 26 (65%) rating caregivers as able to adequately capture patients' severity of illness.

Of 70 caregivers surveyed, 63 (90%) reported that FASTER training was easy to understand; all (100%) agreed that the intervention would improve care of hospitalized children and help identify sick children in their community.

Discussion: We observed no difference in recorded frequency of clinician visits with FASTER monitoring. However, the tool was rated positively by caregivers and clinicians., Implementation appears feasible but requires optimization. These feasibility data may inform a larger trial powered to measure morbidity and mortality outcomes to determine the utility of FASTER in detecting and responding to clinical deterioration in low-resource settings.

Clinical Trial Registration: ClinicalTrials.gov, identifier: NCT03513861.

Keywords: low-resource setting, early warning score, critical illness, low middle income country, pediatrics, child health, global health

INTRODUCTION

Pediatric mortality in resource-poor settings continues to be high, with under-five mortality rates in Africa in 2020 at 76 per 1,000 children or 1 in every 13 children (1). These deaths are often due to preventable and treatable conditions, including neonatal diseases, lower respiratory tract infections and diarrheal illnesses (2). Management of severe illness in low-resource settings is often conducted on general hospital wards under significant resource constraints, rather than in intensive care units. According to the World Health Organization (WHO), the African region experiences both the greatest burden of disease and the lowest density of health workers at 2.2 healthcare professionals per 1,000 population (3). This health care worker shortage results in overburdened medical staff, overcrowded facilities and limitations in the inpatient monitoring (4–6), with worsening illness often under-recognized and associated with substantial mortality (7, 8).

Early recognition and management of critical illness have shown to improve outcomes in upper-middle and high income countries (9–11). Prediction models that enhance early identification of the sickest children are needed in lower resource settings to guide timely referral and transport of patients, efficient allocation of resources, and counseling regarding anticipated clinical trajectories (12, 13). Empowering family members to assist with timely recognition of clinical deterioration in their hospitalized child may allow for expedited clinical response and improve health outcomes. The first phase of this prospective, feasibility study at Kenyatta National Hospital (KNH) in Nairobi examined the adequacy of the simple 3-point FASTER bedside assessment tool (**Figure 1**) as a potential method for enlisting caregivers to identify and communicate patient deterioration and demonstrated that FASTER assessment by caregivers is feasible in low-resource settings (14). In addition, caregiver assessments correlated strongly with professional research team assessments, using established severity of illness systems [Bedside Pediatric Early Warning Score or PEWS (15)], and with fatalities within the first 48 h of admission (14). In the current report, we examine the second phase of this feasibility study, namely the impact of caregiver assessments and signaling using the FASTER monitoring tool on frequency of clinician assessments and explore caregiver and clinician experiences with this intervention.

MATERIALS AND METHODS

Eligibility

Children aged 2 months to 12 years admitted to the KNH pediatric wards or "acute rooms" (ward rooms with higher nurse to patient ratios) within the previous 16 h with severe febrile illness were eligible. Inclusion diagnoses included malaria, sepsis or septic shock, pneumonia, and meningitis or encephalitis. Patients were excluded if their primary diagnosis was related to major bleeding or hemorrhagic shock, severe trauma or burn, major surgery, known congenital heart disease, if an adult caregiver would not be consistently present for the entire 24 h study period or if the caregiver was not proficient in English or Swahili.

Study Stages, Intervention and Study Arms

The trial consisted of two stages. The goal of the first stage was to establish feasibility and accuracy of the FASTER tool (14). Caregivers had to achieve a preset evaluation performance (70 to 80% sensitivity and specificity) compared to professionals in order for the study to advance to stage 2 which is published elsewhere (14). The goals of the second stage described here were to examine the FASTER clinician response and to preliminarily evaluate the impact on timing of clinical provider bedside visits, in addition to investigating caregivers' and clinicians' experience with the intervention to inform a larger future study on FASTER implementation. In the second stage, caregivers were enrolled 1:1 into intervention or control arms based on a weekly rotating schedule, until target sample size of 75 caregiver/patient pairs per arm was reached. Caregivers in the interventional arm received individualized education regarding family-assisted monitoring, which included video-based and hands-on training provided by a study nurse (14). Caregivers were taught to identify signs of clinical deterioration, namely: presence of chest retractions,

