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Evidenced based medical care of hospitalized children with local adaptations in low-resource settings

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Evidenced based medical care of hospitalized children with local adaptations in low-resource settings

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Editorial: Evidenced based medical care of hospitalized children with local adaptations in low-resource settings

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Editorial on the Research Topic
Evidenced based medical care of hospitalized children with local adaptations in low-resource settings

The series of articles recently published in Frontiers in Pediatrics explored *evidence-based medical care of hospitalized children with local adaptations in low-resource settings*. Successful implementation of life saving medical care for children in local settings was described by Satrom et al. and Wu et al.. Gaps in implementation of diagnostic and therapeutic modalities to prevent childhood morbidity and mortality were clearly illustrated in the studies from Han et al., Menalu et al., Villanueva-Uy et al., and Ba-alwi et al.. We were encouraged to see the innovations captured by recent advances in the identification of neonatal jaundice and the prevention of acute bilirubin encephalopathy (Satrom et al., Villanueva-Uy et al.); and ingenuity, well described by Wu et al. as they highlighted new methods to breathe for infants and children who would otherwise die due to acute respiratory failure secondary to prematurity or lower respiratory tract infections.

The pivotal role of education was emphasized including maternal and village health workers' education in the recognition of neonatal jaundice and neurological dysfunction (Satrom et al.); the creative adaptation of virtual education across continents reported by Le Pichon to train physicians who do not have access to sub-specialty expertise in their own locale (Le Pichon et al.); and partnership was beautifully illustrated by Fant et al. as they reported on the Maseno University-Northwestern University simulation-based medical education collaborative. Household education and prevention were also emphasized in the study of the epidemiology of burns in central China by Han et al.. Neonatal survival studies from Ethiopia and Tanzania highlighted the ongoing challenge of improving newborn survival (Menalu et al., Ba-alwi et al.). Both captured the need for early intervention and treatment.

Prevention is the focus of our specialty as pediatricians and vaccines are our most powerful weapon to prevent infectious diseases and their morbidity and mortality as in the case of the multisystem inflammatory syndrome of COVID. Douangboupha et al. call

for expanded access to SARS-CoV-2 vaccine for children in addition to equitable care for children no matter where they live especially in resource limited settings.

The common thread through all these reports from Asia and Africa is implementation of what we already know works to save the lives of children no matter where they live. There are many barriers to this goal. One challenge is assuring that every child has access to prevention, which is often as simple as maternal education about how to child proof the home to prevent burns and as complicated as barriers to available, accessible, affordable, and effective vaccines. State of the art laboratories are woefully limited in many parts of the world. Availability, accessibility, and affordability of life saving medicines are a barrier to implementation of evidence-based treatment, insulin being a prime example throughout the world.

Authors from Asia, Africa and North America are represented in these studies/publications which remind us of how creative, innovative, ingenious, and relevant we can be in pediatric medicine across the globe. We are also reminded of the inequities in parental education, sub- specialty training, laboratory diagnosis, and medical care. Implementation science is the frontier we as pediatricians need to fully engage across multiple disciplines including political and economic disciplines with innovation and determination in ethical and sustainable partnerships if we are to close every gap identified in these studies. Filling these gaps requires the interdisciplinary expertise of individuals from resource limited areas of a country or continent to be fully funded and in leadership roles to direct implementation research with the goal of adapting the wealth of evidence based medical care for hospitalized children to the local community of every child. Working together in truly equitable, ethically sound partnerships across the globe we can tackle the challenges to health and well-being our children face as demonstrated in this series of articles.

Author contributions

All 4 editors wrote this publications and agree with its publication.

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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Epidemiological and Clinical Characteristics of 5,569 Pediatric Burns in Central China From 2013 to 2019

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Background: Pediatric burns of all the ages are prevalent worldwide, posing a severe health risk to children. This study aims to examine pediatric burns' clinical characteristics and epidemiology in central China.

Methods: The pediatric patients of the Burn Research Center, Department of the First People's Hospital of Zhengzhou City from 2013 to 2019 were retrospectively studied and the relevant data were collected from the hospitalized medical records [e.g., demographic, etiology, length of stay (LOS), age, gender, burn area and depth, number of surgeries, cost, and outcome].

Results: A total of 5,569 pediatric burn patients were included, accounting for 43.9% of the total burn population. Electric burns represented a relatively small proportion (1.17%) but were more likely to lead to disabilities or death than scalds (90.63%) and flames (5.12%). The median age was 2 years [interquartile range (IQR): 1–4] and the boys/girls ratio ranged from 1.3:1 to 1.6:1. The most commonly burnt anatomic sites were the limbs (38.3%), with a median %TBSA (total body surface area) of 6 (IQR: 4–10). The complications of shock and pneumonia accounted for 7.6 and 19.2%, respectively. The peak months of pediatric burns included January, May, and August and the rural/urban ratio reached 1.61:1. The percentage of burn wounds treated surgically increased considerably from 2013 to 2019 (3.8 vs. 37.8%). The median hospital LOS was 15 days (IQR: 8–28 days), with the three high-risk factors (e.g., more surgeries, more %TBSA, full-thickness skin burns). The median cost of hospitalization was 1,511 USD (IQR: 848–2,648 USD) and the main risk factors consisted of full-thickness burns, more %TBSA, longer LOS, and more surgical procedures. Among all the patients, LA50 was 78.63% (95% CI = 75.12–83.45) and the overall mortality reached 0.1% since seven deaths were recorded.

Conclusion: Scalds, flames, contact, and chemicals are the main causes of burns among children aged 1–5 years in central China. Accordingly, various prevention strategies should be employed depending upon the cause of the burn.

Keywords: epidemiology, pediatric, burns, outcome, prevention, cost

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INTRODUCTION

Burns have become the fifth most common cause of nonfatal injuries to children (1). Globally, burns have gradually become a hotspot of public health concern, not just affecting any particular population or region (1–5). Moreover, in hospitalized burn patients, those aged 0 to 5 years represent the highest percentage (6). Scald is the most common type of pediatric burn, followed by flame, contact, chemical, etc. (4). The incidence of burns seems to be closely related to a region's economic development. Pediatric burn occurs much higher in low- or middle-income nations (e.g., Southeast Asia and Africa), whereas it has been declining in the United States over the past decade (7), which is consistent with the previous reports from north China (8), southwest China (9), and south-central China (10). Nevertheless, no relevant reports remain on central China, which prompted us to conduct this survey.

The Burn Research Institute of Zhengzhou First People's Hospital is regarded as an essential center in central China for burn diagnosis and treatment, which comprises 136 beds [includes 10 intensive care unit (ICU) beds]. The institute is located in Henan Province. The large population of over 100 million in this province results in a relatively high incidence of burns. This study primarily involves patients from Henan Province, western Anhui Province, southwestern Shanxi Province, etc. Though pediatric burns account for more than 43% each year, epidemiological investigations and studies have been rare. Using specific epidemiology as the basis, we can effectively prevent pediatric burns, increase the cure rate, and reduce medical expenses (11). To further improve the effectiveness of prevention strategies and therapeutic schemes in central China, the epidemiology and treatment of burns in children hospitalized between January 2013 and December 2019 should be carefully examined.

METHODS

From 2013 to 2019, data were collected on 5,569 burn children hospitalized at the Burn Research Center of Zhengzhou First People's Hospital. In addition, all the data were extracted from the electronic medical record system. The data consisted of ages, genders, dates of injury, dates of admission, burn etiology, %TBSA, burn depth and site, inhalation injuries, number of surgeries, and medical costs. Moreover, clinical outcome, length of stay (LOS), and date of hospital discharge were noted. Based on the collected data, the Burn Index (BI) (12) and the modified Baux score (13) were calculated. The Abbreviated Burn Severity Index (ABSI) (14) scoring system was cited for all the cases to achieve more rigorous results. The results of patient treatment are presented below. As an outcome, "healing" was defined as the wound completely healing with no remnant burned area remaining; as "improvement" for reduced, but not cleared burn areas; as "ineffectiveness" for exacerbation of the burn; and as "death" for the patient's condition worsening and dying (9). Pediatric burns are at high risk of shock, if the following factors are present: a burned area of 10% TBSA or greater, the third-degree burn area of 2% or greater, inhalation injury or exceedingly deep burns (e.g., 4th-degree injuries), and urine output $<$ 1 ml/kg/h (15–17). Pneumonia is most commonly diagnosed in patients who have fever, cough, tachypnea, rales, chest radiographic consolidation, or infiltrates (18).

The Ethical Review Committee of Zhengzhou First People's Hospital has approved this article concerning a longitudinal and retrospective study. Informed consent was not required on account of the study's retrospective nature.

Statistical Analysis

Microsoft Excel 2010 (Microsoft) was used to organize and categorize data, while calculating the descriptive data [e.g., median, SD, average, interquartile range (IQR)]. In addition, GraphPad Prism 8 (GraphPad Software Incorporation, USA) and SPSS version 20.0 software (IBM Corporation, USA) were used to analyze the statistics. The chi-squared test, the Mann–Whitney *U*-test, and the Kruskal–Wallis test were performed to detect the different groups of nonnormally distributed categorical or quantitative variables. Furthermore, the Dunn's test was performed *post-hoc* to compare the two groups. Using the Fisher's exact test for the chi-squared test if the theoretical frequency is <5 or total samples are fewer than 40. ANOVA with one way and Scheffé's test were conducted to compare mean differences between groups of quantitative variables with normal distributions. Multiple linear regression was utilized to analyze the risk factors associated with LOS and total medical costs. Statistical significance is determined by a $P < 0.05$.

RESULTS

General Characteristics

Table 1 summarizes the general characteristics of all the inpatients enrolled in this study. In total, 5,569 pediatric patients in the burn center were investigated for this study from January 2013 to December 2019 (43.9% of 12,665 patients). In 7 years, no significant difference has been observed in the number of burn patients hospitalized. In general, the average age of all the pediatric burn patients was 3.72 $\pm$ 3.05 years, ranging from 1 month to 14 years. Incidence of burns peaked in 2018 and nadir in 2016 (**Figure 1A**). Burns peaked in January, May, and August, whereas they declined to a minimum in November and December (**Figure 1B**). Over the past 7 years, the gender ratio has been relatively constant at 1.4:1. The ratio reached its maximum in 2016 (**Figure 1C**). Approximately, 7.6% of all the inpatients were accompanied by shock, with the maximum incidence occurring in 2015. Furthermore, pneumonia was the most common postinjury morbidity, with the highest percentage found in 2017. The median LOS was 15 days, ranging from 1 to 90 days. Overall, the cure and response rates were 86.3 and 98.5%, respectively. Surgery rates for all the inpatients were 13.3% and the number of pediatric burn surgeries increased significantly from 2013 to 2019. Seven deaths were reported from all the patients, accounting for 0.1% of the total mortality.

Residential Areas

The prevalence of pediatric burns in different habitation areas in the same geographical area varied markedly,

TABLE 1 | Patient characteristics from 2013 to 2019.

Years	Pediatric[a]	Age median (IQR)	Boys /Girls	Shock *N* (%)	Pneumonia *N* (%)	LOS median (IQR)	Cure rate *N* (%)	Response rate *N* (%)	Surgery *N* (%)	Mortality *N* (%)
2013	796 (44.7)	2 (1–3)	1.3:1	51 (6.4)	153 (19.2)	12 (7–12)	693 (87.1)	784 (98.5)	30 (3.8)	0 (0)
2014	838 (46.8)	2 (1–4)	1.4:1	53 (6.3)	135 (16.1)	13 (8–22)	681 (81.3)	827 (98.7)	45 (5.4)	1 (0.1)
2015	802 (46.0)	2 (1–4)	1.3:1	74 (9.2)	155 (19.3)	13 (8–22)	731 (91.1)	793 (98.9)	106 (13.2)	1 (0.1)
2016	736 (43.6)	2 (1–3)	1.6:1	59 (8.0)	121 (16.4)	14 (9–25)	614 (83.4)	722 (98.1)	89 (12.0)	0 (0)
2017	743 (42.1)	2 (1–3)	1.4:1	55 (7.4)	178 (24.0)	18 (10–31)	647 (87.1)	736 (99.1)	112 (15.0)	2 (0.3)
2018	847 (43.1)	2 (1–4)	1.5:1	69 (7.4)	143 (16.9)	17 (10–31)	736 (86.8)	835 (98.6)	121 (14.3)	2 (0.2)
2019	807 (41.5)	2 (1–4)	1.4:1	62 (7.7)	185 (22.9)	16 (10–28)	706 (87.5)	788 (97.6)	305 (37.8)	1 (0.1)
total	5,569 (43.9)	2 (1–4)	1.4:1	423 (7.6)	1,070 (19.2)	15 (8–28)	4,808 (86.3)	5,485 (98.5)	808 (13.3)	7 (0.1)
P-value	0.005	0.314	1.00	0.305	<0.001	0.02	<0.001	0.291	<0.001	0.767

[a]*Hospitalized pediatric burns of 0–14 years old (exclusion of patients discharged within 24 h). IQR, Interquartile range.*

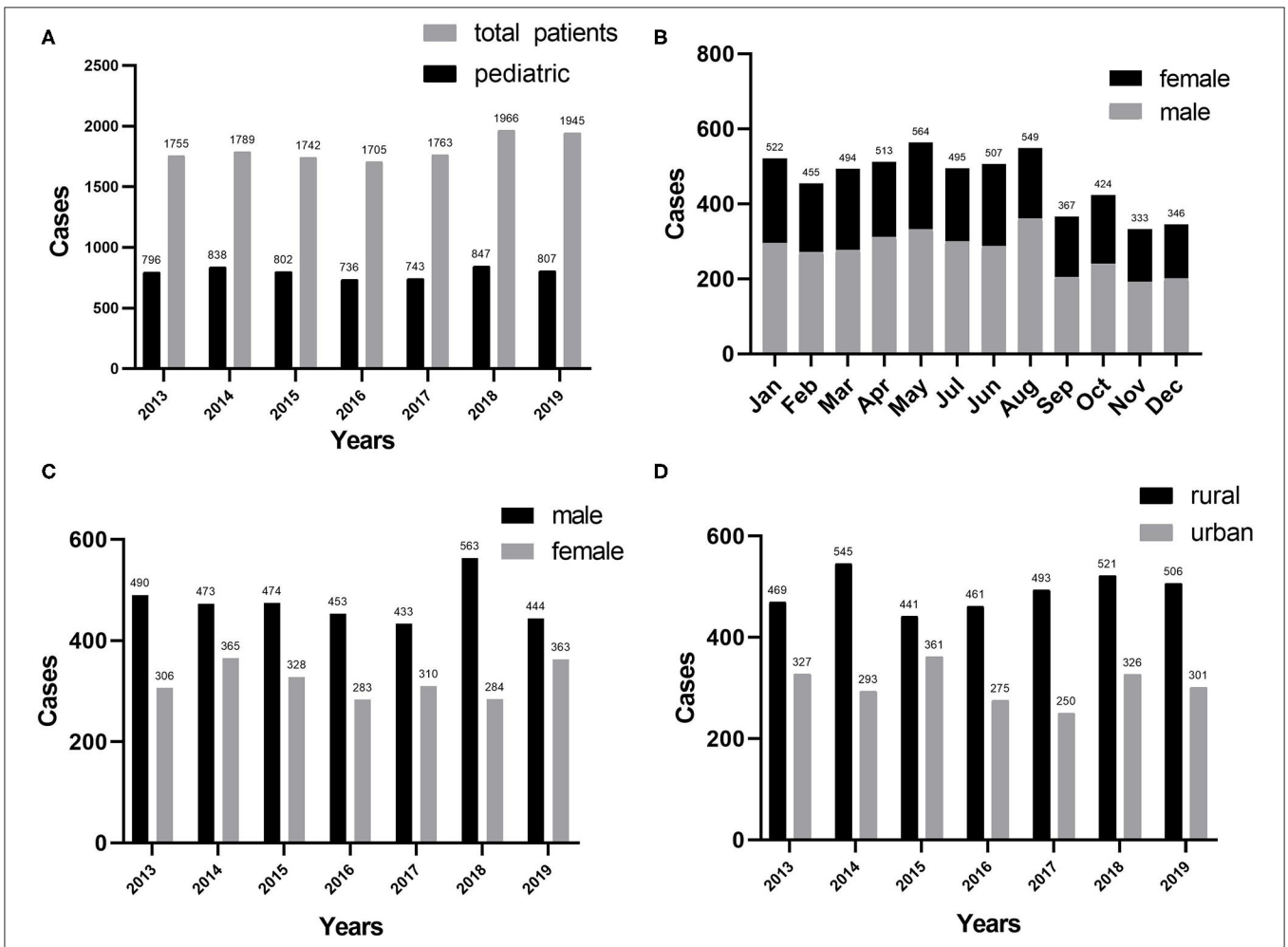

FIGURE 1 | (A) Distribution of pediatric burns ($n = 5{,}569$) by years. **(B)** Pediatric burns by month. **(C)** Distribution of gender by years. **(D)** Regional distribution by years.

with 38.30% in the urban area and 61.70% in the rural area (using the residential address to distinguish rural from urban). Approximately, 1.97:1 was the maximum rural–urban ratio for 2017, 1.22:1 was the minimum rural–urban ratio for 2015, and the average ratio over the past 7 years was 1.61:1. The incidence of burns among children in the rural and urban areas differed significantly ($P < 0.05$) (**Figure 1D**).

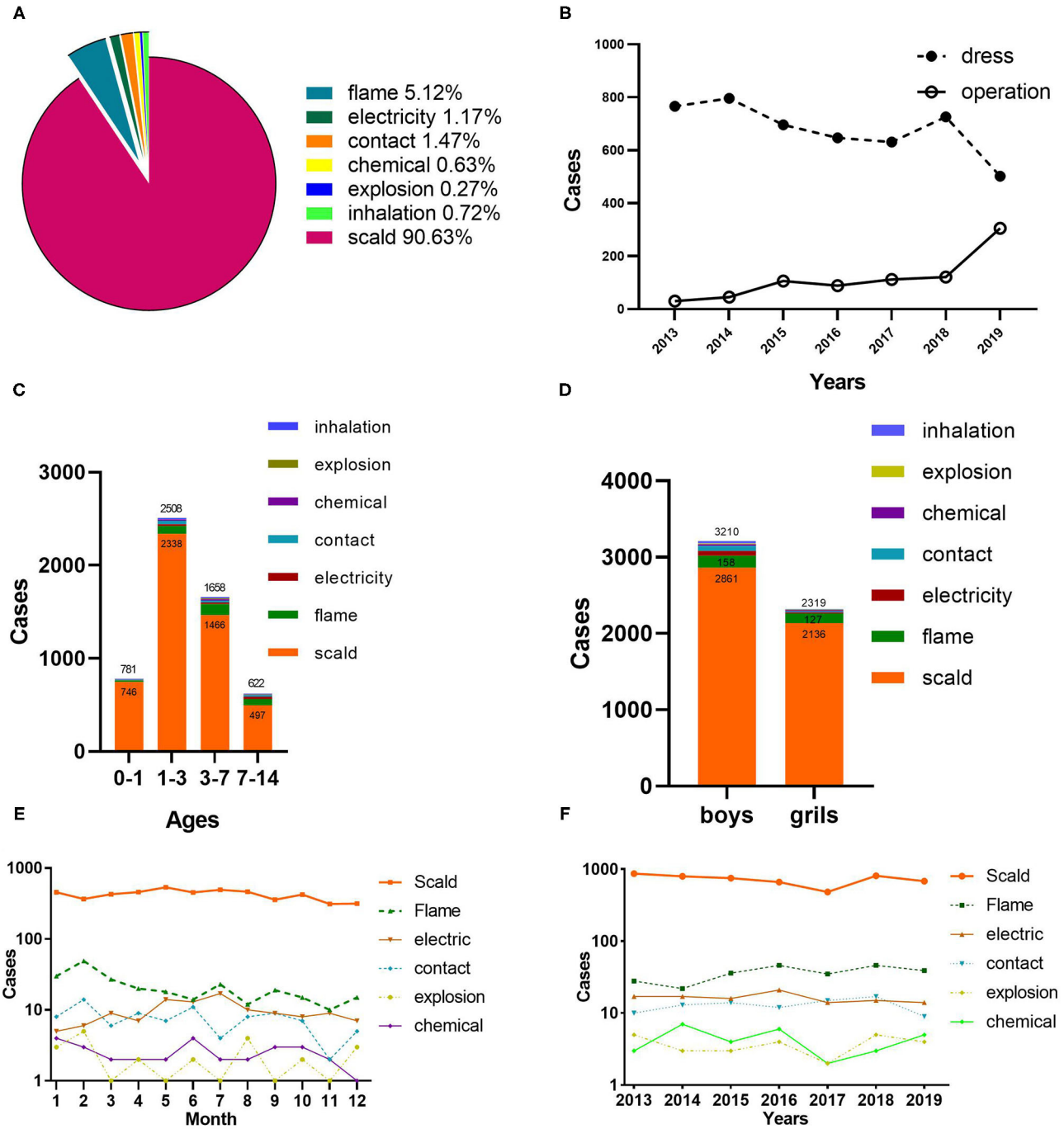

FIGURE 2 | Etiology analysis and therapeutic schedule. **(A)** The proportion of different causes of burns. **(B)** Therapeutic schedule by years. **(C)** Etiology distribution by age. **(D)** Gender distribution of etiology. **(E)** Month distribution of etiology. **(F)** Distribution of etiology by years.

Etiology of Burn Injuries

Scald accounted for most pediatric burns (90.63%), followed by flame (5.12%). In addition, electricity injury, thermal contact injury, chemical burns, explosion injury, and inhalation injury occupied 1.17, 1.47, 0.63, 0.27, and 0.72%, respectively (**Figure 2A**). 65 patients with electrical burns consist of 42 current burns and 23 arc burns. Flame and scalding were the primary causes of burns in all the age groups. Contact and electric burns were less common in the 0–1 age group, whereas they were the third and fourth causes of burns in the other groups, respectively (**Figure 2C**). The gender ratio was also distinct by etiology. Electric burns achieved the maximum

TABLE 2 | Distribution of factors related to hospitalization.

	LOS (days) median (IQR)	LOS/TBSA (days) median (IQR)	Surgery (%)	Surgery no. median (IQR)	Cured *n* (%)	Death *n* (%)	Cost (USD) median (IQR)	Cost/TBSA (USD) median (IQR)
Etiology								
Scald	14 (8–25)	2.1 (1.1–4.3)	484 (9.7)	0 (0–1)	4,180 (83.8)	4	1,512 (855–2,630)	242 (117–461)
Flame	18 (9.75–33)	2.4 (1–7)	55 (21.9)	0 (0–1)	206 (82.1)	3	1,451 (723–2,649)	231 (87–485)
Contact	14 (7.5–25)	3.8 (1.2–12.3)	13 (11.5)	2 (1–2)	92 (81.4)	0	1,414 (643–2,760)	446 (117–1,383)
Electric	24 (13–34)	13.5 (1.3–45.5)	38 (36.9)	1 (1–2)	86 (83.5)	0	1,831 (963–4,210)	874 (164–4,726)
Chemical	14 (7–20)	4.7 (1.3–9.5)	6 (15)	0 (0–1)	31 (77.5)	0	1,374 (872–2,380)	349 (215–1,681)
Explosion	15 (6–28.5)	1.5 (0.7–2.4)	4 (25)	0 (0–1)	8 (50)	0	1,167 (485–2,405)	201 (99–227)
P-value	<0.001	<0.001	<0.001	<0.001	0.103	0.012	0.131	<0.001
Gender								
Girls	14 (7–20)	2 (1–4)	603 (22)	0 (0–0)	2,268 (82.1)	5	1,548 (851–2,755)	238 (173–483)
Boys	15 (8–25)	2 (1–5)	678 (24.7)	0 (0–0)	2,262 (82.4)	2	1,483 (851–2,545)	254 (124–482)
P-value	0.535	<0.001	0.376	0.318	0.471	0.209	0.268	0.025
Age (years)								
0–1	15 (8–26)	2 (1–4)	141 (18)	0 (0–0)	632 (80.8)	0	1,545 (781–2,825)	240 (111–428)
1–3	15 (9–26)	2 (1–5)	701 (28.5)	0 (0–0)	2,016 (75)	5	1,412, (806–2,411)	230 (101–491)
3–7	8 (14–24)	2 (1–5)	276 (16.6)	0 (0–0)	1,378 (82.7)	1	1,436 (793–2,505)	227 (97–494)
7–14	13 (8–26)	2 (1–5)	231 (37.7)	0 (0–0)	515 (84.2)	1	222 (763–2,493)	120 (94–496)
P-value	0.041	0.011	<0.001	<0.001	0.250	0.100	<0.001	0.002
TBSA								
0–10	13 (8–24)	3 (1–6)	939 (22.4)	0 (0–0)	3,448 (82.2)	0	1,419 (818–2,427)	296 (157–580)
11–20	17 (10–28)	1 (1–2)	216 (21.4)	0 (0–0)	830 (82.3)	0	1,870 (1,112–3,614)	126 (72–255)
21–30	25 (14–42)	1 (1–2)	53 (27.6)	0 (0–0)	156 (81.3)	3	1,801 (954–6,395)	76 (39–223)
31–50	32 (20–55)	1 (1–1)	30 (41.1)	0 (0–0)	62 (84.9)	2	297 (112–640)	49 (17–113)
51–100	30 (12–69)	0 (0–1)	43 (98.6)	0 (0–2)	35 (77.8)	2	295 (151–568)	24 (11–55)
P-value	<0.001	<0.001	<0.001	<0.001	0.882	<0.001	<0.001	<0.001
Full thickness burns								
With	28 (16–43)	5.5 (2–13)	198 (39.3)	0 (0–1)	402 (79.3)	5	1,341 (733–2,379)	197 (85–469)
Without	14 (8–24)	2 (1–4)	390 (7.1)	0 (0–0)	4,126 (82.5)	2	1,826 (1,081–3,059)	299 (187–494)
P-value	<0.001	<0.001	<0.001	<0.001	0.005	0.416	<0.001	<0.001
Surgery no.								
0	13 (8–22)	2 (1–4)	0 (0)	0 (0)	3,967 (81.2)	6	1,348 (793–2,193)	216 (104–397)
1	29 (22–38)	5.7 (3.4–10.3)	297 (100)	1 (1)	268 (90.2)	1	3,629 (2,816–4,794)	722 (468–1,091)
2	38 (25–50)	5 (2.8–8.7)	173 (100)	2 (2)	152 (87.9)	0	6,292 (3,866–8,626)	740 (495–1,315)
≥3	43 (28–57)	3.3 (1.7–8.3)	157 (100)	3 (3)	141 (89.8)	0	10,569 (8,515–14,148)	950 (593–2,271)
P-value	<0.001	<0.001	-	-	<0.001	0.004	<0.001	<0.001

LOS, LOS/TBSA, Surgery no., Cost, Cost/TBSA are all expressed in median (IQR: Interquartile range).
Surgery, cured, and Death are all expressed in N (%).
$p < 0.05$ were considered statistically significant.

ratio of 5.3:1.0, followed by contact burns (3.8:1.0), inhalation (3.4:1.0), explosion (2.8:1.0), and chemical (1.5:1.0). Moreover, the lowest proportions were observed for scald burns (1.3:1.0) and flames (1.2:1.0) (**Figure 2D**). Epidemic peaks of burns caused by different etiologies were observed during multiple periods. High-incidence periods for flames were found to be January and February, while scald burns were seen to be May, July, and August. Furthermore, July was distinguished as the peak period for electrical burns. It is noteworthy that scald burns accounted for the maximum proportion of all the months (**Figure 2E**). From 2013 to 2019, scald burns showed a figure of a wave. However, the trends of other etiologies fluctuated insignificantly (**Figure 2F**).