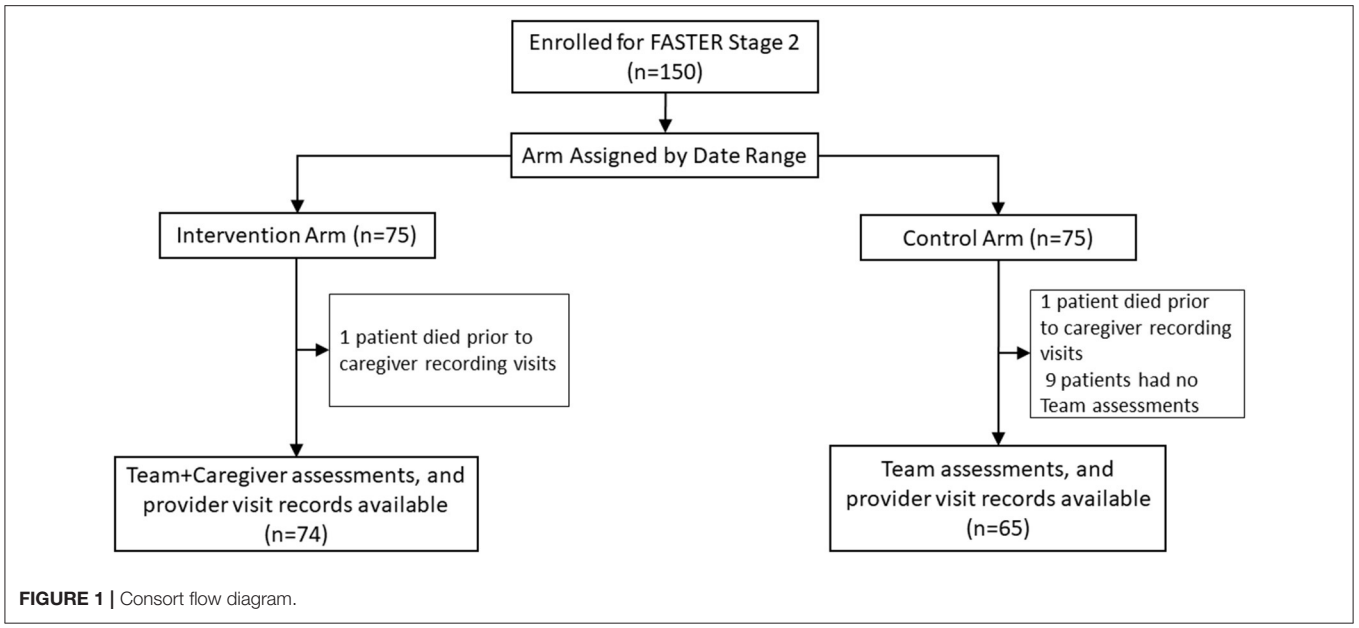

FIGURE 1 | Consort flow diagram.

capillary refill time > 3 sec, and an altered mental status (responsive only to painful stimuli or non-responsive).They were instructed to perform the clinical assessment every hour for 24 h and display a color-coded severity of illness flag, with a red flag indicating high severity of illness (2 or more FASTER signs), a yellow flag for moderate severity of illness (one FASTER sign), and no flag for patients with zero FASTER signs. Control arm caregivers did not receive child clinical assessment training and did not participate in the FASTER clinical monitoring protocol. Caregivers in both arms, however, recorded the frequency of clinician visits to their child's bedside during the first 24 h post enrollment. Study team nurses performed the FASTER assessment on patients in both arms, 4 times during the 24 h study period. Study team FASTER assessments were not shared with clinicians or caregivers given that correlation with validated severity of illness tools (Bedside PEWS) was not yet established at the time of this intervention. Caregivers in the intervention arm and all clinicians caring for children in both arms were surveyed about their experiences using the FASTER intervention.

Ethical approval was obtained from KNH/University of Nairobi and at Seattle Children's Hospital. All caregivers provided written informed consent for participation in the study. The study was registered with ClinicalTrials.gov NCT03513861.

Endpoints and Data Collection

Clinical data for the Bedside PEWS at and 24 h post enrollment, study team FASTER scores, case fatality data and demographic information were collected and entered into a Research Electronic Data Capture (REDCap) form, hosted by the Institute for Translational Health Sciences at the University of Washington (15, 16). Caregivers recorded the FASTER flags raised and frequency of clinician visits on paper forms, which the study team later entered into REDCap.

Sample Size and Statistical Analysis

A sample size ($n = 100$) was calculated to enable detection of a relative increase of 50% in clinician visits to deteriorating patients (defined as FASTER "red-flag" assessment, i.e., 2 or more deterioration signs) on the intervention arm, compared with the control arm. These calculations assumed that 70% of caregiver assessments would be "red-flag." However, the first stage of this study revealed that only 10–15% of assessments were "red-flag (14). This much lower than expected frequency indicated substantially reduced power for the main study. Therefore, the sample size was increased to $n = 150$, the maximum sample feasible given budget and time constraints. The study was a priori not powered to detect differences in mortality between arms. Power calculations and statistical analyses were carried out using R, versions 3.0 through 4.1 (R Foundation for Statistical Computing, Vienna).