Wound Treatment Methods and Surgeries

Figure 2B indicates that wound dressing was the primary treatment for burn wounds, whereas only 30 patients (3.8%) underwent surgery in 2013. In contrast, the surgical treatment significantly increased by 37.8% in 2019. Debridement and skin grafting were highly correlated with cause, age, full-thickness burns, and TBSA among children with burns, with 23.2% of all the patients undergoing surgery (**Table 2**). The majority of

TABLE 3 | Burn site distribution by etiology.

Etiology	Scald	Flame	Contact	Chemical	Electricity	Explosion	Total	*P* value
Limbs	3,287	72	24	6	11	3	3,403	<0.001
Trunk	1,860	119	31	6	9	6	2,031	
Head/Face/Neck	1,458	63	4	8	5	5	1,543	
Hip/Perineum	686	14	6	3	3	1	713	
Hands	499	82	33	14	43	7	678	
Feets	453	38	7	2	6	2	508	

operations involved electric burns, whereas scalds were the least common ($p < 0.01$). The percentage and frequency of operations did not differ statistically significantly between boys and girls ($p = 0.376$). With the increase in TBSA, the frequency of operations and the proportion of patients undergoing operations generally increased ($P < 0.001$). The numbers of surgeries were highest in children aged 0–1 years, while surgeries percentage in children aged 7–14 years was the largest ($P < 0.001$). In the recent years, the frequency and proportion of surgeries in children with full-thickness burns have increased dramatically ($p < 0.001$).

Outcomes

According to this article, the number of operations and full-thickness burns could significantly affect the cure rate. However, no significant difference was found among etiologies, gender, age, and TBSAs (**Table 2**). The cure rate was the maximum in the 7–14-year age group, yet the minimum in the 1–3-year age group ($P = 0.250$). The cure rate showed a roughly increasing trend as the TBSA increased, but it had the minimum for the TBSA higher than 51% ($p < 0.001$). The patients without full-thickness burns achieved higher cure rates than those with full-thickness burns ($P = 0.005$). In addition, the cure rate of children undergoing surgeries had increased distinctly ($P < 0.001$). As indicated by the results of this article, the mortality was extremely low (0.1%) since only 7 of the 5,569 patients died. No significant difference was reported in the distribution of mortality for ages, genders, and etiology, whereas the difference between TBSA ($P < 0.001$) and frequency of operations ($P = 0.004$) was statistically significant.

Burn Sites

Table 3 lists the distribution of the etiology and burn sites. The most common anatomical part of burns was the limb, accounting for 38.3% of hospital patients. The trunk acted as the second burn site (22.9%), followed by the head, the face, and the neck (17.4%). Diverse etiologies of burns could significantly damage different anatomical parts ($P < 0.001$). Besides the flame that principally damaged the trunk, other burns chiefly damaged the limbs. Scolding and electricity were more likely to cause hand burns. Moreover, flames and scalding also resulted in injuries to the head, face, neck, hips, feet, and perineum.

Burn Severity

Most patients found deep partial-thickness and full-thickness for the maximum burn depth (**Figure 3A**). According to **Figure 3B**, the median TBSA was 6% (IQR: 4–10%). Patients with TBSA 0–10% and 11–20% accounted for 83.2 and 12.5%, respectively. Manifestations of TBSA vary markedly in etiology and age (**Table 3**). The Baux score ranged from 1 to 117, with a median of 7 (IQR: 4–11). According to **Figure 3C**, patients with a Baux score <30 were the majority (5,353/5,569, 96.12%), indicating that the mortality was not larger than 1%. The ABSI ranged from 1 to 13 and its median was 6 (IQR: 4–8). Patients with ABSI of 2–3 and 4–5 were 80.19 (4,466/5,569) and 16.30% (908/5,569) (**Figure 3D**), so the probability of surviving was estimated to be 99 and 98%, respectively. The average BI was 4.16 ± 5.19 (median: 3), ranging from 0 to 92. The patients with a BI of <10 accounted for 93% and 43 (5,203/5,569) (**Figure 3E**). The etiology was significantly correlated with the burn severity scores ($p < 0.001$; **Table 4**). Flame burns were significantly higher than other burns for ABSI, Baux score, and BI ($p < 0.001$; **Table 4**). Notably, girls had higher TBSA than boys ($p < 0.001$; **Table 4**). Baux scores were not statistically different with genders. The explosion and flame burns achieved the highest ABSI and Baux scores, whereas the lowest Baux score and BI were electrical burns and chemical burns, respectively, and no statistical difference was found. Obviously, the ABSI score was the highest in the 7–14-year age group ($p < 0.001$; **Table 4**). Moreover, among all the groups, the 3–7-year age group had the maximum BI ($p < 0.001$; **Table 4**). Furthermore, the ABSI and BI did not vary significantly from 2013 to 2019, whereas the TBSA and Baux scores were higher than those of other years ($p < 0.001$; **Table 4**).

Risk Factors Correlated With LOS

The IQR for LOS ranged from 8 to 25 days, with a median of 15 days. **Table 5** lists the distribution of LOS and LOS/TBSA. **Table 6** presents the multiple linear regression of LOS-related factors. Among all of the mentioned elements, more operations could prolong LOS to the greatest extent (standardization factor = 0.273, $P < 0.001$) and the next one was larger TBSA (standardization factor = 0.152, $P < 0.001$). In accordance with the LOS/TBSA analysis results, electric burns were most prominent in the longest LOS, followed by flame burns (**Table 4**, $p < 0.001$). Nevertheless, the distribution of LOS and LOS/TBSA was not significantly different between genders or ages.

Factors Correlated With Treatment Costs

The inpatient cost IQR was 845–2639 USD (median: 1,506 USD). **Table 2** illustrates the cost and the cost/TBSA distribution. **Table 6** lists the results of multiple linear regression in the cost analysis. Medical expenses increased with the length of

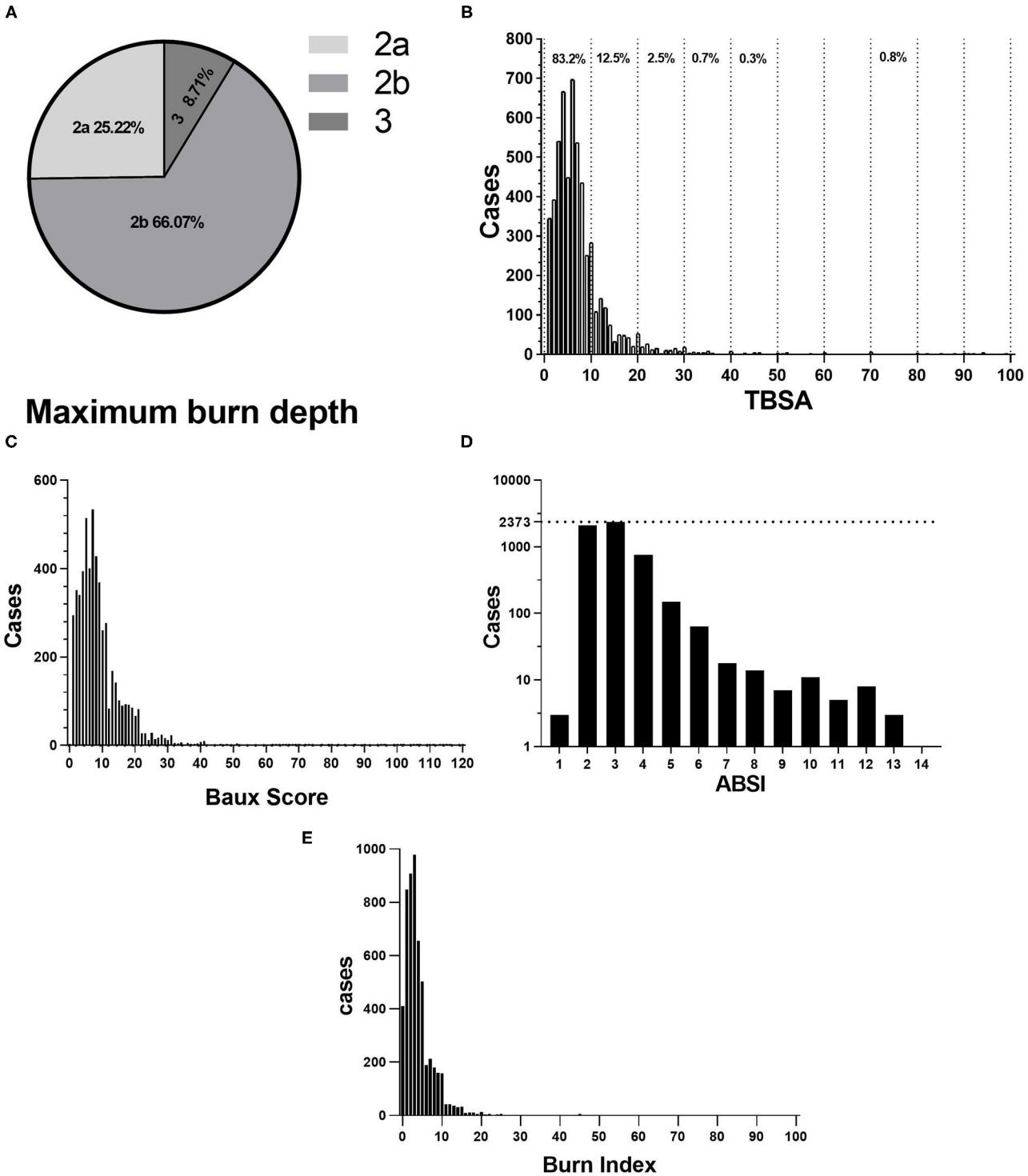

FIGURE 3 | (A) Proportion of Maximum burn dept. 2a for superficial partial-thickness burns, 2b for deep partial-thickness burns, 3 for full-thickness burns. **(B)** Distribution of TBSA. **(C)** Distribution of Baux score. **(D)** Abbreviated Burns Severity Index (ABSI). **(E)** BI.

hospital stay (standardization factor = 0.99, $P < 0.001$). With the increase in the number of operations (standardization factor = 0.177, $P < 0.001$), the statistical results revealed the statistically significant difference ($P < 0.001$), the cost of medical gradually increased, followed by larger TBSAs (standardization factor = 0.076, $P < 0.001$). Among the different etiology of burns, electric

burns cost and cost/TBSA were more than those of other burns. Furthermore, the cost of patients with full-thickness burns was significantly higher than that of patients without it (**Table 2**; $p < 0.001$). Besides, the cost among different ages was significantly different. The 3–7-year group was the highest, whereas no significant difference was reported between genders.

TABLE 4 | Burn severity median (IQR) display.

	TBSA median (IQR)	ABSI median (IQR)	Baux score median median (IQR)	Burn index median (IQR)
Etiology				
Scald	6 (4–10)	5.5 (4.1–7.3)	7 (5–11)	3 (1–5)
Flame	6 (4–13)	7.9 (6–11.98)	7.5 (4–17)	3 (1–7)
Contact	4 (1–9)	6.1 (5–8.35)	4 (2–10)	2 (1–5)
Electric	2 (1–8)	7.1 (6–12)	3 (2–9)	1.5 (1–4)
Chemical	4 (1–7)	6 (4.45–8.70)	4 (2–8)	1 (1–4)
Explosion	8 (4–14.5)	8 (6.4–13.5)	9 (5–15.5)	3 (1–12.5)
P value	<0.001	<0.001	<0.7g001	<0.001
Gender				
Girls	7 (4–12)	6 (5–8.7)	8 (5–12)	3 (2–5.5)
Boys	6 (4–10)	6 (3.9–7)	7 (4–11)	3 (1–5)
P value	0.001	<0.001	0.013	<0.001
Age (years)				
0–1	7 (4–10.25)	4 (3–4)	8 (5–12)	3 (2–5)
1–3	6 (4–10)	4.9 (4–5.5)	7 (5–11)	3 (1–5)
3–7	7.3 (7–8.9)	4 (3–4)	8 (5–12)	14 (8–24)
7–14	6 (4–10)	14 (12–15)	7 (3–13)	3 (1–5)
P value	<0.001	<0.001	<0.001	<0.001
Years				
2013	9 (5–15)	6 (5–7)	10 (6–16)	5 (3–8)
2014	8 (4–14)	6 (5–11)	8 (5–14)	4 (2–7)
2015	7 (3–10)	7 (6–9)	8 (4–11)	4 (2–5)
2016	6 (4–9)	5 (4–7)	7 (4–10)	2 (0–3)
2017	6 (4–9)	4.8 (4–6.7)	7 (4–11)	2 (1–4)
2018	6 (4–8)	4.7 (4–6.3)	7 (4–9)	2 (1–4)
2019	6 (4–8)	4.9 (4–6.65)	7 (4–9)	3 (1–4)
P value	<0.001	<0.001	<0.001	<0.001

IQR, Interquartile range.
$p < 0.05$ were considered statistically significant.

LA50 and the Details of 7 Deaths

LA50 results indicate an upward trend with increasing age (**Table 7**). **Table 8** shows the details of the seven deceased patients. Three cases involved flame burns, while four were scalding burns. The shortest admission time following a burn injury was 2 h, while the longest was 6 days. TBSAs were >20% in all the patients. Four patients had combined inhalation injuries and MODS was the most common cause of death.

DISCUSSION

The cognitive capacity of children for understanding risk factors is inadequate. The risks they face daily may result in burns. Severe burns can permanently harm a child's body, causing crippler or death (19). Consequently, an epidemiological survey of pediatric burns should be conducted. The critical link is how to evaluate the efficacy of existing burn precautionary measures and implement effective personalized prevention methods (20). However, central China's comprehensive investigation and analysis have not been carried out. This study was undertaken to investigate the epidemiology of pediatric burns in central China from 2013 to 2019 and to examine relevant aspects of clinical treatment, with the goal of developing individualized preventative and therapeutic strategies. Moreover, our research results indicated that pediatric burns patients accounted for 43.9% of the total burn patients, higher than the proportions reported previously by other centers (8, 10, 21–23). The mentioned change could be attributed to the fact that the number of burns remained high over the past 7 years as well as a lack of awareness about the prevention of scald burns. Prevention strategies are formulated by first identifying the risk factors that cause burns, then summarizing the appropriate guidelines, and finally avoiding the risks (24). In this study, there was a high prevalence of pneumonia, with the underlying cause being the loss of the natural skin barrier and the immune system being dysregulated due to burns, resulting in high infection rates (25). Uniformly, volatile fluctuations (e.g., pneumonia morbidity, shock rates, inhalation injury rates, and cure rates) were typically observable and, to some extent, unpredictable so that prevention strategies could have been modified according to the existing conditions.

TABLE 5 | Multiple linear regression analysis on related factors of length of stay (LOS).

	Unstandardized beta coefficients	Standardized beta coefficients	t	*P* value	95% CI	
					Lower	Upper
Better outcomes	0.348	0.152	11.966	<0.001	0.291	0.405
Larger TBSA	8.444	0.044	3.455	0.001	3.653	13.234
With inhalation injury	8.850	0.125	9.396	<0.001	7.003	10.696
Full-thickness burns	7.970	0.273	20.794	<0.001	7.219	8.722
More surgeries	−6.944	−0.130	−10.513	<0.001	−8.239	−5.649

$p < 0.05$ were considered statistically significant CI confidence interval.

TABLE 6 | Multiple linear regression analysis of related factors of cost.

	Unstandardized beta coefficients	Standardized beta coefficients	t	*P* value	95% CI	
					Lower	Upper
Larger TBSA	200.371	0.076	5.896	<0.001	0.013	0.027
With inhalation injury	−12,798.316	−0.058	−4.550	<0.001	−1.831	−7.30
Full-thickness burns	−1,072.336	−0.013	−0.983	0.326	−3,211.592	1,066.920
More surgeries	5,933.437	0.177	12.971	<0.001	0.504	0.684
Better outcomes	−1,608.680	−0.026	−2.095	0.036	−0.309	−0.008
Longer length of stay	344.552	0.299	22.131	<0.001	0.031	0.038

$p < 0.05$ were considered statistically significant.

TABLE 7 | Lethal area 50 (LA50) with 95% CIs for each age group.

Age group	Lethal area 50	95% CI
0–3	76.32	72.63–81.47
3–7	78.51	74.35–82.73
7–14	87.37	83.45–96.75
Overall	78.63	75.12–83.45

The etiology of injuries consists of scald, flame, contact, electricity, chemical, etc. In this study, 90.63% of burns were caused by scalding, significantly higher than in previous studies (24, 26, 27). High-temperature liquids (e.g., milk and water) could easily cause burns. In addition, according to the analysis of the data of this article, the second most common cause of burn was flame, comprising 5.12% of all the cases, whereas it was still lower than other existing reports (28). Coal mine gas explosions, natural gas, gasoline, and other flammable substances were the most common causes of flame burns. Other than the 0–1 age group, contact burns were the third most common type of burn. Despite their rarity, electrical burns (1.17%), chemical burns (0.63%), and explosion burns (0.27%) were more serious. Hot metal, thermal friction, and stoves were the primary causes of contact burns. Based on the mentioned findings, individualized preventive strategies for different types of burns, especially scald burn prevention, should be implemented. Therefore, the following practical strategies could be used, i.e., when bathing children, cool the water down to <40°C (29). The water heater temperature should be set below 50°C (30) because children can be severely scalded in 2 ss if the water temperature is 65–70°C (31). Remove any potentially dangerous items that could cause burns or add protective measures and do not place a thermos bottle on the table. The heater and stove should not be accessible to children. All the sockets accessible to children should be covered with unique plastic covers. Moreover, following a burn, it is essential to take corresponding preventative measures (32, 33). Based on this study, scald injuries occurred more frequently in the winter and summer and flame injuries more often in January, February, and December. Summer and winter vacations are invariably the peak period for people to travel or visit relatives or friends, which increase the risk of electrical burns. Following the analysis, fire agencies and community organizations should enhance prevention publicity and education based on the types of burns most prevalent in specific months (34–36). However, peak times are not absolute and all the burns can occur at any time. As a result, it is critical to prevent burns at all the times (37). Accordingly, further evaluations are required concerning the environment around the home and burn prevention measures to ensure that they can reduce the incidence of pediatric burns (38).

Furthermore, pediatric burns were most common in patients aged 1–3 years. The prevalence of burns in this study was inversely related to age. Nevertheless, BI and Baux scores were positively correlated with age. Additionally, the rate of inhalation burns, LOS, LOS/TBSA, cost, cost/TBSA, curative effect, and cure rate changed with age. Physiologically, pediatric burns were broken down into the four groups: infants ($\leq$1 year), young children (>1 and $\leq$ 3 years), preschoolers (>3 and $\leq$ 7 years), and school-age children (>7 and $\leq$ 14 years). As most parents are busy with work in this region, grandparents are the principal caregivers for kids. Despite this, the elderly disregard safety education and a lack of defensive skills, which is one of the leading causes of burn injuries. Generally speaking, burns sustained by school-aged children are significantly reduced due to an increasing understanding of burn prevention (39). Preschoolers are usually more susceptible to burns due to their great curiosity about things around them, uncoordinated movements, and lack of security awareness. Consequently, the annual incidence rate of preschool children is significantly higher than that of other groups. Based on the investigation and analysis, publicity and education on burn prevention should be performed individually according to age (40). Preschoolers should be provided with extensive safety training regarding burn prevention, and guardians' awareness of prevention must be consistently reinforced to deepen and consolidate prevention knowledge (41). By sharing educational materials with guardians, preschool teachers, community workers, and rural committee members can alert them to prevent burns among school-age children. During their visits to kindergartens, elementary schools, and middle schools, professional firefighters should emphasize the importance of burn prevention education for children and teachers. As a result, the government has enacted legislation and regulations aimed at reducing burn injuries (e.g., regular

TABLE 8 | The detail of 7 deaths.

Patient ID	Age	Gender	Etiology	Post-injury admission time	%TBSA	Full-thickness	Surgery no.	Inhalation injury	Death causes
Case 1	4	Girl	Flame	2 h	22	4	1	With	ARDS MODS
Case 2	1	Boy	Scald	3 days	45	5	0	With	Sepsis MODS
Case 3	1	Boy	Scald	5 h	91	0	0	Without	Shock MODS
Case 4	1	Boy	Flame	6 days	21	4	0	With	Sepsis MODS
Case 5	1	Boy	Scald	2 days	35	4	0	Without	Sepsis MODS
Case 6	8	Girl	Flame	8 h	63	34	0	With	ARDS MODS
Case 7	2	Boy	Scald	5 days	25	0	0	Without	Sepsis MODS

%TBSA: total body surface area burned.

inspections of natural gas leaks in houses, as well as mandatory training for burn prevention in the community).

Surgery is a reliable means of removing necrotic tissue from the wound, thus keeping the patient's prognosis positive. As observed in the research results of this article, surgery has increased in recent years. Comparatively, active surgical treatment increased the cure rate by nearly 9%. It is noteworthy that pediatric burns mainly resulted from scalds, and the local vascular congestion of burn areas was gradually damaged. This resulted in most of the wounds being deep and the second-degree burns. Moreover, most burn patients' parents choose conservative dressings unless the burn is a full-thickness burn. Besides, as revealed by the statistical analysis, patients with full-thickness burns underwent surgery 20.2% more frequently than those without full-thickness burns. Recent studies have shown that timely removing necrotic skin could reduce costs, shorten healing times, and achieve more beneficial outcomes (42, 43). Likewise, such burns with partial thickness were initially treated by surgery in our center rather than conservatively. After the necrotic epidermis and part of the dermis were removed, a biological dressing was applied to the wound. By adopting this treatment strategy, we would be able to completely debride the wound, reduce the inflammation of the wound, shorten the wound healing time, and avoid the pain associated with conservative dressing. As a consequence, this study was inconsistent with prior research (44), whereas it achieved favorable clinical results. Consequently, to treat burn wounds more accurately, a healthy living environment should be created through the formulation of public policies (45), and clinical evidence-based programs should be encouraged.

The outcomes of clinical treatment are affected by many factors (46). Findings in this study indicated that the cure rate was not related to age and gender, but performed strongly positive correlations with etiology, TBSA, surgery, and full-thickness burns. The following points can illustrate the mentioned results. First, burns of all the types, full-thickness burns, a greater TBSA, or more surgeries generally indicated a higher burn severity and tended to fulfill the operation indications quite easily. Second, patients with severe burns were in unstable condition and even life-threatening, so they usually chose to be completely cured before being discharged, while patients with relatively mild burns tended to be discharged for outpatient treatment. This article indicated that mortality was significantly correlated with surgery and TBSA, but only slightly with other factors. According to statistics, the mortality rate was 0.1%, lower than other previous studies (25, 47). The total LA50 in this study was 78.63%, which is similar to previous studies (48). Explaining the situations below can illustrate the phenomenon above. On the one hand, it is generally acknowledged that inhalation injuries, extensive burns, severe shock, and infection are high-risk factors that significantly impact mortality. Our burn center has substantially reduced mortality for patients with severe burns by establishing a burn intensive care unit and other measures to monitor and treat them more effectively. On the other hand, patients without inhalation injury accounted for 99.2% in this study, whereas only 2.1% had a TBSA above 30%, which may account for the lower mortality rate than in other studies (8, 23, 49, 50). Additionally, our burn center has significantly improved the level of pediatric burn diagnosis and treatment.

The median cost was 1,511 USD in this study (IQR: 848–2,648 USD) (average: 2,299 $\pm$ 3,699 USD), differing from that recorded in Chongqing (9). These differences may be attributed to the regional economy and social-economic status, burn severity, treatment expectations, and treatment strategies. Furthermore, this article also shows that different TBSA, frequency of surgery, burn depth, inhalation injury, outcome, and LOS are correlated with cost, but not with age or gender, which can be explained as follows. First, the larger the burn area, the more complicated the treatment will be, and full-thickness burns require multiple surgical treatments, resulting in high treatment costs. Second, inhalation injury significantly increased the risk of pulmonary infection, contributing to sepsis. Flames or chemicals can cause inhalation injury that is more susceptible to pulmonary infection, one of the causes of sepsis. For this reason, comprehensive treatment strategies are usually more expensive and cost-consuming. Third, the parents preferred to discharge until the wound healed. In addition, the median LOS was 15 days (IQR: 8–25 days), which approximated the findings of existing studies (1, 24, 41, 51, 52). Analogous to cost, according to research results, LOS was associated with the etiology, TBSA, etc. Among the factors above, surgeries and deep burns were major factors in LOS. Based on the explanation of the cost

above, the underlying cause may be related. Overall, patients with major burns or full-thickness burns are more likely to undergo repeated surgeries and secondary complications. Having more staff involved in their treatment and ancillary care increases cost and LOS.