The primary outcome was the effect of the intervention on the association between severity of illness and the number of clinician (nurse and physician) visits to the patient's bedside. The study was not powered to detect changes in mortality, as preliminary data on frequency of caregiver flagging of deterioration was not known and additional information about the feasibility of the intervention was needed in order to plan for a larger trial designed and powered to detect mortality or morbidity outcomes. Given the existing literature on healthcare provider shortage and limitations of inpatient monitoring in Sub-Saharan Africa, and the fact that early recognition of severe illness is key for successful outcome, the frequency of clinician patient reassessment was chosen as the primary outcome for this pilot study (3–11). We used research-team FASTER assessments, available on both arms, as proxy for the child's real-time condition severity. Since intervention-arm caregiver FASTER flags were very similar to research-team assessments (14), if caregiver flag affected provider behavior in the desired manner, then the difference in frequency

TABLE 1 | Demographic and clinical characteristics of patient/caregiver pairs.

Participant characteristic	Control *n* (%)	Intervention *n* (%)	Sum *n* (%)
Child characteristics			
Child number	65	74	139
Child median age in years (range)			
	1.1 (0.2–12)	0.9 (0.2–10)	
Child Sex			
Male	42 (65)	36 (49)	78 (56)
Female	23 (35)	38 (51)	61 (44)
Child diagnosis			
Pneumonia	35 (54)	45 (61)	80 (58)
Meningitis	25 (38)	28 (38)	53 (38)
Malaria	20 (31)	14 (19)	34 (24)
Gastroenteritis	6 (9)	14 (19)	20 (14)
Malnutrition	9 (14)	5 (7)	14 (10)
Bronchiolitis	8 (12)	5 (7)	13 (9)
Anemia	3 (5)	6 (8)	9 (6)
Sepsis/Septic Shock	4 (6)	4 (5)	8 (6)
Dehydration	3 (5)	1 (1)	4 (3)
Encephalitis	0 (0)	3 (4)	3 (2)
Number of child diagnoses			
1	22 (34)	29 (39)	51 (37)
2	33 (51)	25 (34)	58 (42)
3+	10 (15)	20 (27)	30 (22)
Caregiver characteristics			
Type of caregiver			
Mother	62 (95)	72 (97)	134 (96)
Father	1 (2)	0 (0)	1 (1)
Grandparent	0 (0)	1 (1)	1 (1)
Aunt/Uncle	2 (3)	1 (1)	3 (2)
Caregiver language			
Swahili	36 (55)	48 (65)	84 (60)
English	29 (45)	26 (35)	55 (40)
Caregiver highest level of education			
Primary	26 (40)	21 (28)	47 (34)
Secondary	25 (38)	42 (57)	67 (48)
Certificate	4 (6)	7 (9)	11 (8)
Diploma	9 (14)	4 (5)	13 (9)
Degree	1 (2)	0 (0)	1 (1)

of clinician bedside visits to patients with higher vs. lower research-team FASTER assessments would be greater on the intervention arm. This intervention effect was estimated in a regression model as an interaction between arm and FASTER assessment (dichotomized as red-flag vs. less severe), with the number of hourly visits being the response variable. We used Poisson regression with a random intercept for grouping by patient, adjusting for admission PEWS, age under 6 months and gender.

In both arms, clinician visits were recorded hourly by caregivers. Missing-data patterns suggested that during late-night hours, most caregivers rested and did not record visits consistently; this time also coincides with lower clinician-visit frequency. We therefore performed the primary analysis on data collected between 06:00 to 22:00. During hours with no clinician visit, control-arm caregivers left the data entry form blank, whereas intervention-arm caregivers generally entered zeros for such hours (**Supplementary Table 1**). To overcome this reporting difference, in the primary analysis we treated blank entries as zero. In sensitivity analysis, blank entries were excluded. In secondary analysis, we tested for a potential indirect clinical intervention impact by comparing the change in PEWS over 24 h between arms, among surviving patients, using simple linear regression.

Survey data were collected from 40 health care providers and 70 caregivers to explore their perspectives regarding the benefits and challenges of the FASTER monitoring tool (**Supplementary Material 2**). Using both open and closed ended questions, it assessed the overall clinician and caregiver experience with FASTER; challenges, general value and caregivers' understanding of the tool. Research nurses recorded the verbal responses in either Swahili or English to survey

TABLE 2 | Clinician survey of FASTER intervention.