The findings indicate that current pediatric burn treatment and prevention are beneficial, albeit at a low level, implying that more advanced preventative strategies should be implemented. There are limitations to this study, however, as explained below:

1. Even though our burn center is the largest in Central China with the highest number of burn hospitalizations, this study represents only the pediatric burn epidemiology in that region.
2. Outpatients were excluded from the analysis of patients, despite their higher number than inpatients.
3. There was an insufficient sample size (7 deaths) to investigate risk factors for mortality.

CONCLUSION

An in-depth description of the pediatric burns epidemiology and clinical characteristics was presented in this article, which includes the number of burns in Central China, age, gender distribution, etiology, severity, complications, and surgery of pediatric burns from 2013 to 2019. Additionally, the LOS, LA50, and cost were analyzed. The following conclusions of this article can be drawn. In total, 0–3 years of age is the primary age of onset of pediatric burns. Scald burns are considered the main prevention target. Therefore, prevention and treatment strategies should be based on the risk factors above. First, education regarding safety should be gradually increased for guardians. Second, dangerous elements (e.g., scald, flame, and electricity) should be kept away from pediatrics. Third, the level of medical care for pediatric burns should be continuously improved.

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 Ethical Review Committee of Zhengzhou First People's Hospital. 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

ST is responsible for the design of the study. DH is responsible for the data collection and essay writing of the study. RL is responsible for the data analysis of the study. All authors contributed to the article and approved the submitted version.

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Bacteriological Profile and Predictors of Death Among Neonates With Blood Culture-Proven Sepsis in a National Hospital in Tanzania—A Retrospective Cohort Study

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Background: Neonatal sepsis is still a major cause of death and morbidity in newborns all over the world. Despite substantial developments in diagnosis, treatments, and prevention strategies, sepsis remains a common problem in clinical practice, particularly in low-resource countries.

Methods: A retrospective cohort study of 238 neonates with positive blood culture-proven sepsis (in Muhimbili National Hospital) was conducted from January 2019 to December 2020. The outcomes of hospitalization were survival and death.

Results: In total, 45.4% mortality resulted from 238 neonates who had sepsis exclusively based on blood culture positivity. A significant association was found between very low birth weight (VLBW), hyperglycemia, mechanical ventilation, and high neonatal mortality. Among the different clinical presentations of neonatal sepsis, lethargy, vomiting, and respiratory distress were found to be frequently associated with neonatal mortality. Furthermore, sepsis with Gram-negative bacteria and early-onset sepsis were also associated with high neonatal mortality. Of the 108 neonatal deaths, the largest proportion (40%) was observed with *Staphylococcus aureus*, and the remaining 38% was caused by *Klebsiella*, 14% by *Escherichia coli*, 5% by *Pseudomonas*, 4% by *Acinetobacter*, and 2% by *Streptococcus*. No neonatal deaths from *Serratia* infection were observed. The overall resistance of isolated organisms to the recommended first-line antibiotics was 84% for ampicillin and 71.3% for gentamicin. The resistance pattern for the recommended second-line antibiotics was 76.2% for ceftriaxone, 35.9% for vancomycin, and 17.5% for amikacin.

Conclusion: VLBW, early-onset sepsis, clinical and laboratory parameters like lethargy, vomiting, and hyperglycemia, sepsis with Gram-negative bacteria, and being on mechanical ventilation are strong predictors of death in neonatal sepsis. In addition, this study discovered extraordinarily high resistance to conventional antibiotics. These

findings give light on the crucial aspects to consider in preventing this disease and poor outcomes.

Keywords: neonatal sepsis, sepsis, bacteriological profile, antibiotic susceptibility, Gram-negative bacteria, Gram-positive bacteria

INTRODUCTION

Neonatal sepsis is a clinical condition defined as an infection in newborns accompanied by or caused by an infection of the blood, typically bacterial and rarely fungal. Its symptoms and clinical features include temperature instability, respiratory difficulties, and refusal to eat (1). Neonatal sepsis can be categorized as early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS is defined as the onset of signs and symptoms of infection within 72 h of life and may be associated with pathogen isolation or not. In LOS, signs and symptoms are present after 72 h of life (2). Sepsis is the most common reason for infant mortality, with around 2.4 million fatalities each year or 6,700 per day (3). Neonatal deaths that occur around the world each year total to ∼4 million. About 30–50% of the total newborn fatalities in underdeveloped nations are caused by neonatal sepsis (4). Early detection, appropriate antibiotic medication, and aggressive supportive care are all elements of prompt diagnosis (4). The risk of newborn death is greatest during the first 28 days of life, and children below 5 years are most vulnerable to sepsis. According to the findings of a new study, more than three-quarters of neonatal deaths occur in the first week of life, with one-third of all neonatal deaths occurring on the first day after birth (5).

Antimicrobial resistance is a major factor in the development of sepsis and septic shock. Every year, over 214,000 newborns die from sepsis caused by resistant infections (6). Neonatal sepsis is a serious global health issue, resulting in significant health burdens due to medical expenses and productivity loss as well as negative consequences on health and quality of life. Africa experiences the slowest decrease in mortality globally, where neonatal mortality decrease has been slower compared to maternal and child mortality reductions—with stillbirth rates being the slowest (7). Neonatal fatalities occur quickly, necessitating rapid medical interventions. According to a study conducted in Tanzania by Mangu et al. newborn fatalities accounted for 11.3% of all in-hospital deaths (8). Most neonatal deaths occur in the first week of life.

To ensure the efficient and long-term detection of newborn sepsis, there is a need to understand the diagnosis, etiology, and treatment of neonatal sepsis at all levels of the health system. The response to antimicrobial drugs may vary substantially over time and across regions, undermining the efficacy of empirical therapy (9).

This study was conducted to understand the bacteriological profile and predictors of death among neonates with blood culture-proven sepsis in Muhimbili National Hospital, Tanzania. This hospital is the national and tertiary referral hospital that receives sick neonates from different health facilities, whether private or public, across the country and is thus a critical spot to determine retrospectively the efficacy of medications provided in combating neonatal infections in the last 2 years.

MATERIALS AND METHODOLOGY

Study Design, Area, and Period

A retrospective cohort study of recorded data from hospital pediatric database and files was used to study neonates who were admitted to the neonatal department, diagnosed with sepsis, and had positive blood cultures. This study was conducted from January 2019 to December 2020 in the neonatal department of a tertiary referral and teaching hospital—Muhimbili National Hospital in Dar es Salaam, Tanzania. Patient medical records including clinical symptoms, hematological parameters, pathogen types, and antimicrobial susceptibility were reviewed. A data collection sheet was designed and used to obtain socio-demographic data and other relevant factors related to neonatal sepsis, like maternal fever, prolonged rupture of the membrane (PROM), mode of delivery, birth weight of the baby, gestational age (<37 completed weeks was considered as premature), the temperature of the infant, vomiting, respiratory rate, jaundice, umbilical redness, convulsions, and inability to breastfeed.

Study Population

A total of 238 neonates with positive blood cultures were included in the study. The sample size was determined using the single-population proportion formula based on the prevalence of positive blood cultures of 19.2% as found by Mkony et al. (10) in the same hospital. Allowing 5% margin of error (MOE) with 95% confidence interval (CI), ($z/2 = 1.96$) using a single-population proportion (p) formula, 1 - p being the proportion of the population that does not possess the character of interest, the sample size was calculated as follows:

$$n = (Z_{\alpha/2})^2 * p * (1\text{-}p)/MOE^2$$

Inclusion/Exclusion Criteria

All neonates who were admitted with blood culture positives within the specified time were included in this study. However, clinically suspected cases with negative blood cultures as well as neonates with positive blood cultures but with incomplete or missing records were excluded from this study. All neonates who died <3 days from birth were not included in the study. Blood cultures with *Staphylococcus* coagulase-negative as well as yeast infections were excluded from the study.

Data Collection

The primary researcher collected information from the hospital's pediatric database and files on all positive blood culture-proved sepsis cases admitted between January 2019 and December 2020.

The medical files were traced using the patients' card number on the registry. Data collection sheets were employed; the data sheets were filled after reading through the manually filled files containing written histories and investigations performed by patients during their stay. Age, sex, birth weight, gestational age at birth (term or preterm), Apgar score at 5 min, place of delivery, mode of delivery, and specific clinical features, such as jaundice, temperature instability (hypothermia, hyperthermia), respiratory distress, poor feeding, vomiting, convulsions, poor reflexes, pallor, jaundice, and umbilical redness, are among the neonatal data collected. Maternal obstetric history of PROM that lasted more than 24 h, maternal urinary tract infection, antibiotic usage, and presence of chorioamnionitis were all noted. Blood culture profile, hemoglobin levels, random blood glucose (RGB) levels, white blood cells, platelets, and C-reactive protein (CRP) levels were among the laboratory features investigated. Anemia was defined as hemoglobin level <10 g/dl, while leucopenia was defined as total white blood count $<5{,}000/mm^3$, leukocytosis was defined as total white blood count >20,000/mm, and thrombocytopenia was defined as a platelet count of $<150{,}000/mm^2$. According to the Muhimbili National Hospital, CRP was considered positive when it rises above 5 mg/L, while in other studies CRP is considered positive when it is elevated above 10 mg/L (11). Hospitalization outcomes were documented as survival at discharge and at death. Any neonate who died 3 days or more from birth at the neonatal unit was considered deceased (mortality). The total sample size of neonates determined was then divided into two groups. Group A consisted of neonates who lived until discharge, while Group B consisted of neonates who died while in the hospital.

Blood Culture Specimen Collection

Under aseptic conditions, each study patient has two blood specimens that were taken for the blood cultures from different peripheral venipuncture sites at 1/2- to 1-h intervals by the hospital protocol; however, the times were not documented. Approximately, 2–5 ml of blood was drawn and kept in aerobic culture bottles, and the sample was immediately transported to the Central Pathology Laboratory at Muhimbili National Hospital (MNH) for processing. Antimicrobial sensitivity testing was carried out at MNH for ampicillin, cloxacillin, and gentamicin, which are used as first-line antibiotics, as well as ceftriaxone, vancomycin, and amikacin, which are used as second-line medications for the treatment of newborn sepsis. The results were classified as resistant, intermediate, or sensitive. During data analysis, isolates with intermediate resistance were labeled as resistant.

Statistical Analysis

The extracted data was processed using SPSS 20.0 software by performing descriptive and inferential statistics. Student's *t*-test was used to compare the means. Statistical significance was established if the *p*-value was <0.05 at 95% CI. The parameters that had significant correlations with death were considered potential risk factors for a poor outcome in newborn sepsis. These variables were used to get the odds ratio by using risk estimate analysis.

TABLE 1 | Distribution of case fatality rate (CFR) of 238 study neonates with culture-proven sepsis based on infant and maternal factors.

Characteristics	Number (*n*)	Number of deaths (CFR%)
Age		
≤72 h	109	61 (56.0)
>72 h	129	47 (36.4)
Sex		
Male	128	57 (44.5)
Female	110	51 (46.4)
Body weight, kg		
<1.5	73	40 (54.8)
1.5–2.5	94	41 (43.6)
≥2.5	71	27 (38.0)
Gestational age		
Term, >37 weeks	87	34 (39.1)
Preterm, <37 weeks	151	74 (49.0)
Place of birth		
Health facility	227	101 (44.5)
Home	11	7 (63.6)
Mode of delivery		
SVD	162	81 (50.0)
C/S	76	27 (35.5)
Apgar score at 5 min		
<7	41	19 (46.3)
>7	197	89 (45.2)
PROM		
<24 h	180	78 (43.3)
>24 h	58	30 (51.7)
Maternal UTI		
Yes	22	6 (27.3)
No	216	102 (47.2)
Antibiotic use		
Yes	16	5 (31.2)
No	222	103 (46.4)
Chorioamnionitis		
Yes	15	10 (66.7)
No	223	98 (43.9)

PROM, prolonged rupture of membranes; UTI, urinary tract infection.

Ethical Consideration

The study was approved by the ethics committee of Muhimbili National Hospital, Tanzania.

RESULTS

Baseline Characteristics

Out of a total of 238 newborns with positive blood cultures (128 male and 110 female), 108 died (57 male, 51 female), accounting for a mortality rate of 45.4% (44.5% male, 46.4% female) of the neonates with blood culture-proven sepsis. **Table 1** shows that the case fatality rate for early-onset sepsis was 55.9% (61 out of 109), which was higher than the 36.4% rate for late-onset sepsis (47 out of 129). The case fatality rate was 66.7% in infants whose mothers

TABLE 2 | Comparison of neonates with sepsis between those who survived and those who died according to clinical features and laboratory parameters.

Parameter	Alive (*N*)	Deceased (*N*)	Alive (%)	Deceased (%)	*P*-value
Poor feeding					
Yes	29	29	50	50	0.418
No	101	79	56.1	43.9	
Lethargy					
Yes	36	52	40.9	59.1	0.001
No	94	56	62.7	37.3	
Vomiting					
Yes	28	48	36.8	63.2	0.001
No	102	60	63.0	37.0	
Convulsions					
Yes	9	15	37.5	62.5	0.085
No	121	93	56.5	43.5	
Temperature instability					
Yes	95	78	54.9	45.1	0.883
No	35	30	53.9	46.1	
Pallor					
Yes	38	39	49.4	50.6	0.278
No	91	69	56.9	43.1	
Jaundice					
Yes	83	64	56.5	43.5	0.471
No	47	44	51.7	48.3	
Respiratory distress					
Yes	80	92	46.5	53.5	0.001
No	50	16	75.8	24.2	
Umbilical redness					
Yes	18	10	64.3	35.7	0.268
No	112	98	53.3	46.7	
Thrombocytopenia					
≤150,000/ul, yes	58	55	51.3	48.7	0.334
>150,000/ul, no	72	53	57.6	42.4	
Leukopenia					
≤5,000/ul, yes	39	22	63.9	36.1	0.087
>5,000/ul, no	91	86	51.4	48.6	
Leukocytosis					
>20,000/ul, yes	9	15	37.5	62.5	0.085
≤20,000/ul, no	121	93	56.5	43.5	
Hb level					
≤10 g/dl	30	21	58.8	41.2	0.449
>10 g/dl	100	87	53.5	46.5	
RBG level					
>6.9 mmol/l, high	10	19	34.5	65.5	0.004
<3.5 mmol/l, low	21	25	45.7	54.3	
3.5–6.9 mmol/l, normal	99	64	60.7	39.3	
CRP					
>5 mg/L, positive	77	75	50.7	49.3	0.101
≤5 mg/L, negative	53	33	61.6	38.4	

TABLE 3 | Risk estimate analysis of the association factors to death among septicemic babies.

	Number		Percent			Deceased	
Parameter	**Alive**	**Deceased**	**Alive**	**Deceased**	***p*-values**	**Odds ratio**	**95% confidence interval**
Age							
≤72 h	48	61	44.0	56.0	0.002	1.536	(1.158–2.037)
>72 h	82	47	63.6	36.4			
Mode of delivery							
VD	81	81	50	50	0.035	1.407	(1.002–1.977)
CS	49	27	64.5	35.5			
Birth weight							
<1.5 kg	33	40	45.2	54.8	0.044	1.441	(1.003–2.071)
>2.5 kg	44	27	62.0	38.0			
Lethargy							
Yes	36	52	40.9	59.1	0.001	1.583	(1.208–2.075)
No	94	56	62.7	37.3			
Vomiting							
Yes	28	48	36.8	63.2	0.001	1.705	(1.309–2.221)
No	102	60	63.0	37.0			
Respiratory distress							
Yes	80	92	46.5	53.5	0.001	2.206	(1.409–3.456)
No	50	16	75.8	24.2			
RBG level							
>6.9 mmol/l, high	10	19	34.5	65.5	0.009	1.669	(1.205–2.311)
3.5–6.9 mmol/l, normal	99	64	60.7	39.3			
Mechanical ventilation							
Yes	3	23	11.5	88.5	0.001	2.206	(1.779–2.939)
No	127	85	59.9	40.1			
Gram-negative bacteria							
Yes	55	63	46.6	53.4	0.014	1.424	(1.07–1.895)
No	75	45	62.5	37.5			

VD, vaginal delivery; C/S, cesarean section; RBG, random blood glucose.

had chorioamnionitis (10 out of 15 neonates). Furthermore, neonates with birth weights of <1.5 kg (54.8%), preterm infants (49.0%), and those delivered at home (63.6%) had a higher case fatality rate than those with birth weights >1.5 kg (43.6%), term infants (39.1%), and those delivered at a health facility (44.5%), respectively. In addition, newborns whose mothers had PROM for more than 24 h had a 60% case fatality rate (30 out of 50 neonates). There was a reduction in case fatalities in neonates whose mothers utilized antibiotics during pregnancy (31.2%).

Table 2 shows that infants with vomiting (63.2%), lethargy (59.1%), convulsions (62.5%), and respiratory distress (53.5%) died at a higher rate than those with other clinical characteristics. Random blood glucose (RBG) levels (65.5%) as well as leukocytosis (62.5%) were the laboratory indicators related to a higher frequency of newborn deaths due to neonatal sepsis. There was no significant difference between neonates with positive CRP, thrombocytopenia, and leukopenia who survived or died due to neonatal sepsis.

Associating Factors for Death Among Septicemic Babies

All the variables in the study were subjected to odds ratio analysis to determine whether variables had a positive correlation with neonatal death or poor prognosis among neonates with sepsis. The results of the analysis are provided in **Table 3**. It was observed that the following factors were all significant in determining their association to death in neonates with sepsis: very low birth weight (OR, 1.441), early-onset sepsis (OR, 1.536), vomiting (OR, 1.705), lethargy (OR, 1.583), respiratory distress (OR, 2.206), high RBG level (OR, 1.669), positive blood culture

for Gram-negative bacteria (OR, 1.424), and being on mechanical ventilation (OR, 2.206).

Causative Bacteria of Neonatal Sepsis

According to the results in **Table 4**, Gram-positive bacteria (120 out of 238 neonates) predominated in causing newborn sepsis as compared to Gram-negative bacteria (118 out of 238 neonates). Gram-negative bacteria (53.8%) outnumbered Gram-positive bacteria in early-onset sepsis. In late-onset sepsis, Gram-positive bacteria predominated (60.0%) over Gram-negative bacteria. *Klebsiella* species (56.2%), *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas* species were shown to predominate in early-onset newborn sepsis. *S. aureus* is the most common cause of late-onset sepsis. **Figure 1** shows that sepsis caused by Gram-negative bacteria was related to a higher proportion of neonate mortality than Gram-positive bacteria. Of the 108 neonatal deaths, the largest proportion (40%) was observed with *S. aureus*, and the remaining 38% was caused by *Klebsiella* species, 14% by *E. coli*, 5% by *Pseudomonas* species, 4% by *Acinetobacter* species, and 2% by *Streptococcus* species. No neonatal deaths from *Serratia* species infection were observed.

A greater proportion of neonates with Gram-positive infections were neonates with low birth weight. Majority of the neonates were *Staphylococcus*-infected and were mostly <2.5 kg at birth. A similar distribution was observed in the Gram-negative-infected neonates. *Klebsiella* infection was dominant among the neonates <2.5 kg (low birth weight) (**Table 5**). Gram-negative sepsis predominates in the preterm group (about 37.8%), while Gram-positive sepsis was at about 25.6%. However, when it comes to specific causative bacteria, we can see that *S. aureus* and *Klebsiella* are equally prevalent as a cause of neonatal sepsis in preterm infants with 24.4%. Gram-positive bacteria (24.8%) outnumber the Gram-negative bacteria (11.8%) in the term neonates. Furthermore, *S. aureus* had a higher percentage (24.8%) than *Klebsiella* spp. (6.3%). Overall, *S. aureus* was nearly equally responsible for sepsis in the preterm (24.4%) and term neonates (24.8%) (**Table 6**).

Antibiotic Susceptibility and Resistance Pattern of Isolated Organisms

Table 7 displays the antibiotic sensitivity and resistance trends of the isolated microorganisms. Overall, 84% of the isolated organisms were resistant to the recommended first-line antibiotics for ampicillin and 71.3% for gentamicin. Cefotaxime had a resistance pattern of 78.1%, ceftriaxone had a resistance pattern of 76.2%, vancomycin had a resistance pattern of 35.9%, and amikacin had a resistance pattern of 17.5%. The *Staphylococcus* infections were shown to be 95.7% resistant to penicillin and 80.43% resistant to ampicillin. Klebsiella was resistant to ampicillin in 92.3% of cases, cefotaxime in 82.5% of cases, and gentamicin in 69.2% of cases. *E. coli* was resistant to gentamicin in 86.7% of cases, ampicillin in 75% of cases, and ceftriaxone in 93.7% of cases. *Acinetobacter* was completely resistant to ampicillin and 80% resistant to gentamicin. *Streptococcus* was completely resistant to gentamicin, completely resistant to penicillin G, and completely resistant to imipenem. *Proteus* was found to be completely resistant to ceftriaxone, completely resistant to ciprofloxacin, and completely resistant to aztreonam.

TABLE 4 | Distribution of microorganisms according to time of infection.

	EOS, *N* (%)	LOS, *N* (%)	Total	*P*-value
Gram-positive				
Staphylococcus aureus	48 (41.0)	69 (59.0)	117	0.089
Streptococcus spp.	0	3 (100)	3	0.083
Gram-negative				
Klebsiella spp.	41 (56.2)	32 (43.8)	73	0.071
Pseudomonas spp.	5 (71.4)	2 (28.6)	7	0.198
Acinetobacter spp.	3 (37.5)	5 (62.5)	8	0.6
Escherichia coli	13 (46.4)	15 (53.6)	28	0.981
Serratia spp.	0	1 (100)	1	0.351
Proteus spp.	1 (100)	0	1	0.32
Gram-positive	48 (40.0)	72 (60.0)	120	
Gram-negative	63 (53.8)	55 (46.3)	118	0.039

DISCUSSION

Prompt diagnosis and treatment are crucial in decreasing infant sepsis mortality and sequelae. As a result, it is crucial to identify neonates who are at risk of developing sepsis and, if sepsis develops, to identify the characteristics linked with a bad prognosis as soon as possible. The mortality rate of newborn sepsis varies in institutions and countries. According to this study, the mortality rate is 45.4%. This was significantly higher than a study conducted in the same hospital in 2012, which found 13.9% (12). This demonstrates that the death rate owing to neonatal sepsis has increased significantly at Muhimbili National Hospital. This increase could be attributed to rising antibiotic resistance. Kayange et al. found a death rate of 28.5% of infants with positive blood cultures in a 2010 study at Bugando Medical Center in Tanzania (13). Different and some similar rates have been found in other studies conducted in South China (9.5%) (14), Uganda (15.2%) (15), India (36%), Bhutan (20.5%) (16), Nigeria (32.2%) (14), Niger (38.24%) (17), Zambia (43%) (18), and Congo (21%) (19). The discrepancies in death rates between studies can be attributed to a variety of factors, including socioeconomic factors, geographical factors, equipment levels, and the efficacy of each hospital's preventative and therapeutic strategies (19).

Additionally, this study evaluated the major predictors of death in patients with culture-proven sepsis. The significant predicting factors of death for culture-proven sepsis were found to include a birth weight of <1.5 kg, early-onset sepsis, lethargy, vomiting, respiratory distress, hyperglycemia, sepsis with Gram-negative bacteria, and mechanical ventilation. This study indicates that low birth weight (<1.5 kg) is a risk factor for death (OR, 1.441) in neonates with sepsis. A similar finding has been reported in studies from different countries (17, 19, 20). Newborns with weight <1.5 kg had increased mortality, possibly due to impairments in humoral and cellular immunity as well as

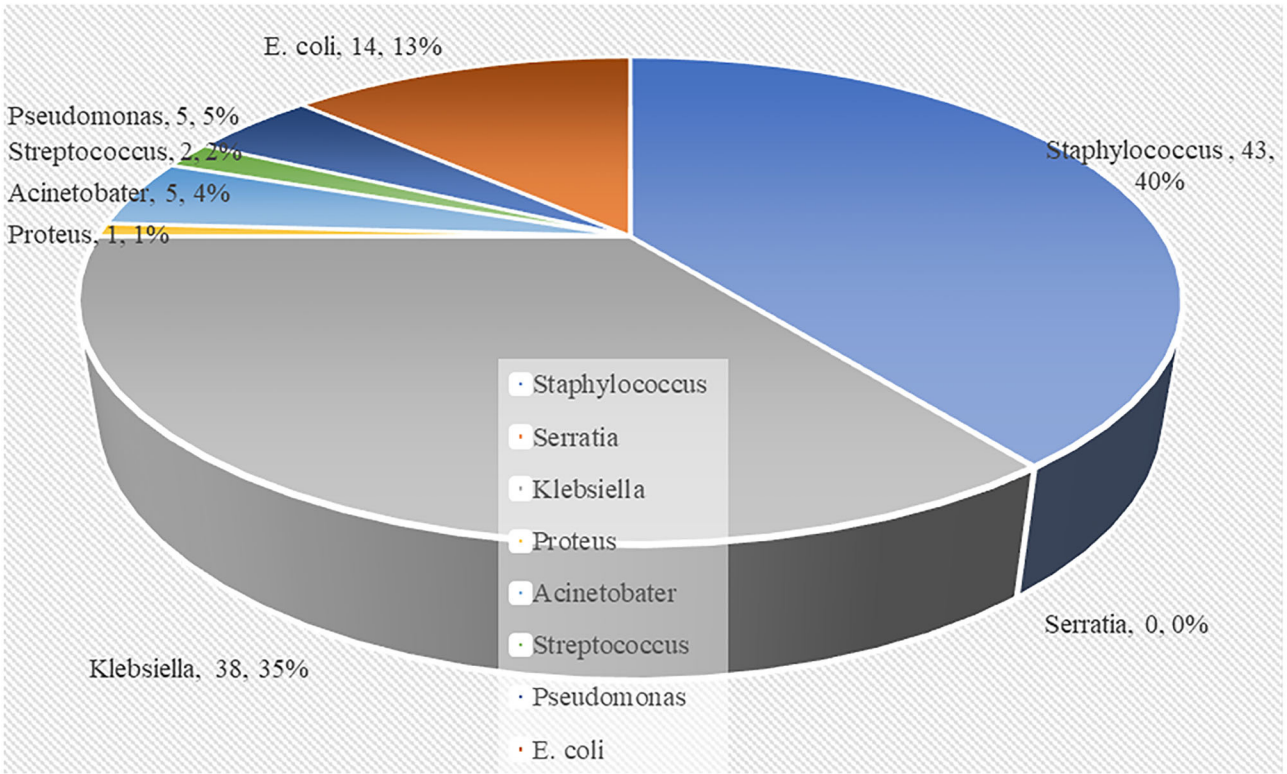

FIGURE 1 | Pie chart showing the distribution of deceased neonates according to the causative bacteria.

prolonged hospitalization, which raises the risk of nosocomial infection. Infection is a big concern, and it compounds the already bad outcome for a baby born prematurely (17). Similarly, an Indian study (14) revealed that lethargy (OR, 1.583) and hyperglycemia (OR, 1.669) are significant predictors of neonatal death. Respiratory distress (OR, 2.207), vomiting (OR, 1.705), and mechanical ventilation (OR, 2.206) were also associated with high neonatal mortality in this present study. TNF, IL-1, IL-6, and IL-8 have been shown to be elevated in individuals with acute respiratory distress syndrome and septic shock. These cytokines' levels in the blood may help determine sepsis severity and prognosis (21, 22).

According to this study, Gram-positive bacteria (50.4%) predominated in causing newborn sepsis as compared to Gram-negative bacteria (49.6%). In contrast, a 2012–2016 study in South China reported that Gram-negative bacteria ($n = 371$) outnumbered Gram-positive bacteria ($n = 218$, 35.2%) and fungi ($n = 30$, 4.8%) (23). However, Gram-negative sepsis (OR, 1.424) was found to be a significant predictor of neonatal sepsis mortality when compared to Gram-positive sepsis in this present study. Other research yielded similar outcomes (12, 24). A greater mortality rate could be related to significantly higher CRP and IL-6 levels in Gram-negative bacteremia than in Gram-positive bacteremia (24). There are evidences for two separate mechanisms by which Gram-negative bacteria generate systemic reactions. Bacteria enter the circulation *via* a normal or damaged epithelium, triggering systemic immunological responses (such as enhanced vascular permeability, leukocyte–endothelial adhesion, complement, and clotting pathways) that lead to multiorgan failure. Toxins or circulating microorganisms are not necessary as direct stimuli for intravascular inflammation, according to a second idea (25). In our study, *S. aureus* was the most common cause in both early-onset sepsis and late-onset sepsis, but the percentage was higher in LOS at 58.97%. It must be noted that this percentage included all neonates, either alive or dead, with positive blood cultures. In a study by Said et al. *Staphylococcus capitis*-related sepsis was identified as an independent risk factor for severe morbidity in low-birth-weight infants with late-onset sepsis (26). *Staphylococcus epidermidis* has also been reported as the most prevalent pathogenic bacterium species in the LOS group (27). In this study, it can be observed in **Table 1** that the majority of these neonates with sepsis have an extremely low birth weight (<1.5 kg; 73 out of 238) and low birth weight (1.5–2.5 kg; 94 out of 238), for a total proportion of 70.2% neonates. Furthermore, it was discovered that preterm neonates predominated (151 out of 238), accounting for ∼63.4% of the overall sample. The presence of *S. aureus* in LOS may also be because very-late-onset sepsis is frequently diagnosed in newborns with extremely low birth weight who are usually hospitalized for several weeks after birth. The intravascular catheters required for their care, prolonged antimicrobial drug exposure, the persistence

TABLE 5 | Distribution of microorganisms according to birth weight classification.

Causative bacteria	Birth weight, *n* (%)				*P*-value
	<1.5 kg	1.5–2.5 kg	>2.5 kg	Total	
Gram-positive	25 (10.5)	44 (18.5)	51 (21.4)	120	0
Staphylococcus aureus	24 (10.1)	44 (18.5)	49 (20.5)	117	0
Streptococcus spp.	1 (0.4)	0 (0)	2 (0.8)	3	0.2
Gram-negative	48 (20.2)	50 (21.0)	20 (8.4)	118	0
Klebsiella spp.	35 (14.7)	27 (11.3)	11 (4.6)	73	0
E. coli	9 (3.8)	13 (5.6)	6 (2.5)	28	0.56
Acinetobacter spp.	2 (0.8)	5 (2.1)	1 (0.4)	8	0.362
Pseudomonas spp.	2 (0.8)	3 (1.3)	2 (0.8)	7	0.983
Proteus spp.	0 (0)	1 (0.4)	0 (0)	1	0.463
Serratia spp.	0 (0)	1 (0.4)	0 (0)	1	0.463

TABLE 6 | Distribution of microorganisms according to gestational age classification.

Causative bacteria	Gestational age, *n* (%)			*P*-value
	Pre-term	Term	Total	
Gram-positive	61 (25.6)	59 (24.8)	120 (50.4)	0
Staphylococcus aureus	59 (24.4)	58 (24.8)	117 (49.2)	0
Streptococcus spp.	2 (0.8)	1 (0.4)	3 (1.3)	0.907
Gram-negative	90 (37.8)	28 (11.8)	118 (49.6)	0
Klebsiella spp.	58 (24.4)	15 (6.3)	73 (30.7)	0.001
E. coli	21 (8.8)	7 (2.9)	28 (11.8)	0.177
Acinetobacter spp.	6 (2.5)	2 (0.8)	8 (3.4)	0.490
Pseudomonas spp.	3 (1.3)	4 (1.7)	7 (2.9)	0.251
Proteus spp.	1 (0.4)	0 (0.0)	1 (0.4)	0.447
Serratia spp.	1 (0.4)	0 (0.0)	1 (0.4)	0.447

of immature host defensive mechanisms, prematurity, and a prolonged stay in the neonatal intensive care unit (NICU) are the most prominent risk factors for their predisposition (28). These findings imply that differences in host responses and pathogenicity mechanisms of different pathogenic microbes should be considered in the treatment of bacteremia patients and that new antimicrobial counter-measures beyond standard antimicrobial drugs are urgently needed (24). The routine reporting of Gram stain reaction laboratory data could significantly improve newborn sepsis.

The EOS group had a death rate 55.9% greater than the LOS group (36.4%), indicating that factors such as maternal genitourinary tract infections directly affect the occurrence of infant sepsis. Ogunlesi and his colleague found comparable results (14). Nevertheless, LOS has also been linked to an elevated mortality rate in some studies (29, 30).

Overall, the isolated organisms were resistant to 84% of ampicillin and 71.3% of gentamicin. Ceftriaxone resistance was 76.2%, cefotaxime resistance was 78.1%, vancomycin resistance was 35.9%, and amikacin resistance was 17.5%. Inappropriate antibiotic use may be a contributing factor to the hospital's extremely high levels of antibiotic resistance documented in this and previous research (9, 31). Between 1999 and 2012, investigations conducted at MNH and Bugando in Tanzania (1, 10, 12–14, 32) showed a progressive increase in resistance not just to first-line antibiotics but also to alternative drugs such as cefotaxime, vancomycin, and amikacin. Surprisingly, in this investigation, we observed an alarming increase in resistance to ceftriaxone, gentamicin, and amikacin compared to previous studies conducted in the same setting in 2012 (10, 12) showing an unprecedented increase in antibiotic resistance. In our study, we discovered an alarmingly high level of vancomycin resistance. Out of 62 isolates tested for *S. aureus* sensitivity and resistance, 22 (35.5%) were resistant to vancomycin. Vancomycin has been the first-line treatment for methicillin-resistant *S. aureus* since its discovery (33). The emergence of vancomycin resistance poses a serious threat to public health around the world. A recent study (34) found that vancomycin-resistant *S. aureus* was recently discovered in Egyptian slaughterhouses. According to recent reports from Michigan, USA, *S. aureus* has decreased susceptibility and resistance to vancomycin in July 2021 (33). As a result, it is critical to monitor these infections and conduct additional research to determine why antimicrobial resistance is increasingly becoming a problem.

The strengths of this study include a single center for all investigations, ensuring that records and common practice

TABLE 7 | Antibiotic susceptibility and resistance pattern of isolated organisms.

Antibiotics	Category Number tested (%)	Gram-positive bacteria *N* (%)		Gram-negative bacteria *N* (%)					
		Staphylococcus aureus	*Streptococcus* spp.	*Klebsiella* spp.	*E. coli*	*Pseudo-monas*	*Proteus* spp.	*Serratia*	*Acinetobacter*
Penicillin G	Sensitive 3 (4.2)	3 (4.3)	0 (0)						
	Resistant 68 (95.8)	67 (95.7)	1 (100)						
Ampicillin	Sensitive 13 (16.0)	9 (19.6)	1 (100)	2 (7.7)	1 (25)	0 (0)			0 (0)
	Resistant 68 (84.0)	37 (80.4)	0 (0)	24 (92.3)	3 (75)	2 (100)			2 (100)
Amoxicillin–clavunate	Sensitive 57 (40.4)	29 (40.8)	1 (100)	20 (40.8)	4 (30.8)	1 (50)		1 (100)	1 (25)
	Resistant 84 (59.6)	42 (59.2)	0 (0)	29 (59.2)	9 (69.2)	1 (50)		0 (0)	3 (75)
Oxacillin	Sensitive 5 (15.2)	5 (15.6)	0 (0)						
	Resistant 28 (84.8)	27 (84.4)	1 (100)						
Cloxacillin	Sensitive 0 (0)		0 (0)						
	Resistant 1 (100)		1 (100)						
Piperacillin–tazobactam	Sensitive 22 (44.0)	4 (36.4)		11 (57.9)	3 (33.3)	3 (60)	1 (100)		0 (0)
	Resistant 28 (56.0)	7 (63.6)		8 (42.1)	6 (66.7)	2 (40)	0 (0)		5 (100)
Cefoxitin	Sensitive 19 (33.9)	18 (35.3)	1 (50)	0 (0)	0 (0)				
	Resistant 37 (66.1)	33 (64.7)	1 (50)	2 (100)	1 (100)				
Ceftriaxone	Sensitive 19 (23.8)	8 (50)		7 (17.1)	1 (6.3)	3 (60)	0 (0)	0 (0)	
	Resistant 61 (76.2)	8 (50)		34 (82.9)	15 (93.7)	2 (40)	1 (100)	1 (100)	
Cefotaxime	Sensitive 14 (21.9)	2 (100)		7 (17.5)	2 (16.7)	2 (40)			1 (20)
	Resistant 50 (78.1)	0 (0)		33 (82.5)	10 (83.3)	3 (60)			4 (80)
Ceftazidime	Sensitive 12 (23.1)	1 (25)		8 (22.9)	1 (14.3)	2 (33.3)			
	Resistant 40 (76.9)	3 (75)		27 (77.1)	6 (85.7)	4 (66.7)			
Aztreonam	Sensitive 15 (30.0)	2 (22.2)		10 (38.5)	1 (20)	2 (66.7)	0 (0)	0 (0)	0 (0)
	Resistant 35 (70.0)	7 (77.8)		16 (61.5)	4 (80)	1 (33.3)	1 (100)	1 (100)	5 (100)
Imipenem	Sensitive 83 (96.5)	42 (97.7)	0 (0)	28 (100)	8 (100)	2 (66.7)			3 (100)
	Resistant 3 (3.5)	1 (2.3)	1 (100)	0 (0)	0 (0)	1 (33.3)			0 (0)
Meropenem	Sensitive 59 (69.4)	15 (46.9)	1 (100)	27 (84.4)	12 (85.7)	1 (50)			3 (75)
	Resistant 26 (30.6)	17 (53.1)	0 (0)	5 (15.6)	2 (14.3)	1 (50)			1 (25)
Vancomycin	Sensitive 41 (64.1)	40 (64.5)	1 (50)						

(Continued)

TABLE 7 | Continued

Antibiotics	Category Number tested (%)	Gram-positive bacteria *N* (%)		Gram-negative bacteria *N* (%)					
		Staphylococcus aureus	*Streptococcus* spp.	*Klebsiella* spp.	*E. coli*	*Pseudo-monas*	*Proteus* spp.	*Serratia*	*Acinetobacter*
	Resistant 23 (35.9)	22 (35.5)	1 (50)						
Clindamycin	Sensitive 59 (80.8)	58 (81.7)	1 (50)						
	Resistant 14 (19.2)	13 (18.3)	1 (50)						
Ciprofloxacin	Sensitive 72 (46.8)	29 (40.3)	0 (0)	26 (46.4)	14 (73.7)	2 (100)	0 (0)	1 (100)	0 (0)
	Resistant 82 (53.2)	43 (59.7)	1 (100)	30 (53.6)	5 (26.3)	0 (0)	1 (100)	0 (0)	2 (100)
Gentamycin	Sensitive 35 (28.7)	18 (31.6)	0 (0)	12 (30.8)	2 (13.3)	1 (33.3)	0 (0)	1 (100)	1 (20)
	Resistant 87 (71.3)	39 (68.4)	1 (100)	27 (69.2)	13 (86.7)	2 (66.7)	1 (100)	0 (0)	4 (80)
Amikacin	Sensitive 33 (82.5)			22 (95.7)	6 (50)	2 (100)	1 (100)		2 (100)
	Resistant 7 (17.5)			1 (4.3)	6 (50)	0 (0)	0 (0)		0 (0)
Sulfamethoxazole–trimethoprim	Sensitive 15 (16.3)	8 (16)	0 (0)	4 (14.8)	3 (27.3)				0 (0)
	Resistant 77 (83.7)	42 (84)	2 (100)	23 (85.2)	8 (72.7)				2 (100)
Erythromycin	Sensitive 5 (12.8)	5 (13.5)	0 (0)						
	Resistant 34 (87.2)	32 (86.5)	2 (100)						
Chloramphenicol	Sensitive 28 (63.6)	3 (60)		16 (72.7)	8 (72.7)	0 (0)			1 (25)
	Resistant 16 (36.4)	2 (40)		6 (27.3)	3 (27.3)	2 (100)			3 (75)

Cells shaded in gray indicate the isolates that were not tested.
N, number of isolates tested.

were consistent; the laboratory analyses were done in one microbiology laboratory; and a relatively large and recent cohort of neonates with proven sepsis were included, making the obtained information for antimicrobial resistance and bacterial profiles relevant to the local population. However, because this is a retrospective study, it has some limitations. Because of the lack of intra-observer reliability, variable degrees of clinical skills/awareness in NICU settings, and incomplete documentation, retrospective chart reviews that attempt to capture the clinical features of neonatal sepsis are frequently incomplete. The procedure for collecting blood samples for cultures was also not documented in the files, and therefore we had to rely on information from the microbiology department about what the standard procedure should be. We were likewise unable to determine the precise timing of random blood glucose levels. It should be noted that there was no consistency in testing specific antibiotics against bacterial isolates at Muhimbili in this study, thus resulting in different susceptibility results.

CONCLUSION AND RECOMMENDATION

Infant demography research has found a significant connection between VLBW and early-onset sepsis as well as neonatal mortality in the newborn population. High blood sugar levels and mechanical ventilation were also identified as risk factors for neonatal mortality. As a result of neonatal sepsis' clinical manifestations, such as lethargy, vomiting, and respiratory distress, newborn mortality was found to be associated with these symptoms. Gram-negative bacteria are typically found in septicemic newborns who have died. Early detection and treatment of these risk factors would dramatically lower the likelihood of serious and life-threatening problems in newborns as well as the likelihood of mortality in these babies. In addition, this study discovered an abnormally high level of resistance to common antibiotics, which is of great concern. Antibiotic resistance may be due to overuse and misuse of antibiotics. We advocate for a change of currently prescribed antibiotics in our setting, the need to do a blood culture as

soon as sepsis is suspected, and the need for a prospective study which we are currently undertaking to bridge the gaps found in this study and also provide updated data for policy.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: These are retrospective datasets analyzed for the purposes of this study and can only be shared upon reasonable request and subsequent approval from the Ethics Committee. Requests to access these datasets should be directed to archangelmntim@yahoo.co.uk; nura_abd@yahoo.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Muhimbili National Hospital, Tanzania. 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

NB-a contributed to the data collection, data analysis, and manuscript preparation. JA contributed to the manuscript preparation. MN contributed to the manuscript preparation and revision. RT contributed to the data analysis and manuscript preparation. MM and HN contributed to the data collection and data analysis. HJ contributed to the conceptualization, design, and manuscript preparation. All authors contributed to the article and approved the submitted version.

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Time to death and its predictors among neonates who were admitted to the neonatal intensive care unit at tertiary hospital, Addis Ababa, Ethiopia: Retrospective follow up study

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Backgrounds: Neonatal death is the major problem in developing world. Burden and predictors of neonatal mortality vary across countries and even among regions of a country, so understanding the problem concerning these factors is essential to overcome the problem. Therefore, this study aimed to determine time to death and its predictors of neonatal mortality among neonates who were admitted to the neonatal intensive care unit of Tertiary Hospital, Addis Ababa, Ethiopia.

Methods: A hospital-based retrospective cohort study was employed among 434 neonates admitted in Tertiary hospital, Addis Ababa, Ethiopia. A Kaplan Meier curve and a log-rank test were used to estimate the survival time and compare survival curves between variables. The cox proportional hazard model was also fitted to identify predictors.

Results: A total of 434 neonates included in the study, 11.1% of which were died, and the incidence rate was 19.2 per 1000 live births. The time to death of neonates was 17 days. Independent predictors of neonatal mortality were incomplete maternal antenatal follow up[AHR: 3.7 (95% CI:1.86,7.60)], low(Appearance, Pulse, Grimily, Activity, and Respiration(APGAR)score[AHR:5.0 (95%CI:1.51–15.04)], perinatal asphyxia [AHR:5.2 (95%CI:1.92–14.30)], preterm 4.2 (95%CI: 1.32–8.83)]. Moreover, small for gestational age [AHR:4.8 (95%CI:2.33–9.72)], respiratory distress[AHR: 2.5 (95%CI: 1.24–5.09)], sepsis [AHR: 3.4 (95%CI: 1.71–4.01)], low birth weight[AHR: 7.3 (95%CI:2.69,1.91)], and tracheoesophageal fistula [AHR: 2.2 (95%CI: 1.13–4.32)].

Conclusion: The overall incidence rate was 19.2 deaths per 1,000 live births. Emphasis should be given to incomplete Antenatal care follow

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up, small for gestation, preterm, low birth weight, low 5th min APGAR score, neonatal sepsis, respiratory distress, perinatal asphyxia, and tracheoesophageal fistula.

KEYWORDS

neonatal mortality, survival status, time to death, predictors, Ethiopia

Introduction

Globally, it is estimated that ~6,500 neonatal deaths occurred every day. Of those, about a third of all neonatal deaths occurred within the first day after birth, and three-quarters occurring within the first week of life (1). Besides, the neonatal mortality rate was 37% in 1990, 31% in 2000 and 18% in 2017 (2). Despite, there is a decline in neonatal mortality from 1990 to 2017, it is slower than post-neonatal and under-5 mortalities (2–5). Neonatal death is unevenly distributed based on age, socio-demographic population groups, and other factors (2, 6). The 2022 global report bared that the highest neonatal mortality reported in Sub-Saharan Countries which was 27 deaths per 1,000 live births with 43% of global newborn deaths, followed by central and southern Asia which was 23 deaths per 1,000 live births, with 36% of global newborn deaths. Moreover, a child born from Sub-Saharan Countries is 10 times more likely to die than child born from high income countries (7).

The three major causes of neonatal mortality in developing countries include prematurity, infections, and perinatal asphyxia (2, 8, 9). Newborns that need intensive medical attention are often admitted into a special area of the hospital called the neonatal intensive care unit [NICU]. A new initiative called the Global Strategy for Women's, Children's, and Adolescent's Health [2015–2030] and the third Sustainable Development Goal [SDG] has been established to ensure healthy lives and promote wellbeing for all ages (2). The SDG goal 3 geared toward preventing deaths of newborns specifies that all countries should aim to reduce neonatal mortality to at least as low as 12 deaths per 1,000 live births by 2030, but without strengthened commitment to newborn survival, many countries couldn't meet the SDG goal to end preventable neonatal deaths (2).

In Ethiopia, a 2020 report estimated that neonatal mortality rate for Ethiopia was 27 deaths per 1,000 live births. The rate of neonatal mortality decreased from 47.8 deaths per 1,000 live births to 27 deaths per 1,000 live births in 2001 and 2020, respectively (10). Over two-thirds of neonatal deaths are mainly due to infections and neonatal medical conditions (11–13). The neonatal causes of death are prematurity [21.8 %], infections [18.5 %], asphyxia [31.6 %] which together account for nearly 70% of deaths in this age group (14).

In particular, under-five mortality rates declined from 166 to 67 deaths per 1,000 live births in 2016. Similarly, infant mortality decreased from 97 to 48 deaths per 1,000 live births in the same period, but the neonatal mortality decreased from 54 to 29 per 1,000 live births (14–17). This indicates the trend of neonatal mortality reduction in Ethiopia is moving at a slow step compared to the reduction of infant and under-five mortality over the same period. National analysis data showed that multiple birth neonates, neonates born to mothers who did not utilize ANC and neonates from rural area were predictors of neonatal mortality (18).

Despite different initiatives and implementations that have been implemented to prevent neonatal death, it is still high and not reduced as expected in developing countries including Ethiopia. Although several studies were made in different countries on the survival status and predictors of mortality among neonatal intensive care unit [NICU] admitted neonates, but only a few studies were done in Ethiopia. Moreover, studies regarding neonatal mortality have focused on rate and little has been done on the time to death and predictors.

Therefore, this study aimed to determine the time to death and its predictors of neonatal mortality among neonatal intensive care unit admitted neonates at Tertiary Hospital Addis Ababa, Ethiopia.

Abbreviations: AHR, Adjusted Hazard Ratio; AIDS, Acquired Immune Deficiency Syndrome; ANC, Anti Natal Care; AOR, Adjusted Odds Ratio; APGAR, Appearance, Pulse, Grimily, Activity, and Respiration; CSA, Central Statistical Agency; EBF, Exclusive Breast Feeding; EDHS, Ethiopian Demographic and Health Survey; EONS, Early Onset Neonatal Sepsis; FMOH, Federal Ministry of Health; GA, Gestational Age; GHO, Global Health Observatory; HBsAg, Hepatitis B Surface Antigen; HMD, Hyaline Membrane Diseases; HR, Hazard Ratio; LBW, Low Birth Weight; NICU, Neonatal Intensive Care Unit; NMR, Neonatal Mortality Rate; RDS, Respiratory Distress Syndrome; SDG, Sustainable Development Goals; TASH, Tikur Anbessa Specialized Hospital; UNICEF, United Nations International Children Emergency Fund.

Methods

Study setting, period, design

A retrospective cohort study was conducted at tertiary hospital Addis Ababa Ethiopia among live-born neonates who were admitted to NICU from 1 January 2015 to 30 December

2018. Addis Ababa has ten sub-cities at which the City lies at an altitude of 7,546 feet [2,300 meters] (19). There are three referral hospitals in Addis Ababa, Tikur Anbessa Specialized Hospital, Pawlos Hospital and Yekatit 12 Hospital, among this Tikur Anbessa Specialized Hospital (TASH) was randomly selected. TASH is a country's largest and iconic referral hospital for Ethiopia. The Tikur Anbessa Specialized Hospital NICU ward can accommodate a maximum of 60 patients with an average of 20–40 patients daily admission (20, 21).

Eligibility criteria

All live-born neonates who were admitted to NICU of Tikur Anbessa Specialized Hospital from 1 January 2015 to 30 December 2018, Addis Ababa, Ethiopia were included. Whereas, Neonates of incompletely registered NICU logbooks and lost records at the time of data reviewing were excluded from the study.

Sample size determination and sampling procedure

The sample size was determined by using double population proportion in a STATA statistical program considering the following assumptions: 95% CI, power 80%, $P1 = 10$ % $P2 =$ 20% (22), and 10 % incomplete data, yielding a total sample size of 434.

A sampling frame was prepared from the medical record of neonates that were admitted in NICU from 1 January 2015 – 30 December 2018 [$N = 12{,}888$], then for each year, proportional allocation was taken, Randomly, the 2^{nd} MRN was selected in the same fashion for the rest 3 years, and then systematic sampling was employed every 30^{th} (Supplementary 1).

Study variables

Time to death was an outcome variable. Independent variables includes:-socio-demographic factors (maternal age, neonatal age, and sex); maternal health factors [(Antenatal care) ANC follow up, RH (Rhesus) factor, blood group; maternal medical disorders like hypertension, diabetic mellitus, HIV/AIDS, and others, and gynecologic-obstetric related factors like gravidity, parity, mode of delivery, multiple pregnancies, premature rupture of membrane, abortion, prolonged labor); neonatal factors (Age at admission, sex, the weight of neonate, date of admission and discharge. APGAR score, gestational age, maturity, neonatal medical conditions: asphyxia, congenital malformation, preterm, sepsis, hypothermia, RDS (respiratory distress syndrome), MAS(Meconium aspiration syndrome), HMD (Hyaline membrane disease), jaundice, and TEF (trachoesophageal fistula)]; health service-related factors (duration of hospital stay, access to emergency obstetric care, resuscitation efforts).

Operational definitions

Censored: didn't know survival time exactly due to study ends, loss to follow-up, withdrawal or being survived from study.

- Low APGAR score: a score < 7.
- Event: death after NICU admission.
- Asphyxia: a neonate with an APGAR score of <7.
- Time to death: it is the time from admission at NICU to the occurrence of the outcome/event.
- Time scale: days from admission of a neonate to the occurrence of an outcome.
- Time origin: date of admission or start time of the cohort.
- Complete ANC follow up: ANC visit$\geq$4 times at current pregnancy period.
- Multigravida: recorded gravida of $\geq$2.
- Multiparity**:** recorded parity of $\geq$2.
- Preterm birth: any infant born before 37 weeks of gestational age.
- Low birth weight (LBW): birth weight $<$2500 gm.