Clinician	Physician	Nurse	Clinical officer	Sum
	Count (%)			
Role	14 (35)	22 (55)	4 (10)	40 (100)
Days of exposure to FASTER intervention				
1–5	5 (36)	8 (36)	0 (0)	13 (32)
6–20	2 (14)	8 (36)	1 (25)	11 (28)
>20	7 (50)	6 (27)	3 (75)	16 (40)
Overall Impression of FASTER monitoring				
Good	8 (57)	6 (27)	2 (50)	16 (40)
Not good	1 (7)	6 (27)	1 (25)	8 (20)
Didn't notice much	4 (29)	6 (27)	1 (25)	11 (28)
Ambiguous/missing	1 (7)	4 (18)	0 (0)	5 (12)
Challenges of FASTER intervention: increased work				
No	10 (71)	13 (59)	3 (75)	26 (65)
Yes	4 (29)	9 (41)	1 (25)	14 (35)
Challenges of FASTER intervention: false flags				
No	6 (43)	16 (73)	3 (75)	25 (62)
Yes	8 (57)	6 (27)	1 (25)	15 (38)
Challenges of FASTER intervention: parents demanding				
No	8 (57)	12 (55)	3 (75)	23 (57)
Yes	6 (43)	10 (45)	1 (25)	17 (42)
Would FASTER intervention improve care of a very sick child in resource-limited settings?				
No	1 (7)	6 (27)	0 (0)	7 (18)
Yes	13 (93)	16 (73)	4 (100)	33 (82)

questions from caregivers, as not all caregivers in the study were literate. Clinicians responded to survey questions in writing.

Qualitative responses to open ended survey questions by caregivers and health care providers were short and concise. One research team member categorized individual responses to each question into themes based on content (JC). Summaries of these data were created from the categorization of themes. Two additional research team members (BW, AV) reviewed the thematic categorization of survey responses and data summaries. Any differences in opinion were discussed and modified until consensus among the research team was achieved to improve reliability of the data summaries.

RESULTS

Demographics of Study Population

Enrollment at KNH occurred between July and November 2017. Of the 150 caregiver/patient pairs enrolled, 139 were included in the analysis, 74 in the intervention arm and 65 in the control arm (**Table 1** and **Figure 1**). Two patients were excluded because they deteriorated and died so quickly that caregivers did not have time to record provider visits. Nine additional patients, all in the control arm, were excluded because no study-team FASTER assessments were performed. Among included patients, median age was 0.9 years (range 0.2–10) in the intervention arm and 1.1 years (range 0.2–12) in the control arm; with 38 (51%) and 23 (35%) female in intervention vs. control arms. The most prevalent admission diagnoses in both arms were pneumonia (80 [58%]), meningitis (58 [38%]) and malaria (34 [24%]). Nearly all caregivers in both arms were patients' mothers (134 [96%]), with the most common level of education being primary (47 [34%]) or secondary school (67 [48%]) (**Table 1**). Among included patients, 16 of 139 (12%) died in the hospital, nine of them on the intervention arm. Eight patients (four in each arm) died within 2 days of enrollment. Case-fatality rate did not vary by child age, however death within 2 days of enrollment was associated with age: 6 of 8 infant fatalities occurred within 2 days, compared with 2 of 4 deaths among those aged 12–23 months, and no fatalities among children 2 years or older; all 3 late deaths (>1 one week) occurred in this age group (*post-hoc* Chi-Squared $p = 0.01$). Admission PEWS was strongly associated with early death: 7 of 41 patients with bedside PEWS $\geq$ 10 (17%) died within 2 days, compared with only 1 of 76 (1%) who had PEWS between 5 and 9, and 0 of 22 with PEWS < 5 ($p = 0.003$).

Forty clinicians responded to the survey questions (**Supplementary Material 2**) reflecting on their experiences with the use of the FASTER monitoring tool, of which 14 (35%) were physicians, 22 (55%) nurses and 4 (10%) clinical officers (**Table 2**). Of 74 caregivers in the intervention arm, 70 (94%) responded to the survey questions (**Table 3**).

Effectiveness of FASTER Monitoring Tool

On average, clinicians were significantly responsive to patient condition. Patients with admission PEWS of $\geq$10 received on average 0.79 (SD 0.89) and 0.70 (SD 0.40) visits/hour

TABLE 3 | Caregiver feedback of FASTER intervention.

Caregiver survey questions	Count (%)
Number of caregivers (all female)	70 (100)
Training easy to understand?	
Yes	63 (90)
No	7 (10)
Clinicians responded as expected?	
Yes	51 (73)
No	18 (26)
Challenge of FASTER intervention—fatigue	
Yes	13 (19)
No	57 (81)
Challenge of FASTER intervention—stress	
Yes	18 (25)
No	52 (75)
Challenges of FASTER intervention—clinician interaction	
Yes	3 (4)
No	67 (96)
Challenges—other*	
Yes	8 (11)
No	62 (89)
Would FASTER improve care very sick hospitalized child in this setting?	
Yes	70 (100)
Would FASTER monitoring help recognize a sick child in your community?	
Yes	70 (100)

*See qualitative data in results section.