Data collection tools and procedures

Data was collected by using a checklist developed from neonatal intensive care unit registration book format, which was prepared nationally as an "Ethiopian NICU form. The checklist consisted of new-born information recorded at admission and records of maternal information which were collected using a uniform extraction format developed by taking in to account all the relevant variables in the standard NICU registration book. Then all medical records that fulfill the inclusion criteria were reviewed retrospectively.

The checklist was prepared in English. A pretest was done on 5% of the sample size in Yekatit 12 hospital before the time of the actual data collection. The checklist was also examined by experts to check for content validity.

The data reviewers and supervisors were 8 BSc and 3 MSc Nurses. Before starting the actual work, one-day training and orientation were provided to chart reviewers on the objectives of the study, data reviewing techniques, how to keep confidentiality of information, how to fill the data abstraction checklist and data quality management. Close supervision was carried out by supervisors and investigators to ensure data quality. Then, the collected data was checked for its completeness and consistency before analysis.

TABLE 1 Socio-demographic characteristics of neonate and mother in NICU, TASH, Addis Ababa, Ethiopia, from 1 January 2015 – 30 December 2021.

Variables	Category	Outcome [$N = 434$]		Row total
		Death	Censored	
		Count [%]	Count [%]	Count [%]
Sex of a neonate	Male	27 [11.3]	212 [88.7]	239 [55%]
	Female	21 [10.8]	174 [89.2]	195 [45%]
Maternal age	≤20	4 [7.4]	50 [92.6]	54 [12.4%]
	20–34	34 [13.0]	228 [87.0]	262 [61%]
	35–45	10 [8.8]	104 [91.2]	114 [26.5]
	≥45	0 [0.0]	4 [100.0]	4 [0.04%]
Neonatal age	0–1day	21 [12.9]	142 [87.1]	163 [37.6]
	1–7days	12 [7.6]	145 [92.4]	157 [36.1]
	7–14days	9 [11.1]	72 [88.9]	81 [18.7]
	14–28days	6 [18.2]	27 [81.8]	33 [7.6]

Data processing and analysis

Data was coded, cleaned, edited and entered using Epi-data version 4.21 and exported to STATA SE version 14 for analysis. The event of interest was death. The time to death was calculated in days between the date of admission and the date of death. The log-rank test employed to illustrate whether considered covariates in the Kaplan Meier curves are statistically significant and in line with the Kaplan Meier curves. The bivariable cox regression was done and those variables having p-value < 0.25 in the bivariable analysis were included in the multivariable cox-proportional hazards regression model. Then, those variables with P-value ≤ 0.05 at 95% confidence interval were considered as statistically significant.

Kaplan Meier survival curve together with log-rank test was fitted to test the survival time of neonates, and their survival curves didn't cross over each other. A goodness-of-fit (23) test was employed to assess the proportional hazard [PH] assumptions for each predictor variable. The result showed that variables included in the model satisfied the proportional hazard assumption [p-value was $0.7156 > 0.05$], which indicates that the PH assumption has been met.

Results

Socio-demographic characteristics of mother and neonate

About 434 charts were reviewed with a response rate of 100%. Around 54 [12.4%] of mothers were below age twenty, 262 [61%] between 20–34 years old, 114 [26.5] between 35–45, and 4 [0.04%] were above 45.

Among 239 males 27 [11.3%] of neonates died, and among 195 females 21[10.8%] of them died. The pattern of neonatal death in the 1st 24 h,1st 7 days, within the first 14 days, and the 1st 28 days was 12.9,7.6,11.1, and18.2%, respectively (Table 1).

Maternal health conditions

Neonates born from mothers who had a complete antenatal follow up during their current.

Pregnancy, their death was 48/1,000 neonates, but neonates born from mothers of incomplete ANC was 360/1,000 neonates, and 615/1,000 for neonates born from mothers who did not have antenatal follow up were died.

About 24 [11.9%] of neonates born from primigravida mothers, 201 [46.3%] were died, and 24 [10.3%] of neonatal death was from multi gravid mothers 233 [53.7%] (Table 2).

Maternal obstetric conditions

About 15 [10.9%] of neonates born from mothers who had problems of obstetric problems died and 33 [11.1%] of neonates died born from mothers who did not have such problems (Table 3).

Maternal medical and related conditions

Neonates born from hypertensive mothers had 18% neonatal death risk than neonates born from non-hypertensive mothers 13.3%. HIV positive mothers had 29% hazard for neonatal death, but HIV negative mothers had 19% hazard of neonatal death (Table 4).

Neonatal medical conditions/assessments

Regarding the neonatal medical conditions; the common medical problems identified were respiratory distress 121 [28%], perinatal natal asphyxia 143 [33%],low APGAR score [<7,194 [44.7%], low birth weight 84 [20%], Prematurity or SGA 88 [21%], sepsis 133 [31%], preterm birth 95 [23%], hypothermia 140 [32.3%], meconium aspiration syndrome 79 [18.2%], neonatal jaundice 177 [40.8%], neural tube defects 31 [7.1%], and trachea esophageal fistula 134 [31%]. Concerning causes of death, PNA 43 [30.1%], sepsis 31 [23.3%], LBW 41 [49%], Respiratory distress 35 [28.9%], low Apgar score 42 [21.6%], SGA 38 [43.2%], preterm 32 [33.7%], hypothermia 12 [8.6%], MAS 3 [3.8%], jaundice 25 [14%], neural tube defects 3 [9.7%] trachesophageal fistula 33 [24.6%] were identified medical conditions related to neonatal death in their NICU stay (Table 5).

TABLE 2 Maternal health conditions in NICU, TASH, Addis Ababa, Ethiopia, from 1 January 2015 – 30 December 2021.

Variables	Category	Outcome [$N = 434$]		Row total
		Death	Censored	
		Count [%]	Count [%]	Count [%]
Gravidity	Prim gravida	24 [11.9]	177 [88.1]	201 [46.3]
	Multigravida	24 [10.3]	209 [89.7]	233 [53.7]
Parity	Primipara	28 [11.8]	209 [88.2]	237 [54.6]
	Multipara	20 [10.2]	177 [89.8]	197 [45.4]
Antenatal follow-up	Complete	17 [4.8]	340 [95.2]	357 [82.3]
	Incomplete	23 [36]	41 [64]	64 [14.75]
	None	8 [61.5]	5 [38.5]	13 [3]
maternal blood group	A	12 [9.8]	111 [90.2]	123 [28.3]
	B	14 [10.6]	118 [89.4]	132 [30.4]
	AB	8 [10.5]	68 [89.5]	76 [17.5]
	O	11 [11.6]	84 [88.4]	95 [22]
	Unknown	3 [37.5]	5 [62.5]	8 [1.8]
RH factor	RH positive	1 [2.6]	38 [97.4]	39 [8.99]
	Rh-negative	44 [11.4]	343 [88.6]	387 [89.2]
	Unknown	3 [37.5]	5 [62.5]	8 [1.8]
Onset of labor	Spontaneous	36 [10.0]	323 [90.0]	359 [82.7]
	Induced	12 [16.0]	63 [84.0]	75 [17.3]
The current mode of delivery	Normal vaginal delivery	28 [10.0]	251 [90.0]	279 [64.3]
	Assisted vaginal delivery	5 [11.1]	40 [88.9]	45 [10.37]
	Cesarean section	15 [13.6]	95 [86.4]	110 [25.4]

The time to death of a neonate

A total of 434 neonates who were admitted to the NICU of TASH during the study period have been followed from 0 to 28 days. The overall time to death was 17 days [95%CI: 16.71–19.35] with a minimum and the maximum follow up time of 1 and 23 days. In this study, 48 [11.1%] of the neonates died during the follow-up period. Out of 386 censored, 310 [80.3%] were alive and discharged to home, 65 [16.8%] referred and 11 [2.9%] were lost to follow-ups.

The overall incidence rate was 19.2 [95% CI: 14.5, 25.03] deaths per 1,000 live births in 2499 person-day observations]. The cumulative proportion of surviving at the end of the1st, 7th, 14th, and 23rd days was 99.8, 87.5, 66.3, and 61.2%, respectively. The overall probability of survival of neonate was about 0. 612 [95% CI: 0.46–0.73] for the follow-up period of time (Figure 1).

Survivorship function between groups of neonates

Those neonates who were diagnosed as small for their gestation had a longer survival time than those who were appropriate for their gestation and large for their gestation 9.8 [95% CI: 8.54–11.06], and the median survival time for small for gestation was 10 [95% CI:7.72–12.2]. The Kaplan-Meier graph curve shows the mean and median survival time of those neonates who had low admission weight was 11 days with [95% CI: 8.82–12.81], and 10 days of median [95% CI: 7.72–12.27], respectively, and for those who had a normal admission weight, their mean survival time was 21 days [19.98–22.10], which was longer than the mean survival time of low birth and big baby. The mean and median survival time of preterm was 10.5 [9.14–11.9], 11 [7.8, 14.23] and for post-term neonates, their mean survival time was 16.8 [12.12–17.3], which was shorter than the mean survival time of term neonates 21 days [19.6–22.2].

Predictors of neonatal mortality

Results of the multivariable cox proportional hazard regression analysis revealed that neonates who were small for their gestational age were 5 times more likely to die as compared to those who were appropriate for their gestations [AHR:4.8 (95% CI: 2.33–9.72)].

Those neonates who had an APGAR score of less than 7 at 5th min were about 5 times more likely to die as compared

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TABLE 3 Maternal Gynecologic, and obstetric conditions at NICU, TASH, Addis Ababa, Ethiopia, from 1 January 2015 – 30 December 2021.

Variables category		Outcome [$N = 434$]		
		Death	censored	
		Count [%]	Count [%]	Row total
Maternal, gynecologic and	Yes	15 [10.9]	123 [89.1]	138 [32]
obstetric problems	No	33 [11.1]	263 [88.9]	296 [68]
Abortion	Yes	4 [8.2]	45 [91.8]	50 [36]
	No	11 [12.4]	78 [87.6]	89 [64]
PROM	Yes	1 [10.0]	9 [90.0]	10 [7.2]
	No	15 [11.0]	113 [89.0]	128 [92.8
Prolonged labor	Yes	2 [5.3]	36 [94.7]	38 [27.5]
	No	13 [13.0]	87 [87.0]	100 [72.5
Previous C/S	Yes	6 [15.0]	34 [85.0]	40 [29]
	No	9 [9.2]	89 [90.8]	98 [71]
Placenta Previa	Yes	3 [18.8]	13 [81.3]	16 [11.6]
	No	12 [9.8]	110 [90.2]	122 [88.4
Oligohydramnios	Yes	2 [14.3]	12 [85.7]	14 [10]
	No	13 [10.5]	111 [89.5]	124 [90]
Chorioaminities	Yes	1 [10.0]	9 [90.0]	10 [7.2]
	No	14 [10.9]	114 [89.1]	128 [92.8
Poly hydramnios	Yes	0 [0.0]	5 [100.0]	5 [3.6]
	No	15 [11.3]	118 [88.7]	133 [96.4
Cephalo-pelvic	Yes	2 [11.8]	15 [88.2]	17 [12.3]
disproportion	No	13 [10.7]	108 [89.3]	121 [87.7
multiple pregnancy	Yes	0 [0.0]	5 [100.0]	5 [3.6]
	No	17 [11.5]	116 [88.5]	133 [96.4

TABLE 4 Maternal medical and related conditions NICU, TASH, Addis Ababa, Ethiopia, from 1 January 2015 – 30 December 2021.

Variables category		Death	Censored	Row total
		Count [%]	Count [N %]	Count [%]
Maternal medical	Yes	19 [21.3]	70 [78.7]	89 [20.5]
problems	No	29 [8.4]	316 [91.6]	345 [79.5]
Hypertension	Yes	8 [18.2]	26 [81.8]	44 [49.5]
	No	6 [13.3]	49 [86.7]	45 [50.5]
HIV	Yes	7 [29.2]	17 [70.8]	24 [27]
	No	12 [18.5]	53 [81.5]	65 [73]
Diabetes mellitus	Yes	9 [39.1]	14 [60.8]	23 [25.8]
	No	17 [25.8]	49 [74.2]	66 [74.2]
cardiac diseases	Yes	6 [30.0]	14 [70.0]	20 [22.5]
	No	13 [18.8]	56 [81.2]	69 [77.5]
TORCH infections	Yes	1 [9.1]	10 [90.9]	11 [12.4]
	No	18 [23.1]	60 [76.9]	78 [87.6]
Others	Yes	7 [26.9]	19 [73.1]	26 [29]
	No	12 [19.0]	51 [81.0]	63 [71]

to those who had an APGAR of >7 [AHR:5.0 (95% CI: 1.51–15.04)]. Pre-term newborns had 4 times increased hazard of death than term newborns [AHR 4.2 (95% CI: 1.32–8.83)]. Neonates who diagnosed and admitted with perinatal asphyxia were 5 times more likely to die as compared to those who were not asphyxiated [AHR: 5.2 (95% CI: 1.92–14.30)]. Neonates born from mothers who did not attend ANC visits during their pregnancy were four times at higher risk of death than neonates born from mothers who had antenatal follow up [AHR: 3.7 (95% CI: 1.86,7.60)]. Low birth weight neonates were 7.3 times more likely to die than normal birth weight neonates [AHR: 7.3 (95% CI: 2.69, 19.91)]. Neonates who were in respiratory distress had nearly 2.5 times more likely to die than those who were not in distress [AHR: 2.5 (95% CI: 1.24–5.09)]. Those who had neonatal sepsis at the time of admission were three times more likely to die than those who did not have sepsis [AHR: 3.4 (95% CI: 1.71–4.01)]. Neonates diagnosed as having TEF had 2.2 times more Hazardous than those neonates who did not have [AHR: 2.2 (95% CI: 1.13–4.32)] (Table 6).

Discussion

The study showed that the overall incidence rate was 19.2 deaths per 1,000 live births. Neonates were followed for 2,499 [95 CI; 2,326, 2,671] days, resulting in an overall incidence rate of 19.2 deaths per 1,000 live births. This finding was lower EDHS 2019 report [33 deaths per 1000 live births], respectively (24), Tigray region 62.5 per 1,000 live births (25), Wolayita Sodo teaching and university hospital 27 per 1,000 live births (26), and Sidama Zone in South nation 41 per 1,000 live births (27). This difference could be due to sample size taken, study design employed, study period, and also might be related to the variation of the health service coverage. Besides, this tertiary hospital gives service to those neonates who were referred from different areas of the country for better management. This made the referral system linked to treat to those client who couldn't' treated in other hospitals. Hence, the report from this hospital is lower than EDHS report. Because, EDHS data included reports from different institution from district hospital to tertiary hospital.

The result of this study showed that about 11.1% newborns were died, which was less than studies done in Cameroon 15.7% (28). The difference could be sources of data; this study reviewed data from only NICU admitted neonates, and might be also related to the quality of health care service given.

In this study, about 70% neonatal deaths were registered in the early neonatal period [0–6 days], and 30 % of were died during the late neonatal period which was inconsistent with study done in Kara Mara, in which 96 % were early

TABLE 5 Neonatal medical conditions or assessments who were admitted at NICU of TASH, Addis Ababa, Ethiopia, from 1 January 2015 – 30 December 2021.

Variable category		Outcome[$N = 434$]		Row total
		Death	Censored	
		Count [%]	Count [%]	Count [%]
Maturity of the newborn	AGA	6 [2]	314 [98]	320 [73.7
	LGA	4 [15.4]	22 [84.6]	26 (41)
	SGA	38 [43.2]	50 [56.8]	88 [20.3]
Gestational age	Preterm	32 [33.7]	63 [66.3]	95 [21.9]
	Term	12 [4]	293 [96]	308 [70.9]
	Post-term	4 [11.8]	30 [88.2]	34 [7.8]
Weight at admission	LBW	41 [49]	43 [51]	84 [19.4]
	NBW	6 [2]	335 [98]	341 [78.6
	BIG BABY	1 [12.5]	8 [87.5]	9 [2]
APGAR score at the first minute	≤3	24 [22.2]	84 [76]	108 [24.9]
	4–6	21 [9]	213 [91]	234 [53.9]
	≥7	3 [3.3]	89 [96.3]	92 [21.2]
APGAR score at 5 min	≤3	28 [37.3]	47 [62.7]	75 [17.3]
	4–6	14 [11.8]	105 [88.2]	119 [27.4]
	≥7	6 [2.5]	234 [87.5]	240 [55.3]
Perinatal asphyxia	Yes	43 [30.1]	100 [69.9]	143 [33]
	No	5 [1.7]	286 [98.3]	291 [67]
Respiratory distress	Yes	35 [28.9]	86 [71.1]	121 [27.9]
	No	13 [4.2]	300 [95.8]	313 [72.1]
Hypothermia	Yes	12 [8.6]	128 [91.4]	140 [32.3]
	No	36 [12.2]	258 [87.8]	294 [76.7]
Neonatal jaundice	Yes	25 [14]	152 [86]	177 [40.8]
	No	23 [8.9]	234 [91.1]	257 [59.2]
Sepsis	Yes	31 [23.3]	102 [76.7]	133 [30.6]
	No	17 [5.6]	284 [9.4]	301 [69.4]
Meconium aspiration syndrome	Yes	3 [3.8]	76 [96.2]	79 [18.2]
	No	45 [12.7]	310 [87.3]	355 [81.8]
Neural tube defects	Yes	3 [9.7]	28 [90.3]	31 [7.1]
	No	45 [11.2]	358 [88.8]	403 [92.9]
Feeding practice	breastfeeding	35 [8.5]	379 [91.5]	414 [95.4]
	Formula feeding	0 (41)	2 [100.0]	2 [0.5]
	Mixed feeding	3 (41)	15 [84]	18 [4.1]
Tracheoesophageal fistula	Yes	33 [24.6]	101 [75.4]	134 [30.9]
	No	15 [5.2]	285 [94.8]	300 [69.1]

neonatal deaths (29) and a study done in NICU at Arba Minch General Hospital, Southern Ethiopia 91% (30). This variation could be explained in terms of variations in the presence of obstetric complications during pregnancy, and failure in early identification and poor management of maternal medical, obstetric and gynecological complications, which determines mortality in the first week of neonatal life. Moreover, this difference perhaps due to study period difference along with advance in the health care system that people's attitudes and awareness about health conditions that bring the neonates for ill health and increase in health-seeking behavior.

In this study, being pre-term newborn had an increased hazard of death than term neonates and was consistent with studies done in Cameroon (28), and Ghana (31) This might be due to preterm babies are not fully prepared to live outside the uterus, as their bodies are not fully matured than full-term babies. In addition, this variation may be due to study period, variation in sample size taken and study design conducted.

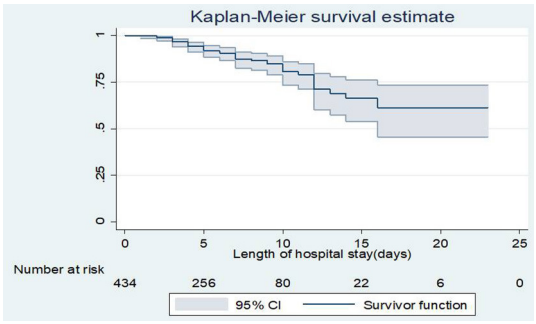

FIGURE 1
Overall Kaplan-Meier survival estimate of neonates admitted to NICU, TASH, Addis Ababa, Ethiopia, from 1 January 2015 – 30 December 2021.

The finding of this study had a lesser hazard of death than studies done in Ghana (32), and a pooled analysis was done on low income and middle-income countries (33), this variation might be due to methodological difference, and presence of less maternal predisposing factors for preterm birth in this study area.

Another significant predictor of neonatal death was perinatal asphyxia. Asphyxiated neonates were more likely to die than neonates without asphyxia, which makes it similar to a study done in NICU of Komfo Anokye Teaching Hospital [KATH] in Ghana (34), and NICU of Gondar university hospital (22). This might be related to asphyxiated neonates failed to establish breathing at birth than non-asphyxiated neonates, but this study finding was different from a study done in Wolayta Sodo about 2 times (26). This might be due to early diagnosis and treatment in Wolayeta Sodo before complications occur.

In this study, an APGAR score of <3 was found to be a significant factor, which was similar with the previous studies done in Cameroon (28), EasternEthiopia (35), Kenya (36), China (32, 37), Swedn (38) and Arba Minch (30) and Eastern. This might be related to 5th min APGAR score which is a useful index of the response to resuscitation efforts, and low APGAR score neonates are risky to be oxygen-deprived than an APGAR of >7. This discrepancy might be explained by the sample size, and obstetrical care, and neonatal resuscitation efforts. Low birth weight neonates were more likely to die than normal birth weight neonates, this was in line with a study done in NICU of Kath in Eastern Ethiopia (35), and in Northern Ethiopia (25). This might be due to a baby with low birth weight is at increased risk for complications of low birth asphyxia, hypothermia, feeding problem, infections, and prematurity, which might increase their risk of death than normal birth weight babies.

Those neonates who were small for their gestational age were more likely to die than those neonates who had appropriate gestational age, which was in line with a study done in Canada (34). Those who had neonatal sepsis at the time of admission were more hazardous to die than those who did not have sepsis, a consistent finding was observed in a study conducted at NICU of Gondar referral hospital (22), Tigray Hospitals (39) and Kenya (36). Neonates admitted with a diagnosis of respiratory distress were more prone to death than those who were not in distress, and was consistent with a study done in Wolayta Sodo (26), but this study had a lesser hazard than a study done in Ghana (32). This study illustrated that about 29% of neonatal death was related to respiratory distress, which was more hazardous than a study done in Kara Mara, Somali region of Ethiopia 24.4% (29). However, it was consistent with studies in Tigray (39), and Gondar (22).

Trachea esophageal fistula (TEF) was the other predictor of neonatal death. Neonates diagnosed as having TEF were more hazardous than those neonates who did not have. In this study, about 24.6% of neonates were died due to diagnosed TEF, which is consistent with previous study (40). Neonates with this condition potentially develop aspiration and faced feeding difficulties resulting in low calories and immunity which affect their growth and development. Neonates could easily dehydrate due to decreased fluid intake, inadequate breastfeeding.

Limitations and strength of the study

Strength of this study includes:- This is an approach to clearly indicate the temporal sequence of the predictor and outcome variable (death); Data reviewing was conducted by trained nurses, and standardized data abstraction tool was used and It enables to estimate the survival time of neonates, and identify predictors for future trend estimation and other related prevention and intervention programs.

Using secondary sources may result in loss of potential predictors, which may not be addressed in this study design like; maternal nutritional status, educational level, and family-related issues. As the incomplete charts were excluded from the study there may be selection bias. This study was done retrospectively which might cause recall bias due to failure of the caregiver to remember what was happened previously.

Conclusion

The overall incidence rate during the 2,499 person-time was 19.2 deaths per 1,000 person-day observation with a time to death of 17 days.

The independent predictors were incomplete or no maternal antenatal follow up, being small for gestation, preterm, low birth weight, low 5th min Apgar score, neonatal sepsis, respiratory distress, perinatal asphyxia, and TEF. This recommended that maternal health during pregnancy, including quality of antenatal care utilization should be further strengthened, and risky pregnant mothers should be identified antenatally. Initiating different strategies to work on early identification,

TABLE 6 Results of the bivariable and multivariable Cox regression on predictors of neonatal mortality in TASH, Addis Ababa, Ethiopia, 1 January 2015 – 30 December 2021.

Variables	Category	Outcome		CHR [95% CI]	AHR [95% CI]
		Died	Censored		
Gravidity	Primgravida	24 [11.9]	177 [88.1]	0.63 [0.36,1.2]	1.7 [0.61–4.5]
	Multigravida	24 [10.3]	209 [89.7]	–	–
Antenatal follow-up	Complete	17 [4.8]	340 [95.2]	–	–
	Incomplete	23 [36]	41 [64]	8.5 [4.5, 16.02]	3.7 [1.86, 7.60]**
	None	8 [61.5]	5 [38.5]	9.4 [4.0–22.0]	4.0 [1.41–10.71]*
Rh factor	Positive	1 [2.6]	38 [97.4]	0.3 [0.04,2.12	0.8 [0.02–17.33]
	Negative	44 [11.4]	343 [88.6]	–	–
	UK	3 [37.5]	5 [62.5]	1.93 [0.6–6.3]	–
Maturity of the newborn	AGA	6 [2]	314 [98]	–	
	LGA	4 [15.4]	22 [84.6]	9 [2.5–32.9]	2.5 [1.32–14.21]*
	SGA	38 [43.2]	50 [56.8]	20 [8.7–49.3]	4.8 [2.33,9.72]*
Gestation age	Preterm	32 [33.7]	63 [66.3]	8.2 [4.2–16]	4.2 [1.32–8.83]*
	Term	12 [4]	293 [96]		
	Post term	4 [11.8]	30 [88.2]	2.7 [0.86–8.3]	0.6 [0.07–5.44]
Weight	LBW	41 [49]	43 [51]	21 [9.03,50.34]	7.3 [2.69,19.95]*
	NBW	6 [2]	335 [98]	–	–
	BIG BABY	1 [12.5]	8 [87.5]	10.6 [1.3, 49]	3.0 [1.23–5.12]*
APGAR score at the first minute	≤3	24 [22.2]	84 [76]	3.9 [1.15–12.7]	3.0 [0.54–10.04]
	4–6	21 [9]	213 [91]	2.7 [0.8–9]	2.4 [0.61–12.03]
	≥7	3 [3.3]	89 [96.3]	–	–
APGAR score at 5 min	≤3	28 [37.3]	47 [62.7]	14 [5.8–33.7]	5.0 [1.51–15.04]**
	4–6	14 [11.8]	105 [88.2]	2.2 [0.8–5.8]	2.0 [0.42–12.02]
	≥7	6 [2.5]	234 [87.5]	–	–
Perinatal asphyxia	Yes	43 [30.1]	100 [69.9]	0.06 [0.03,0.2]	5.2 [1.92–14.30]**
	No	5 [1.7]	286 [98.3]	–	–
Respiratory distress	Yes	35 [28.9	86 [71.1]	0.12 [0.08–0.3]	2.5 [1.24– 5.09]*
	No	13 [4.2]	300 [95.8	–	–
Jaundice	Yes	25 [14]	152 [86]	0.6 [0.3,1.009]	0.9 [0.26–3.13]
	No	23 [8.9]	234 [91.1]	–	
Sepsis	Yes	31 [23.3]	102 [76.7]	0.2 [0.13–0.4]	3.4 [1.71–4.01]**
	No	17 [5.6]	284 [9.4]	–	
TEF	Yes	33 [24.6]	101 [75.4]	0.2 [0.01–0.3]	2.2 [1.13–4.32] *
	No	15 [5.2]	285 [94.8]		

**p < 0.001, *p < 0.05.

quality and continuous care for neonates coming with an assessment of preterm, low birth weight, perinatal asphyxia, respiratory distress, and sepsis and tracheoesophageal fistula and implementing it to ensure quality neonatal 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 AAU, College of Health Science, School of Nursing and Midwifery Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MM, GM, WK, FT, and BA was responsible to conception, design, acquisition of data, analysis and interpretation of data, and was responsible in the writing the original research and preparation of the manuscript for publication. BG and KD were responsible for design, supervision, and reviewing it for accuracy and integrity. All authors play roles in this research article, read, and approved the final manuscript.

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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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Publisher's note

Supplementary material

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Virtual Faculty Development in Simulation in Sub-Saharan Africa: A Pilot Training for Pediatricians in Kisumu, Kenya

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Introduction: Simulation is an effective educational tool increasingly being utilized in medical education globally and across East Africa. Globally, pediatric patients often present with low frequency, high acuity disease and simulation-based training in pediatric emergencies can equip physicians with the skills to recognize and intervene. Northwestern University (NU) in Chicago, IL, USA, and Maseno University (MU), in Kisumu, Kenya launched a predominantly virtual partnership in 2020 to utilize the Jaramogi Oginga Odinga Teaching & Referral Hospital (JOOTRH) simulation center for MU faculty development in simulation based medical education (SBME) for medical students.

Materials and methods: Educational goals, learning objectives, and educational content were collaboratively developed between MU and NU faculty. Virtual sessions were held for didactic education on simulation pedagogy, case development, and debriefing. Mixed educational methods were used including virtual mentored sessions for deliberate practice, piloted case facilitation with medical students, and mentored development of MU identified cases. Trained faculty had the summative experience of an intensive simulation facilitation with graduating MU students. MU faculty and students were surveyed on their experiences with SBME and MU faculty were scored on facilitation technique with a validated tool.

Results: There were four didactic sessions during the training. Seven cases were developed to reflect targeted educational content for MU students. Six virtually mentored sessions were held to pilot SBME with MU students. In July 2021, fifty students participated in a week-long SBME course led by the MU trained faculty with virtual observation and mentorship from NU faculty. MU faculty reported positive experience with the SBME training and demonstrated improvement in debriefing skills after the training. The overwhelming majority of MU students reported positive experiences with SBME and endorsed desire for earlier and additional sessions.

Discussion and conclusions: This medical education partnership, developed through virtual sessions, culminated in the implementation of an independently run simulation course by three trained MU faculty. SBME is an important educational tool and faculty in a resource constrained setting were successfully, virtually trained in its implementation and through collaborative planning, became a unique tool to address gaps for medical students.

KEYWORDS

simulation based medical education (SBME), resource limited settings, Kenya, faculty development, virtual education, global health

Introduction

Global healthcare inequities are multifactorial, and contributing factors include a paucity of practitioners as well as limited access to specialty training (1). Simulation-based medical education (SBME) can be used to address healthcare inequities by allowing medical students and general practitioners to gain skills in specialized patient scenarios they may not typically (or frequently) encounter in their training. For example, simulation training has been shown to improve learners' abilities to manage emergencies (2, 3). In many parts of the world including sub-Saharan Africa, where medical education has historically relied heavily on didactics followed by direct patient care (4), SBME allows for a safe transition between the classroom and the hospital as it can be used to expose trainees to situations that they may not otherwise encounter without putting patients at risk (5). SBME, however, remains in its early stages in sub-Saharan Africa.

Historically, simulation has been thought of as taking place solely in high-fidelity labs with costly technology, making it difficult to implement in resource-limited settings. Successful implementation of SBME in a variety of educational settings, including those with fewer resources, has demonstrated that this is not true. In fact, simulation is quite well-suited to teaching with a variety of resources and can be done *in-situ* (in locations of patient care), with low-fidelity tools, and even virtually. SBME has been implemented in these various forms, including in high-fidelity labs, across the African continent. This educational strategy has been used to train learners on surgical skills in Ghana, Tanzania, Ethiopia, Zambia, Uganda, Kenya, and other countries over the last several decades (6). In Rwanda, a simulation center was established in partnership with a Canadian institution that was utilized by trained local faculty across disciplines (7). The Vital Anesthesia Simulation Training (VAST) course has been used to train anesthetists in Rwanda, Tanzania, Ethiopia, India, Fiji, and Canada on essential non-technical skills (8).

There are three phases of a successful simulation: the case pre-brief, the facilitation of the case, and the case debrief. Faculty educators using simulation must learn how to appropriately develop and select cases, as well as master each of the simulation phases (9, 10). Learning is active and self-paced during simulation; learners apply theory to practice, and self-critique their thought processes and actions. Additionally, learners get real-time feedback from expert faculty during cases to identify areas of improvement and reinforce best practices. Simulation can be used to address a diverse range of topics including clinical care, technical skills, effective communication, and clinical decision-making.

Simulation is particularly useful in pediatrics, where emergencies are less common but can be clinically challenging. SBME allows the learner to practice emergency management skills without causing patient harm when mistakes are made. One Kenya-based study identified that much of inpatient pediatric mortality occurs early in hospitalization (11). In another study, Kenyan providers found their interns ill-prepared for patient care upon graduation from medical school (12). These two studies highlight the need for better trainee preparation and support the use of training aimed specifically at the early recognition of critically ill pediatric patients and their subsequent resuscitation. At Maseno University (MU) in Kisumu, Kenya, clinical education for medical students is largely comprised of didactic lectures, teaching on rounds, case discussions/tutorials, and exams for assessment. In 2017, a new simulation lab was established at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH), the primary teaching hospital for MU. The simulation lab has been used for clinical training in various specialties including anesthesia, obstetrics, and more recently, management of critically ill patients with COVID-19. The COVID-19 pandemic decreased interaction between medical students and patients and created the need to use alternative tools to provide clinical training in a safer environment. A study looking at data from 204 hospitals found a decline in admissions under the age of 5 for medical and surgical care (13), further emphasizing the role of SBME in pediatric training. To address this need for medical students rotating in pediatrics at MU, an online SBME faculty development curriculum was co-created *via*

TABLE 1 Virtual faculty development curriculum.

Curricular goals

To work with pediatric faculty at Maseno University and provide them with a comprehensive training in an educational tool, pediatric simulation, for them to use in teaching their trainees to care for acutely ill children.

Curricular objectives

1. By the completion of this training, the participants will be able to describe and apply the basic pedagogical framework behind simulation in medical education
2. By the completion of this training, the participants will be able to describe and apply the fundamentals of the PEARLS framework for simulation debriefing
3. By the completion of this training, participants will lead and debrief a remote simulation case and receive constructive feedback from their peers
4. By the completion of this training, participants will have the tools to develop, run, and debrief pediatric simulation cases for medical trainees

Curricular activities

Phase of curriculum	Educational method	Educational content
Introduction to Simulation	Didactic Sessions	*Lecture*: Introduction to Simulation *Lecture*: Introduction to Debriefing—the PEARLS framework *Lecture*: Pedagogy of Simulation for Medical Education *Lecture*: Writing Learning Objectives for SBME *Workshop*: Developing a Simulation Case *Lecture*: Different Learner Types, Troubleshooting Facilitation, and Incorporating Communication into the Case
Internal Deliberate Practice	Virtual Simulation Case Facilitation	Faculty learners practiced taking on roles of learner, observer, and facilitator within their learner group and would repeat case facilitator roles as needed
	Virtual Simulation Case Facilitation—Developing a New Case	Faculty learners practiced taking on roles of learner, observer, and facilitator within their learner group for a case they developed
External Deliberate Practice	Virtual Simulation Case Facilitation with NU virtual Mentorship	Faculty learners had observed facilitation of 7 cases with virtual mentorship from NU Simulation faculty with direct feedback. Rotating medical students participated as pilot participants.
Cumulative Experience	Five-day simulation symposium held for medical students	50 medical students participated in simulation facilitated by trained faculty over an intense 5-day period. NU faculty present virtually to assess performance and provide feedback. Every student participated in or observed a neonatal resuscitation case and two others.

a collaboration between Northwestern University Feinberg's School of Medicine's Center for Global Health Education (CGHE) and MU. The curricular goal was to teach simulation and debriefing pedagogy and skills to pediatric faculty educators to use with their medical learners.

Materials and methods

Curriculum development

An online SBME faculty development curriculum was developed in 2020 and then implemented with MU faculty in the department of pediatrics between October 2020 and July 2021. A team from MU, JOOTRH and NU's CGHE was assembled, and a targeted needs assessment was completed through strategic planning sessions. The sessions explored MU faculty as learners (experiences, preferences, expectations, etc.), stakeholder needs, facilitators, resources, and barriers. The team reviewed existing curriculum from NU, and together they used available resources, demography of patients seen at JOOTRH, and educational gaps to guide the selection of educational content and instructional strategies. Pediatric emergency cases were identified through this process and thus targeted for initial case development. The PEARLS (Promoting Excellence and Reflective Learning in Simulation) framework was used to guide debriefing (14). The goal of the curriculum was to train MU faculty in the facilitation of SBME, so that they could independently design and implement a simulation program for medical students during their pediatric rotations at JOOTRH. Brief, intermittent, mixed methods online synchronous educational sessions were used to introduce topics and build SBME mastery in facilitation.

Curriculum implementation

Sessions were held over 12 months using an online collaborative platform, with MU faculty located at the high-fidelity simulation center at JOOTRH, and NUCGHE faculty teaching and facilitating remotely. Introductory content was delivered through didactic sessions that were interspersed with demonstrative videos. Collaborative case development was done with MU and NUCGHE faculty over email and through virtual meetings to reflect the context at JOOTRH and match resources in the simulation lab. Trainings were done entirely virtually, and four educational methods were used: didactic training, internal practice, observed deliberate practice, and ultimately a summative simulation session run independently by learners. Deliberate practice was first done within the group of faculty learners to familiarize themselves with SBME facilitation; practice then continued with mentored sessions in which participating MU faculty facilitated cases in person for medical students, and NUCGHE faculty were available virtually. Directive feedback was provided as faculty practiced simulation debriefing, and self-assessment was encouraged reflecting domains covered in a validated debriefing rubric—the Objective Structured Assessment in Debriefing (OSAD) tool (15, 16). Throughout the sessions, educational and case content was adjusted to reflect learner-driven goals. A capstone experience was supported with MU faculty learners leading a simulation symposium for medical students.

Evaluation

Several strategies were used to evaluate the curriculum implementation. Learner perceptions and feedback were self-reported *via* survey halfway through the curriculum. Additionally, debriefing skills were targeted as a primary assessment outcome and were evaluated *via* the OSAD rubric on initial and final debriefing experiences (15). Assessments were completed by curriculum leadership, and learners were also invited to self-assess after viewing recorded sessions in order to identify personal areas of improvement in the domains of Approaching, Environment, Engagement, Reaction, Reflection, Analysis, Diagnosis, and Application (15). Finally, during the summative experience, the participating medical students at JOOTRH were anonymously surveyed about their experiences and satisfaction.

Results

The virtual faculty development curriculum for SBME is described below (Table 1). Using this curriculum, three MU pediatric faculty were trained in SBME to facilitate cases in pediatric emergencies for medical students rotating through pediatrics. There were six deliberate practice sessions to build SBME skills. Seven clinical cases were developed in collaboration between NU and the MU faculty to address identified educational gaps for MU students, reflecting the clinical experience at JOOTRH (Table 2). As a final component of the curriculum, MU faculty hosted a 5-day simulation symposium for all fifty graduating MU medical students.

MU faculty learners were surveyed online and reported little prior exposure to simulation and reported positive experiences with the curriculum. Two NU faculty assigned OSAD scores to primary and final observed case facilitation, and faculty learners were invited to self-assess as well. Skills were shown to improve from first to last debriefing session when averaging scores among all participants (Figure 1).

Medical students participating in the simulations overwhelmingly reported positive experiences *via* anonymous online survey accessed *via* QR codes. Thirty-five of the fifty students completed the online survey and reported that participating in simulation was useful and valuable, and would recommend it to their peers. All either partially or fully agreed that they were more confident taking care of children after participation in simulation. In a free-text portion of their evaluation, student comments included a request for increased frequency of simulation cases, for earlier incorporation of simulation into their education, and for simulation to be included in other disciplines.

Additionally, one of the pediatric faculty learners who completed the curriculum presented the simulation training program at two international conferences.

Discussion

Through this innovative partnership, three pediatric faculty were successfully trained in simulation-based medical education using a novel curriculum. Medical students reported a high degree of satisfaction with the simulation sessions run by MU faculty.

The rise of virtual meeting platforms during the COVID-19 pandemic allowed the development of a relationship between

TABLE 2 Clinical cases for simulation.

Clinical cases
Neonatal Resuscitation
Neonatal Sepsis
Respiratory Distress Syndrome
Neonatal Jaundice
Hypovolemic Shock from Diarrheal Disease
Pneumonia/COVID Pneumonia
Ingestion (Organophosphate Poisoning)

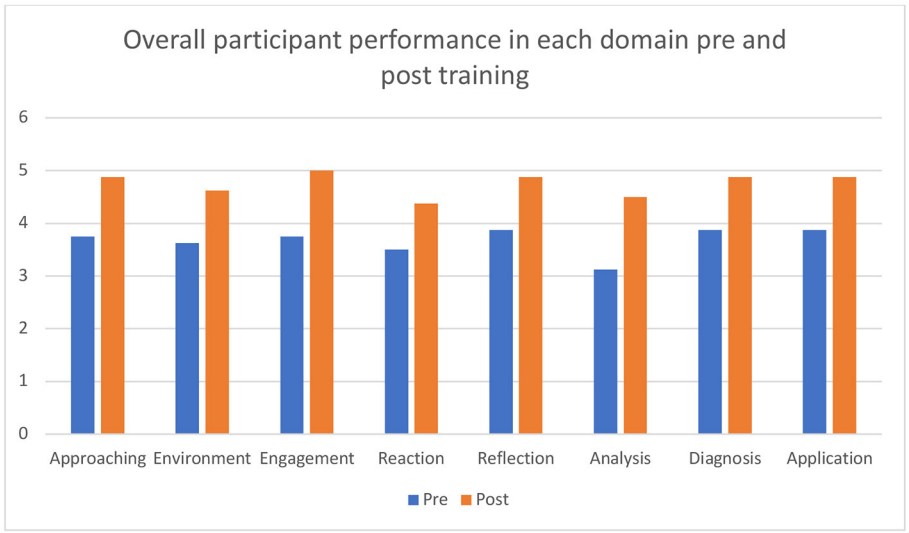

FIGURE 1
Average OSAD scores across all domains before and after facilitator debriefing training.

NUCGHE and MU faculty in a way that would not have otherwise been possible due to restrictions on international travel. By establishing an ongoing virtual partnership, it became possible to collaborate on educational content, goals, and curricular feedback without relying on in-person sessions. The partnership between NUCGHE and MU/JOOTRH developed quickly as busy faculty from both NU and MU held brief virtual meetings at mutually convenient times. Furthermore, by conducting all training sessions online, the mentorship was able to be longitudinal, intermittent, and adaptive to learner needs.

This partnership and curriculum were developed at a key time, as there was a desire to increase the utilization of the high-tech, high fidelity JOOTRH simulation lab. However, its ability to be tailored to individual audiences suggests that this curriculum could also be implemented in variable contexts and potentially lower-tech environments. In educational settings without advanced simulation technology, more emphasis could be placed on *in-situ* simulation; if the simulations are performed in an empty patient room, there need not be a dedicated simulation lab. Additionally, simulations can easily be run with low-fidelity mannequin with simple case adaptations.

There were several limitations of this program. As it was limited to a single institution, only three pediatric faculty were trained in the curriculum; however, these three faculty members are responsible for the bulk of the medical student education in pediatrics at JOOTRH. Time commitment is often a challenge in educational efforts for busy and often overworked medical providers. The virtual, intermittent model helped mitigate this by spreading out content across multiple meetings using spaced repetition of key concepts. Sessions were limited to 2 h and were held at a times most convenient to both learners and facilitators.

One of the most rewarding outcomes of this program was the ability to not only to have three trained pediatric faculty independently implement simulation for pediatric emergencies for medical students, but to also cultivate a medical education partnership through which additional collaborations are evolving. Through this partnership, MU faculty was mentored through a first international conference presentation and NU faculty collaborated with the MU simulation center faculty on a book chapter and a manuscript. The partnership between NUCGHE and MU continues with training in advanced simulation skills, such as rapid cycle deliberate practice. Faculty also continue to collaborate on the development of additional pediatric simulation cases. In the next phase of this partnership, the curriculum has been adapted to be specialty-agnostic, expanding the faculty development program to several other specialties at MU/JOOTRH.

Conclusions

This curriculum represents one model of a virtually implemented faculty development curriculum to improve local capacity of SBME at a medical school in Kisumu, Kenya. Three pediatric faculty continue to facilitate simulations for pediatric emergencies for rotating medical students and have developed an initial case library to use with their students. Trained faculty demonstrated high scores on their case debriefing skills and medical students benefitting from this newly implemented educational tool reported overwhelmingly positive experiences, clamoring for more.

Data availability statement

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

Author contributions

CF led and implemented the curriculum and wrote the primary manuscript. MO, GL, WO, EG, and AD assisted in curriculum content and manuscript preparation. All authors contributed to the article and approved the submitted version.

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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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Applicability of the hour of life approach in hyperbilirubinemia among Filipino term infants

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Background: Hyperbilirubinemia remains a common morbidity among infants. Additional research on bilirubin kinetics and associated risk factors will contribute to providing a more targeted management approach for the Filipino infant.

Objective: To develop a Filipino bilirubin nomogram by studying bilirubin patterns during the first 5 days of life.

Methodology: This prospective study recruited 1,412 stable, full-term infants (≥37 weeks age of gestation) born at the Philippine General Hospital (PGH). Using the Dräger-Minolta JM-103 jaundice meter, transcutaneous bilirubin (TcB) levels were determined at the 3rd, 6th, 12th, 24th, 36th, 48th, 72nd, 96th, and 120th hour of life (HOL). A bilirubin nomogram was created using the averages of 3 TcB forehead and sternal measurements at each time epoch. Simultaneous measurement of TcB and total serum bilirubin (TsB) on a subset of 106 infants was done to determine correlation.

Results: Correlation coefficients were high between TsB and forehead TcB ($r^2 = 0.88$), and between TsB and sternal TcB ($r^2 = 0.91$). The Filipino bilirubin nomogram reflected a steep rise until the 48th hour, followed by plateauing of values. Inadequate nursing and bilirubin levels at 12th and 48th HOL were risk factors for developing significant hyperbilirubinemia at 72nd HOL.

Conclusion: TcB is a reliable, non-invasive bilirubin screening tool. Among healthy, full-term, Filipino infants, their nomogram features a sudden increase in bilirubin values during the first 48 h, followed by a plateau. To aid in identification of infants at risk for significant hyperbilirubinemia, healthcare providers can assess breastfeeding adequacy and perform bilirubin screening at the 24th–48th HOL. Registration No. (RGAO-2016-0686).

KEYWORDS

hyperbilirubinemia, neonatal, nomogram, Filipino, transcutaneous bilirubin, risk factors

Introduction and background

Hyperbilirubinemia, manifested by yellowish skin color, is the most common morbidity in the newborn period (1). The worldwide resurgence of kernicterus—the consequence of severe hyperbilirubinemia—elicited concern for this morbidity. Mortality rate can reach as high as 10% with 70% of the survivors having sequelae of kernicterus (2). Ironically, kernicterus has been described as the most easily preventable form of brain injury in the neonatal period. This has been attributed to delay in recognition and delivery of optimal treatment, especially in low resource settings (3).

The incidence of neonatal hyperbilirubinemia in high income countries has been reported from large country databases. However, the incidence of neonatal jaundice in low to middle income countries is variable since classifications may have been established in the local level, absence of a unified protocol and data obtained mostly from tertiary hospitals (4). Furthermore, early discharge is practiced with clinical follow up not assured, further increasing the risk in the development of severe hyperbilirubinemia (5). Societal awareness of the incidence and complication of neonatal hyperbilirubinemia especially in LMIC countries needs to be strengthen by both pre-discharge and community surveillance (6). Additional risk factors for the development of significant hyperbilirubinemia in low to middle income countries include maternal factors (primiparous, delivery outside the hospital) and neonatal factors (lower gestational age and birth weight, UDP glucuronosyltransferase 1 family, polypeptide A cluster (UGT1A) polymorphisms and sepsis) (7).

In 2004, the American Academy of Pediatrics (AAP) published the hyperbilirubinemia guidelines to better monitor, manage, and follow-up all newborn infants (8). AAP adapted the Hour of Life Approach strategy by Bhutani (9), which utilized a graph identifying risk zones based on the serum bilirubin levels at specific time epochs. This made risk assessment a dynamic process rather than dependent on a single bilirubin level to identify at-risk infants. Unfortunately, only 4.1% of Bhutani's infant population were of Asian descent—a race with a higher incidence of hyperbilirubinemia. Several studies have shown that Asian neonates reach earlier bilirubin peaking as well as higher total bilirubin values (10–12). As such, it is important that each population develop its own nomogram (11). Bilirubin nomograms tailored to certain populations have already been developed: Italian, Greek, American, Hispanic, Brazilian, Indian, Japanese, Thai, and Chinese (13–20). These nomograms showed that some races have higher 95th percentile bilirubin values especially in the first 3 days of life.

Filipinos are believed to have a higher risk of developing significant hyperbilirubinemia (SH). Risk factors, as listed in the AAP guidelines (8), found among Filipino infants include belonging to the East Asian race, high rates of early breastfeeding initiation, and high incidence of Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency (21). While Filipino infants have been included in hyperbilirubinemia studies, they rarely comprise the majority and often grouped under Asian (22) or Pacific Islander descent (23). Studying the bilirubin kinetics among Filipino infants will help in the early recognition and management of significant hyperbilirubinemia.

Objective

This study aimed to develop a Filipino bilirubin nomogram by studying the bilirubin pattern in the first 5 days of a Filipino infant's life.

Significance of the study

There is a dearth of information regarding bilirubin kinetics in the Philippines. In the attempt to develop a Filipino-based bilirubin nomogram, this study will provide new information regarding the reliability of the transcutaneous bilirubin measurement among Filipino infants. Additionally, it also paves the way for identification of specific risk factors for developing significant hyperbilirubinemia centered on the Filipino population.

The eventual development of an hour of life nomogram specific for the Filipino infants will help pediatricians monitor, manage, and follow-up infants at risk of significant hyperbilirubinemia. Moreover, clinical guidelines on management of hyperbilirubinemia may be submitted to the national societies for guidance and implementation.

Methodology

Study design

This is a prospective cohort study which recruited stable full term Filipino infants after birth and monitored bilirubin levels at specific time points up to 120 h of life of stable, with the eventual output of a Filipino bilirubin nomogram.

Study setting

Recruitment of participants was conducted at the Philippine General Hospital (PGH). PGH is a tertiary referral center which is the training hospital of the University of the Philippines. The annual live births in the hospital is around 4,000–6,000 per year. It has a tertiary level NICU with an accredited Fellowship training program in Newborn Medicine. Daily NICU census

ranges from 40–60 sick neonates. There are two maternity wards (total of 76 beds) where the mothers and their stable infants are admitted.

Study population and sampling design

The study used convenient sampling of all eligible infants. The research assistants approached parents of newly born infants who met the following requirements:

Inclusion criteria:

1. Stable, full term (≥37 weeks) newborn infants.
2. <3 h old.
3. Assigned for direct rooming in with mothers in maternity wards.

Exclusion criteria:

1. Small for gestational age infants.
2. Infants who were not given oral feeding.
3. Infants with gastrointestinal anomalies.
4. Infants with lethal congenital anomalies.

Sample size computation

A sample size of at least 1,641 observations was computed with a power of 80% and a 5% level of significance with ABO incompatibility as an independent variable (38% Blood type O and 62% non-Blood Type O) and allowing for a change from a baseline value of 10–20%. This change was correspondent to an odds ratio of 2.25.

The study also correlated transcutaneous bilirubin and serum bilirubin measurements. Based on Ho et al.'s (24) study, with desired $r = 0.1$, power of 0.80, and α of 0.05, at least 83 newborn infants were needed.

Study plan

Definition of terms

Significant hyperbilirubinemia (SH) was defined as having total bilirubin levels ≥95th percentile and would require interventions such as phototherapy (9).

Severe hyperbilirubinemia was defined as having total bilirubin levels reaching ≥99th percentile and would require interventions such as double volume exchange transfusion, aside from intensive phototherapy (8).

Conduct of the study

A trained research assistant approached the mothers whose infants were roomed-in with them in the maternity wards. All infants admitted in the maternity wards were stable infants on exclusive breastfeeding. Once the infant was assessed to meet the inclusion criteria, a written informed consent was obtained from the mother or a legally appointed representative, in case the mother could not provide an informed consent. After an informed consent is obtained, pertinent maternal and infant data were extracted from the medical records. Feeding, urine and stool frequencies were also extracted from the daily monitoring forms in the medical chart. The mothers were approached in case of any clarifications or missing data in the chart.

Transcutaneous (TcB) bilirubin measurement

The research assistants underwent orientation and training on how to use the transcutaneous bilirubinometer, the Dräger-Minolta JM-103 jaundice meter (25). The device determined the yellowness of the infant's subcutaneous tissues through differential measurement of optical densities using blue and green wavelengths. Using two optical paths allowed for more precise measurement of the jaundiced subcutaneous tissues. This was due to the decreased influence of melanin movement and skin maturity.