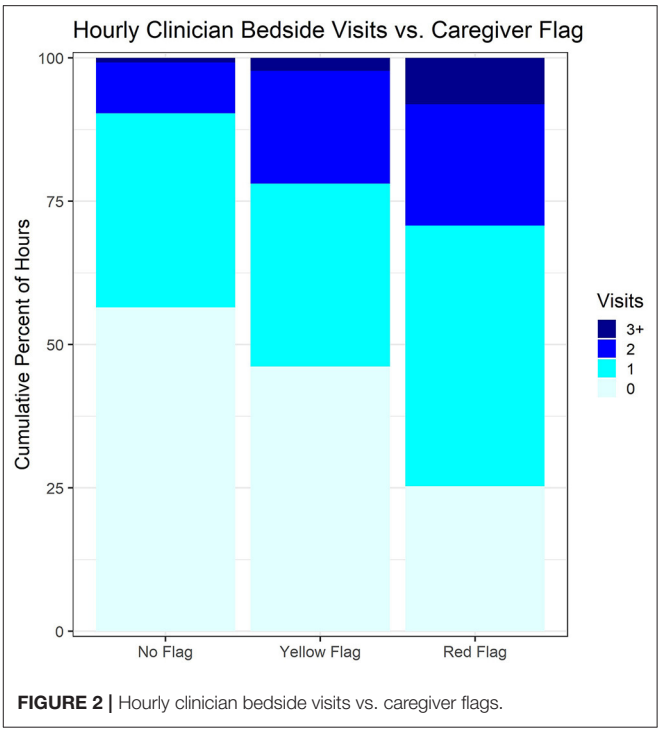

FIGURE 2 | Hourly clinician bedside visits vs. caregiver flags.

on the intervention and control arms, respectively, compared with only 0.39 (SD 0.20) and 0.34 (SD 0.14) with admission PEWS<5 ($p < 0.001$ for linear association with PEWS). A similarly strong association was seen between hourly clinician visits and study-team FASTER scores (**Figure 2**; Chi Squared $p < 0.001$). Model estimates indicated that children in red-flag condition received 41% more visits on average than other children ($p = 0.002$). However, there was no difference in provider responsiveness between the two arms (point estimate for the difference −0.9%, $p = 0.97$) (**Table 3**). In other words, there was no observed intervention effect upon clinician behavior. In the same vein, examining whether there were clinical-course differences between the arms, among children with a 24 h PEWS score the decrease from admission PEWS was not significantly different between the intervention and control arms ($p = 0.68$).

There were 0.57 (SD 0.81) and 0.54 (0.76) visits/hour on average between 06:00 and 22:00 in the intervention and control arm, respectively. Nurse patient reassessments (0.32/hour on average during 06:00–22:00) were somewhat more frequent than physicians' (0.24/hour). There was a diurnal pattern in clinician patient interaction (**Figure 3**). Physicians' visits peaked sharply around 09:00–10:00, with much fewer visits at other hours. Nurse visits peaked abruptly near 06:00, then retained a similar rate through most of the day, tapering off toward evening then dropping sharply late at night.

In a *post-hoc* power simulation keeping the overall dataset size and structure the same as actually collected but simulating intervention-arm visits according to assumed interaction effects at a 1.5x differential effect power was reduced: 50% with alpha = 0.1 and only 30% with alpha = 0.05. However, at 1.65x effect size power reaches 80 and 60%, respectively at alpha = 0.1 and 0.05, and at 1.75x effect size it is >90 and 80%, respectively. A 2x increase in differential clinician visits would almost certainly have been detected.

Overall Impression of FASTER Monitoring Tool

In response to an open-ended survey question, the overall impression of the FASTER monitoring tool was positive for 16 (40%) clinicians, not good for 8 (20%) and 16 (40%) did not notice a difference. Of those who reflected positively, the tool was described as an "innovative way for parents to get involved in the management process" and "an educative tool especially for parents who could identify danger signs." Clinicians who rated FASTER negatively felt it did not work and was challenging. Of those who did not notice a difference, 9 (23%) reported that they rarely saw a flag, either indicating the caregivers were in the control arm or the children were doing well enough that no flags were raised.

Feasibility of FASTER Monitoring Tool

Sixty-three (90%) caregivers reported that the FASTER training was easy to understand, whereas only seven caregivers (10%) described the FASTER training as "difficult" and "confusing" due

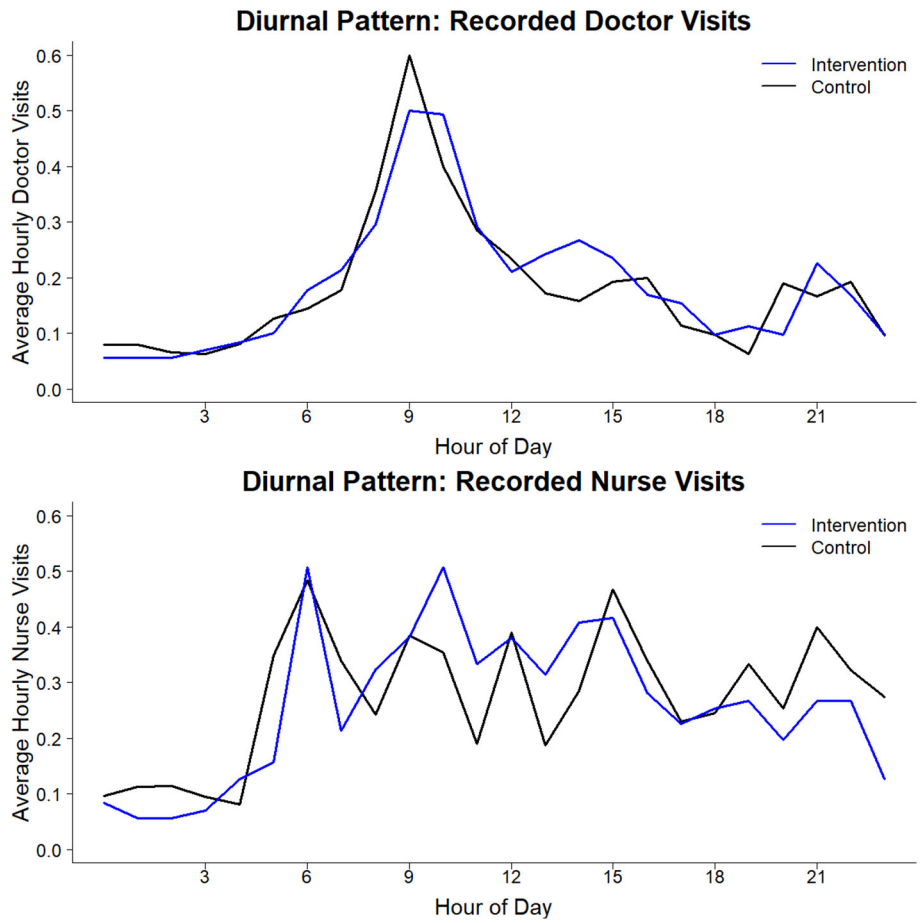

FIGURE 3 | Daytime pattern of clinician patient visits in intervention vs. control arm.

to the complexity of monitoring, especially respiratory status, and raising flags. However, these caregivers also explained that with concentration and repetition, monitoring became easier.

Fifty-one (73%) caregivers felt clinicians responded appropriately to FASTER flags when raised. Only 18 (26%) reported clinicians did not respond as anticipated, either due to lack of enough clinicians or responses were delayed or not as frequent as expected.

In an open ended question, the majority of clinicians [26 (65%)] felt that parents could capture their child's severity of illness and respond adequately all the time [23 (59%)] or sometimes [3 (8%)]. A minority of clinicians [9 (23%)] was concerned that parents became too emotional and interpreted it [FASTER monitoring tool] as a "death sentence."

Challenges of FASTER Monitoring Tool

When asked with closed ended questions regarding the challenges of the tool, increased workload and false signaling, including "parents not pulling down flags," were reported by 14 (35%) and 15 (38%) of clinicians, respectively. Seventeen health care providers (42%) felt the monitoring tool was challenging to use because parents became more demanding. Through open ended questioning, another 17 clinicians reported additional challenges in using the FASTER tool, including the flag system triggering very strong caregiver emotions, as the red flag "is a bad sign for their children" and "is like labeling a child very sick hence giving no hope."

While the majority of caregivers (39 [56%]) reported that the monitoring intervention did not need any modifications or improvements, several caregivers provided suggestions, including: (a) educate caregivers later in the admission once they are more "settled" (4 [6%]), (b) change the frequency and timing of monitoring, as monitoring hourly at night is very difficult (2 [3%]), (c) use a phone rather than flag to notify health care providers (1 [1%]), (d) provide more education to caregivers on how to intervene if a red flag is raised (2 [3%]), and (e) increase the monitoring performed by research staff or clinicians (3 [4%]).

Through open ended questioning, clinicians suggested improving the parental monitoring tool with additional education, training, and frequent reminders for both parents and clinicians (22 [55%]). Several clinicians (8 [20%]) also suggested using a different system than raising flags, given concerns about not seeing the flags in a timely manner, and that

a red flag may represent a "bad omen." They recommended using a bell or alarm system, especially when the hospital is busy.