The device was placed perpendicularly on the forehead and the sternum. Selection of these sites were based on manufacturer's recommendation, based on the principle of sufficient circulation to these areas. The device was pressed gently against the infant's skin until a click was heard. A reading would be shown on the screen. Three determinations were made for both the forehead and the sternum for a total of six determinations per pre-specified time period. Transcutaneous bilirubin (TcB) measurements were done at the 3rd, 6th, 12th, 24th, 36th, 48th, 72nd, 96th, and 120th hour of life (HOL). The TcBs obtained at the different time periods were used to develop the bilirubin nomogram. The device was wiped with 70% alcohol between patients.

Total serum bilirubin (TsB) measurement

To correlate total serum bilirubin with transcutaneous bilirubin values, 106 infants had simultaneous determinations of the TcB bilirubin (average of three determinations of both the forehead and the sternum) and total serum bilirubin (TsB). For each patient, 0.5 ml of venous blood was extracted by trained healthcare professionals. These specimens were placed in a plain microtainer covered with a black carbon paper and sent immediately to the laboratory for analysis. The VITROS XT7600 and 5600 models were used to determine total bilirubin levels in the subset of neonates.

Statistical analysis

The data were encoded in MS Excel. All statistical tests were performed using the IBM Statistical Package for the Social Sciences (SPSS) software. Descriptive statistics were used to summarize demographic profiles. Frequency and proportion were used for categorical variables. Mean and standard deviation were used for normally distributed continuous variables.

Pearson correlation coefficient was computed to correlate TsB and TcB readings. For the development of the bilirubin nomogram, TcB quartiles were determined at the specified time periods. The 95th and the 99th percentile were also determined for significant and severe hyperbilirubinemia, respectively. The 40th centile which was equivalent to the cut off for the low-risk zone in the Bhutani bilirubin nomogram, was also determined.

For the maternal and neonatal risk factors in the development of significant hyperbilirubinemia at the 72nd HOL, independent t-test and Chi square test were used for continuous and categorical variables.

Ethical consideration

Before the start of the study, Ethics Review Board (ERB) approval was secured (UPMREB Code: 2009-018-01). At the maternity wards, written informed consents were provided and explained to the infants' respective parents by trained research assistants. Participation was completely voluntary; participants were given the right to withdraw consent at any time. All data were anonymized. Data forms were stored in locked cabinets. Data were encoded in password protected computers with access limited to the investigators.

Results

Study population demographics

One thousand four hundred and twelve stable, full-term infants, including 36 pairs of twins, were recruited from 2010 to 2014. The infants had the following mean anthropometric measurements: birthweight of 2,872 ± 0.45 g, length of 48.0 ± 2.71 cm, and head circumference of 33 ± 1.7 cm. Most infants were delivered vaginally (61.9%), in cephalic presentation (92.9%), with APGAR scores of 8 becoming 9 at the 1st and 5th minutes of life, respectively.

Mean maternal age was 30.6 ± 7.46 years old; 65.8% was of single civil status. 99.2% received prenatal care with an average prenatal visit of 1.7 ± 0.464 times. Maternal morbidities were as follow: premature rupture of membranes (PROM) (6.2%), bleeding placenta previa (0.9%), diabetes (18.2%), and history of infection (26.8%). Twenty-one mothers (2.9%) were smokers; 15 (2.1%) were alcohol drinkers and 6 (0.6%) mothers admitted to illicit drug use.

All infants were exclusively breastfed at the hospital, with an average of 9.3 ± 2 breastfeeding episodes for the first 24 h. During the first day of life, the average number of urination and stooling per day were 1.5 ± 0.91 and 1.8 ± 0.95, respectively.

Correlation of total serum bilirubin and transcutaneous bilirubin

A subset of 106 stable, full-term infants had data for simultaneous TsB and TcB levels. Correlation coefficients between TsB and forehead TcB was at $R^2 = 0.88$, while those between TsB and sternal TcB was $R^2 = 0.91$ (refer Figures 1, 2).

Mean bilirubin values at different time points

Table 1 showed the mean bilirubin levels at different hours of life. Among infants who subsequently developed SH at the 72nd HOL, the mean bilirubin values were significantly higher than those who did not. There was almost a doubling (1.6–1.8-fold increase) in mean TcB values from 3rd to the 6th hours, 6th to the 12 hour and 12th to the 24th hour. There was a fivefold increase for the first 24 h (3rd HOL to 24th HOL) which slowed down from 24th to 48th HOL (1.3–1.56-fold increase) (see Table 1).

Determination of different bilirubin percentile groupings at different time points

One thousand four hundred and twelve infants had TcB values at the 3rd, 6th, and 12th HOL. Infants were discharged around the 24th HOL which would explain attrition in the number of TcB determinations in the subsequent time points. The mothers were encouraged to return for subsequent determinations but not all returned despite calling or sending text messages. There was a total of 6 TcB determinations (3 on the forehead and 3 on the sternum) in each infant. Subsequently, there were 8,472 TcB determinations ($n = 1,412$ infants) each for the 3rd, 6th, and 12th time period, 7,938 TcB determinations ($n = 1,323$ infants) for the 24th HOL, 6,714 ($n = 1,119$ infants) for the 48th HOL, 5,136 ($n = 856$ infants) for the 72nd HOL, 3,630 ($n = 605$ infants) at the 96th HOL and 2,388 ($n = 308$ infants) at the 120th HOL. Bilirubin values were enumerated into 25th, 40th, 50th, 75th, 95th and 99th percentiles.

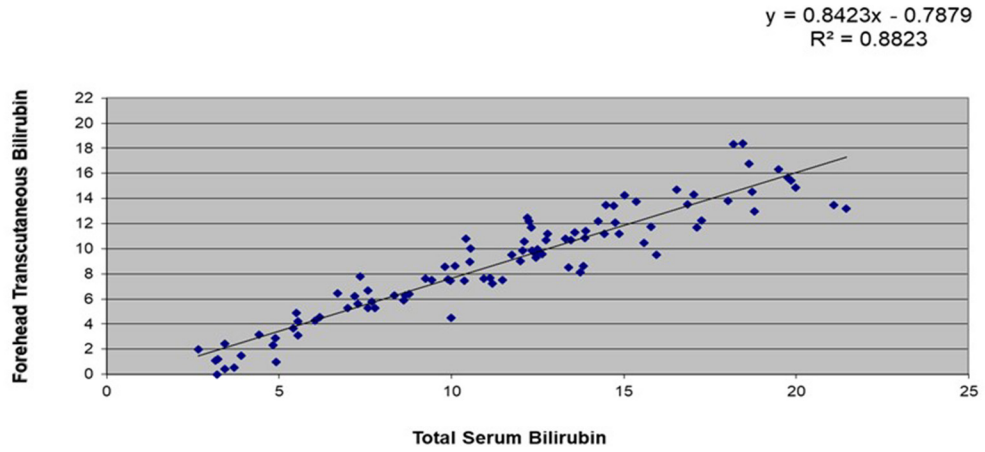

FIGURE 1
Correlation between total serum bilirubin (TsB) and forehead transcutaneous bilirubin (TcB) levels among stable, full-term Filipino infants (n = 106).

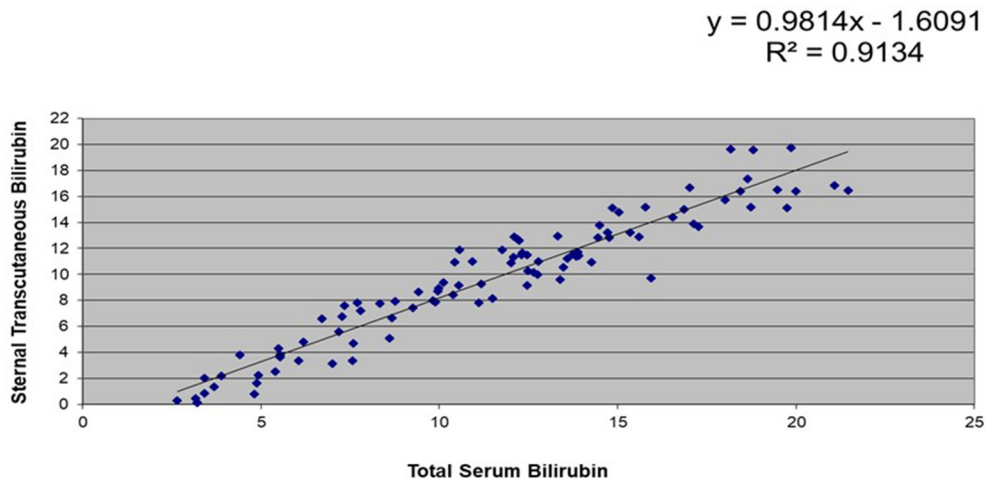

FIGURE 2
Correlation between total serum bilirubin (TsB) and sternal transcutaneous bilirubin (TcB) levels among stable, full-term Filipino infants (n = 106).

Determination of the cut-off for the low-risk zone

<25th percentile

The chances of TcB levels <25th percentile at different time points shifting to levels >95th percentile (High risk zone or HRZ) on subsequent time points were from 0 to 4.6% (see Table 2). Upon further analysis, the risks of bilirubin values ≤25th percentile shifting to the high intermediate risk zone (HIRZ = 75th to the 95th percentile) in subsequent time periods were low at 3.1–8.1%.

<40th percentile

TcB levels <40th percentile at different time points have risks of significant hyperbilirubinemia on subsequent time points ranged from 0 to 4.5% (see Table 2). The risks of shifting to TcB levels between 75 and 95th percentile (HIRZ) were 6.6–9.1%.

<50th percentile

TcB levels <50th percentile have risks of significant hyperbilirubinemia at subsequent time periods from 0.2 to 3.8% (see Table 2). The risk of shifting to TcB levels between 75 and 95th percentile was 0.1–11.1%.

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TABLE 1 Comparison of mean bilirubin levels at different time points and subsequent high risk zone status at the 72nd HOL.

Time points	<95th percentile at 72nd HOL		≥95th percentile at 72nd HOL		*p value*
	n	Mean TcB	*n*	Mean TcB	
3rd HOL	1370	1.4 ± 0.87	42	2.1 ± 1.09	0.00
6th HOL	1370	2.5 ± 1.18	42	3.6 ± 1.24	0.00
12th HOL	1370	4.2 ± 1.35	42	5.6 ± 1.62	0.00
24th HOL	1281	7.4 ± 2.64	42	9.3 ± 2.87	0.00
48th HOL	1077	9.8 ± 2.87	42	14.7 ± 2.27	0.00

TABLE 2 Comparison of different bilirubin percentiles (25th, 40th and 50th) and frequencies of developing significant hyperbilirubinemia (≥ 95th percentile) at different time points.

HOL	Percentiles	Frequency (%) of significant hyperbilirubinemia at different time periods				
		12th HOL	24th HOL	48th HOL	72nd HOL	96th HOL
3rd	25th	0.6	4.6	0.6	0.9	0.8
	40th	2.0	3.9	0.7	1..3	1.1
	50th	2.0	4.0	1.1	1.6	1.4
6th	25th	1.3	3.7	0.6	0.8	0.
	40th	2.0	2.7	0.7	1.1	1.2
	50th	2.1	2.8	1.1	1.3	1.1
12th	25th		4.6	0.6	1.1	1.7
	40th		4.5	1.0	1.6	1.6
	50th		3.8	1.1	1.5	1.5
24th	25th			0.8	1.2	1.8
	40th			0.6	1.3	1.7
	50th			0.6	1.4	1.5
48th	25th				0	0
	40th				0	0.4
	50th				0.2	0.9

Percentile groups and risk of upward shift

25th–50th percentile

Taking bilirubin levels between the 25th–50th percentiles revealed a risk of developing SH at subsequent time periods to be from 2.1 to 4.9% only. However, the risks of shifting to HIRZ were high at 19.9, 18.6, 15.7–16.8, and 12.1–15.3% at 12th, 24th, 48th and 72nd HOL. The risk of shifting to HIRZ at the 96th HOL for bilirubin values from 25 to 50th percentile were 8.5 to 10.7% (see Table 3).

50th–75th percentiles

For TcB levels between the 50th and the 75th percentiles, the risk of developing SH was <5% on subsequent time periods. While shifting to the HIRZ were 19.9, 18.6, 15.7–16.8, and 8.5–10.7% at 24th, 48th, 72nd, and 96th HOL.

75th–95th percentile

Values at the HIRZ remained stable overtime with only <5% shifting to High-Risk Zone.

Plotting the selected bilirubin percentiles

The graph was plotted using the first three quartiles and then the 95th and the 99th percentile. In Figure 3, there was a steep rise in the bilirubin from the 3rd to the 24th hour of life with doubling of the bilirubin levels from the 3rd hour of life to 6th hour of life as well as from the 12th to the 24th HOL. After the 24th HOL, there was around 2–3 mg/dl increase in the bilirubin levels at the 48th HOL. From the 48th HOL to the 72nd HOL, the increase was from 1 to 2 mg/dl only. From 72nd to 120th HOL, the 95th and 99th percentile TcB levels have plateaued. For the 25th, 50th and 75th percentile bilirubin levels, there remained a 1 mg/dl/day increase from the

TABLE 3 25–50th percentile bilirubin levels and subsequent shift to higher percentile groups (75–<95th and ≥ 95th) at different time points.

25-50th percentile	Frequency (%) of shifting to higher risk zones at subsequent time points									
	12th HOL		24th HOL		48th HOL		72nd HOL		96th HOL	
	75-<95th	≥95th	75-<95th	≥95th	75-<95th	≥95th	75-<95th	≥95th	75-<95th	≥95th
3rd HOL	19.9	4.9	18.6	4.7	15.7	3.9	12.1	3	8.5	2.1
6th HOL	19.9	4.9	18.6	4.7	15.7	3.9	12.1	3	8.5	2.1
12th HOL			18.6	4.7	15.7	3.9	12.1	3	8.5	2.1
24th HOL					16.8	4.2	12.9	3.2	9.1	2.3
48th HOL							15.3	3.8	10.7	2.7

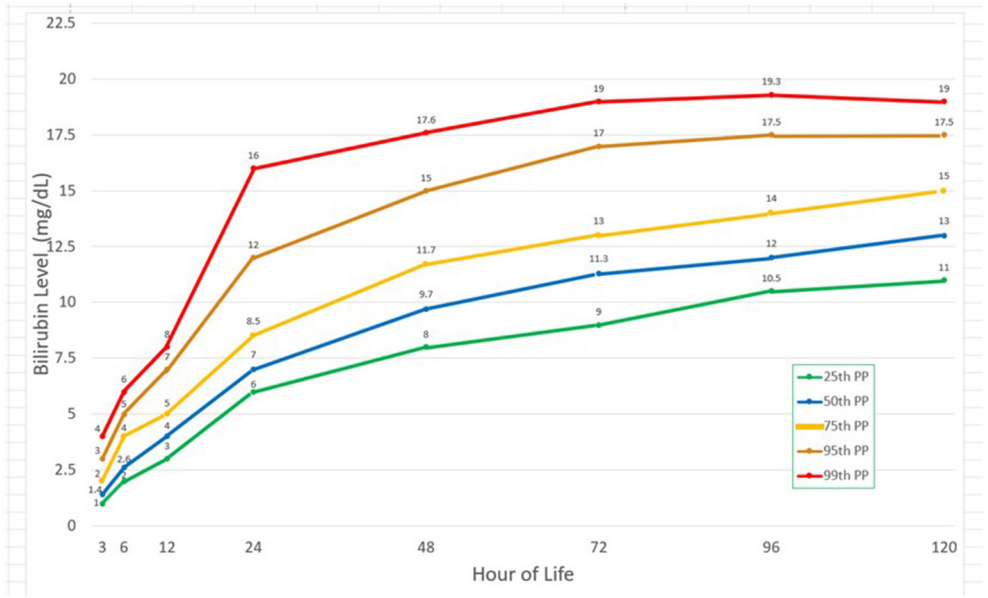

FIGURE 3
Bilirubin values at different time points and corresponding 25th, 50th, 75th, 95th, and 99th percentiles.

72nd to the 120th HOL but the values did not reach 17 mg/dl (significant hyperbilirubinemia).

Risk factors for developing significant hyperbilirubinemia at 72nd HOL

AAP listed risk factors for developing significant hyperbilirubinemia (SH). One of which was of East Asian descent and in this study, all participants were Filipinos. Significant AAP risk factors were presence of bruising (p = 0.001) and cephalhematoma (p = 0.001) while male sex (p = 0.442), younger gestational age (p = 0.227), and history of jaundice in an older sibling (p = 0.772) were not significant (see Table 4).

Additional significant risk factors for developing SH at the 72nd HOL were <3 prenatal care visits (p = 0.026), unspecified maternal infection aside from UTI (p = 0.008), and TcB readings >95th percentile at the 12th and the 48th HOL. Non-significant risk factors were maternal blood type O^+ (p = 0.304), jaundice at the first 24 hours (p = 0.772), fetal presentation (p = 0.093), route of delivery (p = 0.784), PROM (p = 0.078), maternal diabetes (p = 0.643), maternal UTI (p = 0.187) and histories of tobacco smoking (p = 1.0), alcohol (p = 1.0) and substance abuse (p = 0.619) (see Table 5).

All the infants were breastfed. For the feeding patterns, decreased feeding frequency at all time points except at first 24 hours, decreased urine frequency at 12th to 48th HOL, and decreased stool frequency

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TABLE 4 Association of AAP guidelines' risk factors and significant hyperbilirubinemia at 72nd HOL.

Risk factors	No Significant hyperbilirubinemia at 72nd HOL	Significant hyperbilirubinemia at the 72nd HOL	*p* values
1. East Asian race	All Filipino descent		
2. Exclusive breastfeeding	All were exclusively breastfed		
3. G6PD deficiency (patient or relative	Results not available		
4. Sex			0.581
Male	679	19	
Female	691	23	
5. Jaundice in a previous sibling			0.087
Yes	2	1	
No	1,370	41	
6. Cephalhematoma			0.001*
Yes	4	3	
No	1,366	39	
7. Bruising			0.012*
Yes	14	3	
None	1,356	39	
8. Mother's blood type			0.765
Blood Type O	866	26	
Other Blood types	489	16	

*For cells with < 5 numerical values, Fischer's Exact test was performed. For the rest, Pearson's Chi-square was done.

from 12th to 24th HOL were all significant risk factors (see Table 6).

Finalizing the Filipino bilirubin nomogram

Figure 4 is the Filipino bilirubin nomogram with the different risk zone categories. Low Risk Zone (LRZ) which contains bilirubin values <25th percentile, has a <2% risk of developing significant hyperbilirubinemia (>95th percentile or High Risk Zone) at all time points except at the 24th HOL when the risk is at 4.6%. For the Intermediate Risk Zone (IRZ), the 2nd and 3rd quartiles (25th–75th percentiles) have been combined due to having the same risk of developing significant hyperbilirubinemia. The IRZ has a <5% risk of developing SH but an almost 20% risk of shifting to the next zone, the High Intermediate Risk Zone (HIRZ), especially during the first 24 hours of life. The HIRZ has a <5% risk of shifting to the High Risk Zone (HRZ). Still, the HIRZ may be used as a cut-off for starting phototherapy among infants with risk factors. Bilirubin levels in the HRZ (>95th percentile or significant hyperbilirubinemia) will warrant initiation of phototherapy while those in the Very High Risk Zone (>99th percentile or severe hyperbilirubinemia) will require intensive phototherapy while preparing for exchange transfusion.

Discussion

This study showed that there was a high correlation between the TsB and TCB levels among Filipino infants. There was a higher correlation between the TsB and the sternal TcB ($R^2 = 0.91$) compared with the forehead TcB ($R^2 = 0.88$), which could be due to the sternum being covered with clothing, causing less exposure to environmental light. Similarly, a study in Thai infants (26) reflected higher correlation between TsB and sternal TcB compared to forehead TcB. Both studies' results also showed that TcB tends to underestimate TsB values.

There have been concerns about the reliability of TcB among darkly pigmented infants based on how the bilirubinometer uses a light source (xenon) to compute for wavelength differences between skin and subcutaneous tissue (27). However, recent studies have shown TcB readings are not affected by skin color (28). High correlation between TcB and TsB has also been shown among infants of Asian descent such as Japanese (29), Chinese (24), Mongolian (30) and specifically those of Malay descent (darker skin)—Indonesian (31), Myanmar (12) and Thai (26). This study further supports that TcB measurements can reliably estimate total serum bilirubin levels among Filipino infants and as such can be used for bilirubin screening prior to discharge.

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TABLE 5 Association of maternal characteristics and significant hyperbilirubinemia at the 72nd HOL.

Characteristics	No Significant hyperbilirubinemia at 72nd HOL	Significant hyperbilirubinemia at the 72nd	*p* values
Marital status			0.50
Single	648	15	
Married	450	16	
Prenatal care			0.26
Yes	1,381	41	
No	9	1	
No of prenatal visits			0.026*
< 3 visits	389	21	
3 and above	978	21	
History of chorioamnionitis			1.0
Yes	1,369	42	
No	1	0	
Presentation			0.093
Cephalic	1,264	40	
Traverse	88	2	
Breech	88	2	
Route of delivery			0.784
Vaginal	783	23	
Forceps	73	4	
Vacuum	40	1	
Cesarean section	514	14	
PROM (>18 hours)			0.078
None	1,293	38	
Yes	77	3	
Antibiotic use			0.51
Yes	658	18	
No	712	24	
History of diabetes			0.643
No	1,137	36	
Yes	233	6	
Amniotic fluid volume			0.001*
Normal	1,357	39	
Oligohydramnios	13	3	
History of infection			0.001*
Yes	345	20	
No	1,025	22	
UTI			0.187
Yes	336	16	
No	499	17	
Substance abuse			0.619
Yes	8	0	
No	1,362	42	
Tobacco usage			1.0
Yes	21	0	
No	775	28	
Alcohol use			1.0
Yes	18	0	
No	780	28	

*For cells with < 5 numerical values, Fischer's Exact test was performed. For the rest, Pearson's Chi-square was done.

TABLE 6 Association of feeding pattern and significant hyperbilirubinemia at 72nd HOL.

	No significant hyperbilirubinemia at 72nd HOL		Significant hyperbilirubinemia at 72nd HOL		*p value*
	N	Mean ± SD	*N*	Mean ± SD	
3rd HOL					
Weight	1368	2865 ± 446.8	42	2740 ± 432.5	0.074
Feeding frequency	1370	0.6 ± 0.6	42	0.7 ± 0.44	0.042*
Urine frequency	1370	0.1 ± 0.29	42	0.02 ± 0.15	0.103
Stool frequency	1370	0.1 ± 0.11	42	0.2 ± 0.15	0.627
6th HOL					
Weight	1366	2845 ± 445.8	42	2740 ± 432.5	0.073
Feeding frequency	1370	1.3 ± 1.11	42	1.8 ± 0.76	0.001*
Urine frequency	1370	0.90 ± 0.85	42	0.95 ± 0.53	0.730
Stool frequency	1370	0.70 ± 0.62	42	0.8 ± 0.45	0.284
12th HOL					
Weight	1368	2865 ± 446.8	42	2739 ± 432.5	0.074
Feeding frequency	1370	3.12 ± 3.21	42	4.28 ± 2.29	0.020*
Urine frequency	1370	1.21 ± 1.01	42	1.90 ± 0.69	0.001*
Stool frequency	1370	0.8 ± 0.75	42	1.4 ± 0.58	0.001*
24th HOL					
Weight	1370	2866 ± 446.3	42	2740 ± 432.7	0.071
Feeding frequency	1247	9.3 ± 1.99	42	9.3 ± 2.0	0.885
Urine frequency	1365	1.6 ± 0.93	42	2.17 ± 1.05	0.001*
Stool frequency	1365	1.8 ± 0.94	42	2.1 ± 0.92	0.029*
48th HOL					
Weight	1075	2842 ± 454.5	42	2739 ± 432.7	0.151
Feeding frequency	1075	9.8 ± 1.80	42	10.6 ± 1.51	0.004*
Urine frequency	1075	2.6 ± 0.98	42	3.2 ± 0.75	0.001*
Stool frequency	1075	2.2 ± 0.82	42	2.3 ± 0.74	0.788

The Filipino bilirubin nomogram shows a rapid rise in the bilirubin levels up to 72 HOL and subsequently plateaus thereafter. In this study, there is a two-fold increase from the 3rd to the 6th HOL. There is also an almost two-fold increase from the 12th to the 24th HOL where the steepest rise can be seen in the bilirubin nomogram.

For the 95th percentile TcB values, there is an absolute rise of 8 mg/dL within this 12-hour interval. Subsequently, the rise is 2–3 mg/dl from the 24th to the 48th HOL, and only 1–2 mg/dL from 48th to 72nd HOL and from 72nd to 96th HOL. There is a small (<1 mg/dL) increase from the 96th to 120th HOL. In the Philippines, where majority of infants are discharged at the 24th HOL, bilirubin levels at this time point will expect to increase by 3–5 mg/dL at the 72nd HOL. For those who will be discharged at the 48th HOL, only 1–2mg/dL increase has been noted at the 72nd HOL. These findings will assist in the clinicians' decision making on whether to discharge a jaundiced infant at the 24th HOL.

In this study, the 95th and 99th percentile bilirubin levels at the 72nd HOL are 17 and 19 mg/dL respectively. There is minimal increase (<1 mg/dL) in the bilirubin levels thereafter. Peak bilirubin levels have also been seen around the 72nd HOL in both Caucasians and Asians with higher values found in the latter group (20, 32).

Upon plotting the 95th percentiles of the bilirubin values from the 24th to the 96th HOL, marked differences from 4 to 5 mg/dL were observed among the different populations/races. Asians were noted to have higher 95th percentile values at all time points. Notably, the new US nomogram also had higher values even if only <2% of the infants were of Asian descent. For the Filipino nomogram, the 95th percentile values were the highest at the 24th to 48th HOL and second highest at the 72nd HOL among the different populations. It plateaus after the 72nd HOL like the Mongolian and European 95th percentile values as opposed to the other populations where the bilirubin values continue to trend upward. This highlighted the importance of developing a nomogram for specific populations due to different bilirubin kinetics. Furthermore, among Filipino infants, close monitoring for the development of significant hyperbilirubinemia should be done in the first 72 hours of life (see Figure 5) (10, 30, 33–39).