Overall Value of FASTER Monitoring Tool in Resource Limited Settings

The majority of clinicians [33 (82%)] agreed the FASTER intervention would improve care of a very sick child in a resource limited setting. When asked to explain their reasoning, some clinicians (11 [28%]) mentioned the monitoring tool increased the involvement of caregivers by improving their knowledge and ability to identify early warning signs. As one clinician commented, "It will allow mothers to raise their concerns and hence appropriate interventions where necessary leading to better outcome[s]." Twenty (50%) clinicians felt the caregiver monitoring tool helped triage sicker patients first. One clinician stated, "It helps to signal the doctors that the patient/child needs urgent and quick medical attention which help[s] in early diagnosis and early management of the patient to save life." Another explained, "When the flag is put [up] it helps us know the most sick child immediately and we act on it." Seven (18%) clinicians found the parental monitoring tool especially helpful due to the scarcity of clinicians. As one clinician explained, "Since the health workers are limited, it [FASTER monitoring tool] would help in alerting where there is need."

All caregivers (70 [100%]) agreed that FASTER monitoring would improve care of a very sick hospitalized child in their setting. Caregivers provided multiple open-ended explanations, including that with the increased knowledge, they could monitor the progress of their hospitalized child better, communicate better with health care providers, and alert medical staff earlier when the child was sicker or in "danger" and "might save the child's life." Similarly, 70 (100%) caregivers agreed their FASTER skills would help them recognize a sick child in their community. Several caregivers (14 [20%]) recommended broadening the scope of the intervention to outside the hospital settings and to more mothers, because the knowledge gained was so "helpful" and empowering. One mother explained, "Mothers will be empowered to act fast when the child is not doing well." Another mother stated, "It enlightens you on how to be keen on monitoring your child. Even in the future it will still help me because I have learned."

DISCUSSION

This study did not find a difference in the frequency of clinician visits to the patients' bedsides between the FASTER intervention and control arms, nor was there a measurable health benefit in the study for patients receiving FASTER caregiver monitoring, although the study was a priori not powered to detect the latter and powered for a larger difference of the first. Refinement of the implementation process of the FASTER tool is needed to improve its effectiveness particularly through greater acceptability and adoption by clinicians. However, the results of this pilot study add to the evidence (14) that the FASTER bedside assessment tool is feasible for caregivers of hospitalized children in low-resource settings and the tool was overall rated positively by both caregivers and clinicians.

As described by Lambert et al., early warning tools are more than just a "score." They are part of a multifaceted "system" approach to improve child patient safety and clinical outcomes (17). Four integrated components are needed which work together to provide a comprehensive safety system for detection and management of the clinically deteriorating patient: (1) the afferent component which detects clinical deterioration and triggers an appropriate response such as the caregivers' FASTER flag; (2) the efferent component consisting of the medical personnel providing the response, (3) the process improvement component containing elements such as auditing/monitoring/evaluation to enhance patient care and safety and (4) the governance/administrative component focusing on the organizational leadership, safety culture, education and processes required to implement and sustain the system (18). How these four components relate to the current and possible future FASTER implementation at KNH will be described here.

Our data suggest, both through non completion overnight and caregiver feedback, hourly monitoring, especially at night-time, is difficult and a monitoring schedule every 2–4 h may be more feasible. In addition, FASTER flags were not always visible or noticed by clinicians and another form of alarm (bell vs. phone) may be necessary to better trigger the response arm, as suggested by both caregivers and clinicians. Cultural concerns of red flags seen as bad omen need to be further explored with caregiver focus group discussions. Discussing death and prognosis has been described as a cultural taboo in Kenya given concerns of associated stigma and "inviting death" (19). Implementation of FASTER monitoring with sufficient caregiver education on goals to hasten interventions and without the label of a red flag may help address this issue. Given recent data on mortality predictions scores improving by including at least one element of the four top categories of altered consciousness, vital signs, signs of respiratory distress and indicators of malnutrition, addition of mid-upper arm circumference is important to consider to increase sensitivity and specificity of the FASTER tool (20).

The differences in caregiver vs. clinician perceptions of the FASTER intervention may reflect the current paternalistic medical culture that is described at KNH and remains common in many parts of the world (21, 22). Through the FASTER monitoring, caregivers felt empowered and described a positive experience, whereas clinicians rated the intervention slightly less positively, describing one of the challenges of the tool as parents being "more demanding." Since the study lacked resources for extensive outreach and preparation of clinicians, they may have experienced FASTER as a disruption or potential threat. While caregivers appreciated engaging constructively in the medical care of their children, clinicians were caught off-guard interacting with newly educated caregivers who felt empowered in assisting with clinical triage. Other "care by parent schemes" in which parents would assist with some nursing aspects of their hospitalized children (such as measuring temperature, giving medications) have described increased caregiver satisfaction and

parents being capable of acceptable nursing care with little direction (23, 24). It is also possible, however, that caregivers did not feel comfortable sharing negative feedback regarding the monitoring tool as they shared their opinions through study nurses. Successful FASTER implementation may need to achieve improved "buy-in" from clinicians by emphasizing that the medical decision power remains with them, and that caregivers should be recognized as allies and assets, collecting data to help detect patient deterioration earlier so that medical interventions can be provided sooner. Hospital care with parental participation has previously been shown to help alleviate the workload of clinicians (25).

Despite resource limitations, clinicians focus their attention on the sickest children as indicated by the association between frequency of bedside visits and high Bedside PEWS and research team FASTER scores. Yet, given the observed 48 h case fatality rate, much higher than in high resource settings, FASTER caregiver monitoring with modified implementation strategies needs to be evaluated in a larger study to evaluate its effects on earlier recognition and management of clinical deterioration, especially at times with decreased clinician staffing. Based on suggestions from caregivers, expanding the educational aspects of the monitoring tool to mothers in the outpatient setting could lead to earlier medical care seeking in the course of illness, potentially leading to lower "early" fatalities.

The study was performed following a 100-day physician strike in Kenya and during a 151-day national nursing strike, in which the KNH nurses did not participate. Health care seeking behavior during the strike differed with pediatric patient volumes reduced by 20,000 compared to the prior year (26). Hence, the clinician response to the sickest patients may have been better during the study period as compared to the usual times with full volume pediatric wards. The diurnal pattern of physicians' visits, with their presence focused between 09:00 and 10:00 for ward rounds and then diminished during the rest of the day is consistent with many physicians leaving the government hospital for their other sites of employment, reinforcing the importance of developing alternative methods to closely monitor patients in the afternoon, evening, and night hours.

Other factors in addition to hierarchical relationships and competing clinician priorities that have hindered the implementation of clinical best-practices at KNH in the past will need to be addressed in order to improve both the efferent clinician response as well as the process improvement for delivery of the FASTER intervention. Relevant factors include; (1) poor communication between nursing staff and physicians and central administration, (2) lack of objective mechanisms for monitoring and evaluating quality of clinical care due to inadequacies in clinicians' self-regulation or motivation, (3) limited capacity for planning strategic change with chronic overcrowding of patients and staff being overworked, (4) limited management skills to introduce and manage change (21). Audit and feedback interventions with Kenyan pediatric health care providers and hospital administrators have, however, shown that they are committed to improving care, reinforcing quality standards, and enhancing team work (27). Utilizing different approaches that emphasize evidence in decision-making on innovation in healthcare might positively influence future FASTER implementation, e.g., with nurses in the acute sector shown to prefer a combination of practical ("how to") and scientific ("principles") knowledge, while medical professionals placing greater weight on the latter (28). Successful implementation of the FASTER tool in this complex environment will need to be more nuanced than simply training caregivers and clinicians. This will require working with focus groups of nursing, physician, and managerial stakeholders in addition to caregiver representatives to find culturally acceptable, effective, and sustainable ways to better integrate the FASTER tool into practice, achieve comprehensive buy-in and improve care.

There were several important limitations to this study. The study sample size was relatively small and limited to one site with a complex environment. Furthermore, the much lower prevalence of "red-flag" assessments meant that it was only powered to detect a very large intervention effect. The study was performed in a chronically strained healthcare system that had recently gone through further challenges following a prolonged physicians' strike. The study occurred during Kenya's presidential elections, during which political crises and violence led to medical and study staff intermittently not coming to work. Given the political situation and health care provider strikes, patient volumes were lower than usual. Hourly data collection by caregivers, especially at night was limited, likely secondary to caregiver fatigue and stress. This resulted in some missing data, including missing-data disparities between arms, making interpretation of results more difficult. Pediatric admission distribution rotating between four different wards led to decreased total exposure of the FASTER intervention per clinician and may have fostered unfamiliarity with the study and decreased recognition and response to caregiver flags. Clinician training was performed at the beginning of the study only, without auditing or performing further process improvements during the intervention period which may have contributed to decreased clinician participation in FASTER flag recognition. Caregiver survey responses about FASTER could be biased secondary to the interview process by study nurses.

Inpatient mortality remains unacceptably high in many low-income settings. The significant strains placed on limited numbers of clinicians suggest that interventions supporting the recognition of clinical deterioration may be beneficial. The FASTER tool appears to be feasible to implement but did not lead to a difference in the frequency of clinician visits to the patients' bedsides compared to the control arm. However, caregivers reported they felt empowered by the tool and requested that the scope of the intervention be expanded to outside the hospital setting. Additional studies of the FASTER tool following modifications to improve fidelity may improve effectiveness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available from the authors upon receipt and approval of a written request pursuant to the study data management sop.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee and Seattle Children's Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AS, RK, AO, JZ, and JW contributed to conception and design of the study. AS and RK implemented the study. Q-UN and DM assisted in the implementation process. AO organized the database and performed the statistical analysis. JC and BW performed the qualitative data analysis. AS wrote the first draft of the manuscript. AO and JC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.804346/full#supplementary-material

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