The determination of the cut-off for the low-risk zone involved determination of the frequency of developing subsequent SH. In this study, the low-risk zone corresponded

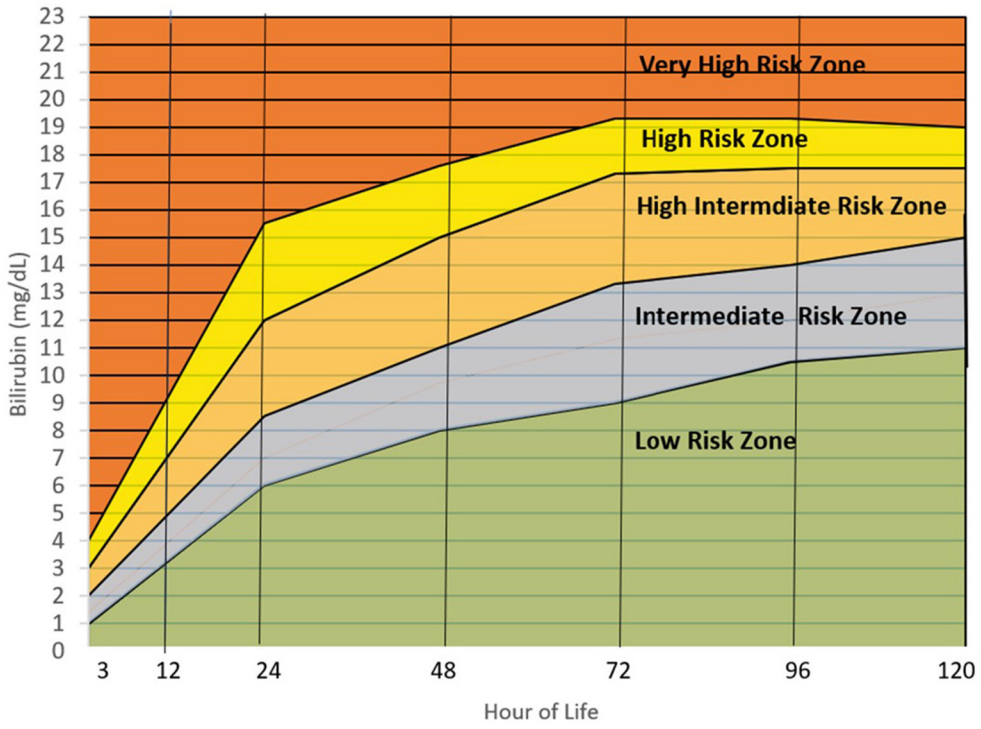

FIGURE 4
Filipino bilirubin nomogram showing the different risk zones. Low Risk Zone or LRZ (0–<25th percentile)-Infants with bilirubin levels falling in this zone have a <5% risk of developing significant hyperbilirubinemia (SH) (>95th percentile or High-risk zone). The infants may be discharge and followed up after 48–72 hours, especially if they were discharged <72 hours of life. Intermediate Risk Zone or IRZ (25th–<75th percentile)-Infants with bilirubin levels in the IRZ have a <5% risk of subsequent SH but have a 15–20% risk of shifting to the High-Risk Intermediate Zone (HIRZ), especially if the bilirubin determination was done in the first 48 hours. For infants with risk factors, bilirubin may be repeated after 24 hours. High Intermediate Risk Zone or HIRZ (>75th–<95th percentile)-Infants with bilirubin levels in the HIRZ, should be further observed and have a repeat of bilirubin determination after 24 hours. In the presence of risk factors such as hemolytic disease, young gestational age, weight loss (>10%), sepsis and others, phototherapy may be started. High Risk Zone or HRZ (95th–<99th percentile)-Infants with bilirubin levels at the HRZ have significant hyperbilirubinemia and require initiation of phototherapy. Very High Risk Zone or VHRZ (≥99th percentile)-Infants with bilirubin levels at the VHRZ have severe hyperbilirubinemia and require immediate intensive phototherapy while preparing for exchange transfusion. Risk factors identified by the AAP and significant in this study are: Gestational age< 38 weeks, inadequate nursing (significant weight loss), male sex, ABO/RH incompatibility, G6PD deficiency, East Asian race, cephalhematoma/bruising, previous sibling requiring phototherapy during the neonatal period. Other risk factors identified in this study are: Inadequate prenatal visits, maternal infection, decreased amniotic fluid, and decreased feeding, urine, and stooling frequency in the first 72 hours.

to the first quartile where the risk of subsequent development of SH was less than 5%. In the Bhutani bilirubin nomogram, the low-risk zone corresponded to bilirubin values < the 40th percentile which has a <5% risk of developing SH (9, 40). Using the 40th or the 50th percentile as the cut-off for the Filipino nomogram will still have a <5% risk of developing significant hyperbilirubinemia but a 10% risk of reaching bilirubin levels in the HIRZ at the 72nd HOL, where infants with risk factors may be started on phototherapy based on the AAP guidelines (8). Furthermore, TcB values between 25 and 50 percentiles have almost a 20% of shifting to the HIRZ in subsequent time points.

The intermediate risk zone in the Filipino nomogram was the combination of the 2nd and 3rd quartile (25th−75th percentile) since both quartiles correspond to a low risk of developing SH (<5%) but with a higher risk (almost 20% in the first 24th HOL) to shifting to the HIRZ. In the Bhutani chart, there is a designated low intermediate risk zone which is from 41st to 75th percentiles (9). In a review of readmissions due to SH, 28% of the infants who were readmitted were initially in Bhutani's low intermediate risk zone prior to discharge (40). This reiterated that even though bilirubin levels were below the 75th percentiles, close follow up for possible development of significant hyperbilirubinemia should be ensured.

With regards to risk factors for the development of SH at the 72nd HOL, all infants in this study were of East Asian descent (Filipino) which was an established risk factor. Another risk factor such as hemolytic anemia due to ABO/Rh blood incompatibility was not determined since infant blood type was not routinely done in the hospital. Maternal blood type O, *per se*, was not found to be significantly associated with SH in this study.

Filipinos have a high incidence of G6PD deficiency at 1: 50 (21). In a study by Silao et al., 16.7% of Filipinos undergoing phototherapy have G6PD deficiency (21). At the time of this study, G6PD deficiency screening was not yet routinely done in the hospital and thus was not determined. To get more

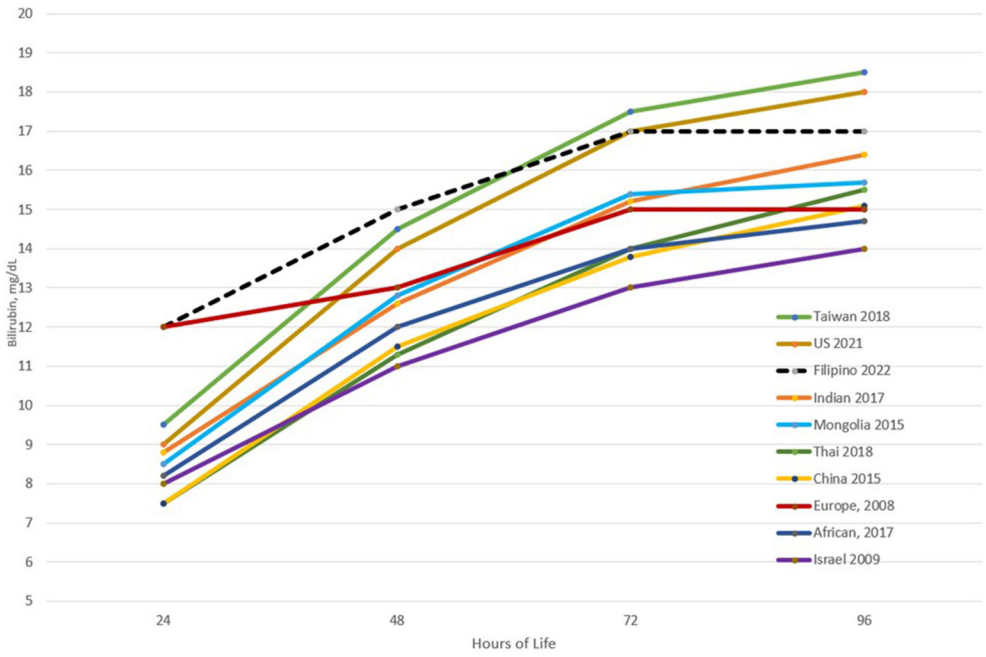

FIGURE 5
Comparison of the 95th percentile bilirubin values at different time points across different populations.

information about G6PD deficiency in the family, mothers were asked if the infant has a sibling with G6PD deficiency, but all mothers were not aware of the condition in the sibling. To determine possible familial reason for hemolysis, report of an elder sibling requiring phototherapy during the neonatal period was not a significant factor for developing SH ($p = 0.087$). Significant risk factors for developing SH at the 72nd HOL were presence of bruising ($p = 0.001$), cephalhematoma ($p = 0.001$), unspecified maternal infection (aside from UTI) ($p = 0.008$) and inadequate prenatal visits ($p = 0.026$).

Inadequate nursing has also been identified as a risk factor for significant hyperbilirubinemia (3). In this study, all the infants were initiated on breastfeeding within 30 mins of life as part of the Essential Intrapartum and Newborn Care protocol. All were exclusively breastfed during the study period. On monitoring of the infants, those who had less frequent feeding, urination, and stooling from the 6th to the 48th HOL had a higher risk of SH. A case control study of infants of Thai descent revealed that early initiation of breastfeeding (1.5 vs. 5.56 h), breastfeeding >8x a day and >10 mins breastfeeding duration were more frequent in the non-jaundice group (41). Lactation counseling starting prenatally and within the first few hours post-delivery focusing on early initiation of breastfeeding, duration, and frequency especially during the first 48 h of life may avert occurrence of SH. Close monitoring of stool and urine frequency, as a surrogate of nursing adequacy, may alert clinicians of any problems with lactation.

In the final Filipino bilirubin nomogram, the AAP risk factors as well as those identified in the study (maternal infection, bruising and cephalhematoma and inadequate nursing) were enumerated as risk factors. Presence of these factors should increase vigilance in monitoring for subsequent development of SH by either delaying discharge for further observation, repeating bilirubin determination after 12–24 h or early clinic follow up 24 h after discharge. Also, presence of the risk factors may lead to earlier initiation of phototherapy at bilirubin values in the high intermediate risk zone (HIRZ) like the AAP recommendations (8).

Strengths and limitations

This is a relatively large cohort of infants where the bilirubin levels were measured in the first 5 days of life. Feeding patterns in addition to other known risk factors were determined. The limitation of this study is the attrition rate over time due to the early discharge and non-follow up of the infants. Still the total measurements were >1,000 in later time points. Infant blood type and G6PD deficiency determinations were not routinely determined in the hospital. Information from

these will better help in the screening and management of the infants.

Conclusion and recommendation

Transcutaneous bilirubin levels highly correlate with total serum bilirubin levels among Filipino newborn infants. A Filipino nomogram has been developed which showed a rapid rise of bilirubin levels in the first 3 days of life. Bilirubin rise is greatest during the first 24 hours of life, and plateaus after the 72nd hour of life. Presence of bruising and cephalhematoma are important risk factors for the development of SH. Inadequacy of nursing within the first 48 HOL is a modifiable risk factor which can be averted by early lactation counseling and monitoring. The Filipino bilirubin nomogram shows a unique bilirubin kinetics and as such, will better assist the bilirubin screening and subsequent management of Filipino infants.

Author's note

This work was presented at NIH Anniversary, Bayanihan Hall, Pioneer St. UNILAB, Mandaluyong Metro Manila Philippines in March 2016.

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 NIH Ethical Review Board (Dr. Jacinto V. Mantaring III—Head). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MV-U wrote the protocol, supervised the conduct of the study, and also did some of the statistical analysis. HU assisted in the supervision of the conduct of the study and the review of the manuscript. MA computed for the sample size as well as assist in the statistical analysis. All authors contributed to the article and approved the submitted version.

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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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The use of virtual tools in narrowing the impact of health disparities in neurology

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The concept of Epilepsy Treatment Gap (ETG) refers to the proportion of people with epilepsy who are not being appropriately treated. The ETG in the USA approaches 10%, with historically underserved populations and rural populations disproportionately affected. The ETG in Low-and Middle-Income Countries (LMIC) is reported to be 5–10 times higher than in high-income countries. The growing availability of reliable internet access offers a unique opportunity to provide better care to children and adults with epilepsy. In this paper we explore various telehealth (TH) initiatives that have leveraged the availability of easy and free access to an internet connection in reducing the ETG in underserved regions of the world. We describe several interventions targeted to reach patients and providers in rural areas of the United States and in LMIC. First, we examine initiatives that were developed to improve patient access to coordinated care and education regarding epilepsy and seizures. Next, we describe an intervention designed to improve knowledge of epilepsy diagnosis and treatment for providers in LMIC. We conclude with a brief overview of the use of virtual tools in diminishing the ETG.

KEYWORDS

neurology, education, epilpesy, virtual medicine, telehealth, treatment gap

Introduction

Despite improvements in care for epilepsy, the global burden of epilepsy remains high with approximately 46 million people affected in 2016 (1). In 2001 the International League Against Epilepsy introduced the concept of Epilepsy Treatment Gap (ETG) as the proportion of people with epilepsy who are not being appropriately treated (2). The ETG in the USA approaches 10%. However, there is evidence that the ETG is higher in historically underserved populations (3) and in rural populations (4). Furthermore, while improvements in care have reduced the burden of epilepsy in developed countries, the burden remains high in Low-And-Middle-Income-Countries (LMIC)- where multiple barriers prevent patients from receiving effective treatments,

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including counterproductive cultural beliefs and practices, and lack of access to physicians with a basic knowledge of epilepsy diagnosis and treatment (1). It is estimated that about three quarters of people with epilepsy living in LMIC don't get necessary treatment (5). Epilepsy is most prevalent in children younger than five and among older adults (6). The burden of disease is especially heavy in children and adults with breakthrough seizures. However, it is estimated that up to 70% of patients with epilepsy can become seizure free with proper antiepileptic treatment (5). The growing availability of reliable internet access offers a unique opportunity to utilize telehealth (TH) services to provide better care to children and adults with epilepsy. In this paper we explore various initiatives that have leveraged the availability of easy and free access to an internet connection in reducing the ETG in underserved regions of the world. We will describe several interventions that were targeted to reach patients and providers, in rural areas of the United States, and in LMIC. In the first part of the paper, we will examine initiatives that were developed to improve patient access and knowledge, while in the second half we will describe an intervention designed to improve knowledge of epilepsy diagnosis and treatment for providers.

TABLE 1 Epilepsy videos and number of families who completed each video.

Video #	Educational video	Number completed
	GROUP 1	
1	What is epilepsy?	10
2	What is a seizure?	12
3	What's the difference between a seizure and epilepsy?	6
4	Are there different kinds of seizures?	6
5	Are there things that can increase the chances that my child will have a seizure?	5
6	What should I do if my child has a seizure?	2
7	Are there precautions I need to take for my teen?	3
16	Do kids with epilepsy have other symptoms?	3
17	FAQs about epilepsy	3
	TOTAL COMPLETION GROUP 1	50
	GROUP 2	
8	How do you diagnose epilepsy?	0
9	How do medications treat epilepsy?	1
10	What is neurostimulation and how does it treat epilepsy?	3
11	What is ROSA and how does it treat epilepsy?	1
12	Can you treat epilepsy with surgery?	1
13	What is the ketogenic diet, and does it treat epilepsy?	1
14	**TOTAL COMPLETION GROUP 2**	7
	GROUP 3	
14	What is a tonic-clonic seizure?	1
15	What is an absence seizure?	5
	TOTAL COMPLETION GROUP 3	6

This table represents the 17 videos that were created by the Children's Mercy Hospital Team. The number of completions indicates the number of families who completed the demographics, pre survey, video and post survey. It is further broken down into 3 groups. Group 1 includes 9 videos that provide general information regarding seizures and epilepsy. Group 2 includes 6 videos which discuss diagnoses, treatment plans, and nonpharmacological therapies. Finally, Group 3 includes 2 videos which are specific to seizure types.

Reaching the patient

With the COVID19 pandemic, the use of TH in the United States became a necessity. Out of this necessity, general acceptance of telemedicine has grown, including in the management of pediatric epilepsy (7). With the increase of TH services, new applications have arisen to improve access and to leverage the power of synchronous and asynchronous virtual connections to improve education for patients, families, and caregivers in LMIC (8). One way in which this technology has naturally evolved is in the care of complex patients living in remote areas. In this first example we show how remote connections *via* TH can be used to manage even the most complex patients.

Leveraging virtual communications to provide expert advice

The first example is a case report that demonstrates how one can leverage the power of TH to care for complex patients in remote areas. In July 2021 one of our neurology providers (JBLP) was approached by a provider working in the Kurdistan region of Iraq, asking for assistance with the care of a 9-month-old infant with a complex medical history. The child was the mother's sixth pregnancy. Four of the children (two girls and two boys) died early in life (between 45 days of life and 3 years old); at least one of these children had a history of epilepsy. The other sibling is a healthy 9-year-old boy. The patient, an infant girl, was born full term without complications. She was hospitalized at 1 month of age with cold like symptoms. A head CT revealed "brain atrophic changes". She developed failure-to-thrive and seizure like activity. Several EEGs showed both focal and generalized epileptiform activity. The team in Iraq was able to obtain exome testing in Germany that revealed a homozygous likely pathogenic variant in the *C2orf69* gene, consistent with a genetic diagnosis of the autosomal-recessive *C2orf69*-related neurodevelopmental-disorder. Variants in *C2orf69* associate with mitochondrial respiratory enzyme chain dysfunction. This rare disorder has been reported in less than a dozen patients, most of middle eastern ancestry (Turkish, Pakistani,

and Kurdish) (9). At the time of the consultation, the child was treated with levetiracetam and phenobarbital, she struggled with feeding, had developed failure to thrive, and was having daily breakthrough seizures. With the help of a dietician from the Charlie Foundation and a Neurologist with experience in the management of mitochondrial diseases, both in the United States, the team in Iraq was able to initiate a ketogenic diet. Several meetings were arranged using synchronous Zoom videoconferencing for the team in the United States to meet the child and the family. The child achieved ketosis and since starting the diet has been stable with rare breakthrough seizures and good weight gain. Clinically she is more alert and interactive. The team continues to follow the child with regular updates and lab results using the WhatsApp messaging application. This example illustrates how by leveraging the power of virtual communications, providers in LMIC can reach out for consultations for patients with rare and complex metabolic disorders (in this case a mitochondrial disease) and successfully manage these children.

YouTube as an educational instrument

In the second example we demonstrate the asynchronous use of YouTube to facilitate patient and family education and engagement in the care of children and youth with epilepsy (CYE). Family engagement has been shown to have significant impacts on the care of children with chronic diseases, including improved compliance with medication regimen, disease outcome, and quality of life (10). Family engagement is contingent on a basic understanding of the illness that affects the children.

Method

We created a series of 17 videos in English and 17 videos with identical content in Spanish (**Table 1**). The videos are approximately 2–3 min in length and are publicly available on YouTube. We also targeted patients with epilepsy and/or seizures seen in the Neurology Clinic at Children's Mercy Kansas City. To leverage these videos, a quality improvement project was initiated in the department to "prescribe" videos to patients, based on their specific disease and duration. This was printed in the patient depart paperwork with a QR code that took them to a REDCap survey including: demographics, a pre-test, the prescribed video(s), and a post-test. This study was completed as part of the REACT project (Reaching out for Epilepsy in Adolescents and Children through Telemedicine), sponsored by a Health Resources and Services Administration (HRSA) grant. The YouTube Channel hosting the REACT videos was established on August 7, 2020, the first videos were initially made public on March 11, 2021. Advertisements are suppressed. A web page describing the REACT program, including video descriptions and the YouTube links to the videos, was added to the Children's Mercy web site (https://tinyurl.com/25dwyc9n). We monitored overall traffic to the videos to assess response utilizing YouTube analytics for the period from March 11, 2021 to May 22, 2022. We focused on the channel overview and the video with the highest viewership. For that video, we reviewed audience retention patterns (dashboard view), traffic source and device type.

Results

During the period evaluated, the REACT channel had 2,752 views, 91,300 impressions (presentation of video thumbnail) and a total watch time of 71.6 h. The highest source of traffic was YouTube search (40.5%), followed by suggested videos and external links, including those provided through the Children's Mercy web site (**Table 2**). The video with the highest traffic was "¿Qué es una crisis de ausencia?" [What is an absence seizure?], published May 5, 2021 with 1,308 views averaging 1:49 min (**Figure 1A**). This video had 25,600 impressions and a click-through rate of 3.9%. Traffic to this video originated primarily from YouTube search (54.2%) followed by "Suggested videos" (29.3%). The most common search terms leading to the video were "crisis de ausencia" (absence seizure—26.8%), "crisis de ausencia en niños" (absence seizure in children—6.3%) and "crisis de ausencia en adultos" (absence seizure in adults—4.1%). Location information for viewers is limited, but 12 views originated from Mexico and 11 from Peru. Traffic to the video has been consistent (**Figure 1**), with a spike of 26 views on Nov 18, 2021. The majority of traffic originated from mobile phones (74.3%), followed by computers (13.4%). The Spanish absence seizure video is 2:36 in duration. Average duration of view was 1:49. Viewers tended to remain engaged with the video until the credits at 2:15 into the content (**Figure 1B**).

To assess how these videos impact patients and their families we asked patients who were seen in one of our neurology clinics to complete the REDCap survey, as mentioned above. Of the 17 videos, 16 of the videos had at least one participant evaluation. A total of $n = 40$ people completed the demographics form and of these, $n = 24$ completed at least one video with the pre and post survey (**Table 3**). For the purpose of this data sample, we will focus on these 24 unique participants. This sample consisted of 75% of families having a CYE, 79% participating were Female, 71% reported Non-Hispanic/Latino ancestry, 79% reported White, 25% live in an urban setting, 42% in suburban setting, and 33% in a rural setting, and 87% reported having graduated from high school, 50% are married, 41.7% single and 8.3% divorced. Participants viewed an average of 2.6 videos (range 1–9 videos, **Table 4**). When we examined pre and post-test scores for all of the completed videos there was an average 28% improvement in correct response rate (range −33% to 100%).

TABLE 2 Views and traffic sources for the REACT YouTube channel.

Traffic source	Views (% of total)	Watch time (h)	Average view duration	Impressions	Impressions click-through rate (%)
Total	3,003	67.3623	0:01:28	91,300	1.99
YouTube search	1,159 (39)	31.2549	0:01:41	65,681	1.38
Suggested videos	526 (17.5)	14.0978	0:01:37	16,479	2.68
External	481 (16)	4.9905	0:00:57		
Browse features	260 (8.7)	6.7979	0:01:34	5,218	2.82
Playlists	201 (6.7)	2.887	0:00:51	2,093	8.22
Channel pages	134 (4.5)	3.0065	0:01:21	1,373	7.94
Direct or unknown	132 (4.4)	1.0288	0:00:37		
Other YouTube features	65 (2.2)	1.7986	0:01:42		
Playlist page	45 (1.5)	1.5003	0:02:00	456	8.11

Video analytics from the YouTube channel "REACT" where the 34 videos are located publicly.

Reaching the provider

While the ETG is significant in developed countries, it is exacerbated in LMIC. It is estimated that 80% of patients with epilepsy live in LMIC (5), yet these regions have the lowest access to proper diagnostic and management resources and physicians with adequate knowledge of epilepsy. This disparity in care is further intensified in rural regions (11, 12). The situation in Egypt with regards to epilepsy is representative of many LMIC. Egypt is classified by the World Bank as LMIC (https://data.worldbank.org/?locations=EG-XN). Egypt has an incidence of epilepsy of approximately 350,000 cases resulting in excess of 354,000 disability-adjusted life-years (a measure of disease burden calculated by adding years of life lost due to death and disability) (1). A cross-sectional study of children in the Al Kharga district and Al Queseir City found a prevalence of epilepsy of 9.7/1,000 with 59.4% of these cases being idiopathic, consistent with findings in other developing countries (13). Access to care remains limited, resulting in many patients suffering from regular breakthrough seizures. Egypt has a unique healthcare system in comparison to the United States. There are a total of four types of hospitals: university, Ministry of Health, military, and private. For this study we focused on university and military hospitals that are both private and public. University hospitals provide free health care services to anyone and free education to medical students, while military hospitals serve military personnel and their families (14). Providers who work for the government receive salaries from the public budget and those in the private sector are paid through performance-based incentives. There is no referral system and there is no existing structured electronic health record system (15).

Method

Seven years ago, one member of the epilepsy team at Children's Mercy Kansas City (AA) developed several educational activities, both virtual and in-person, designed for neurology providers at several Egyptian universities, hospitals, professional organizations and the military all located in Cairo. This ongoing program consists of monthly virtual lectures presented on a variety of neurology and epilepsy topics such as: approach to the workup, comorbidities, pharmacological and non-pharmacological treatments, programmatic approach to organizing an epilepsy center, seizure precautions, handling familial and patient concerns, epilepsy surgery programs. These activities have multiple forms of engagement, including question and answer sessions, direct patient observations, workshops, conferences, symposia, virtual case studies, virtual and in-person lectures. Monthly virtual case reports presented by Egyptian providers offered an opportunity for constructive feedback. For data analysis purposes these activities were categorized as passive learning (e.g., virtual lectures) and active learning (e.g., case reports) (**Table 5**).

Results

A cross-sectional survey of providers who attended the various activities was conducted from February to March 2022. Of the physicians, 40% are professors, 33% are assistant lecturers/specialists, 20% are lecturers/consultants and 7% are residents. Of the respondents, 53% identify as female and 47% as male. There is a broad representation of age, with 60% being between the ages of 26%–45% and 40% being between

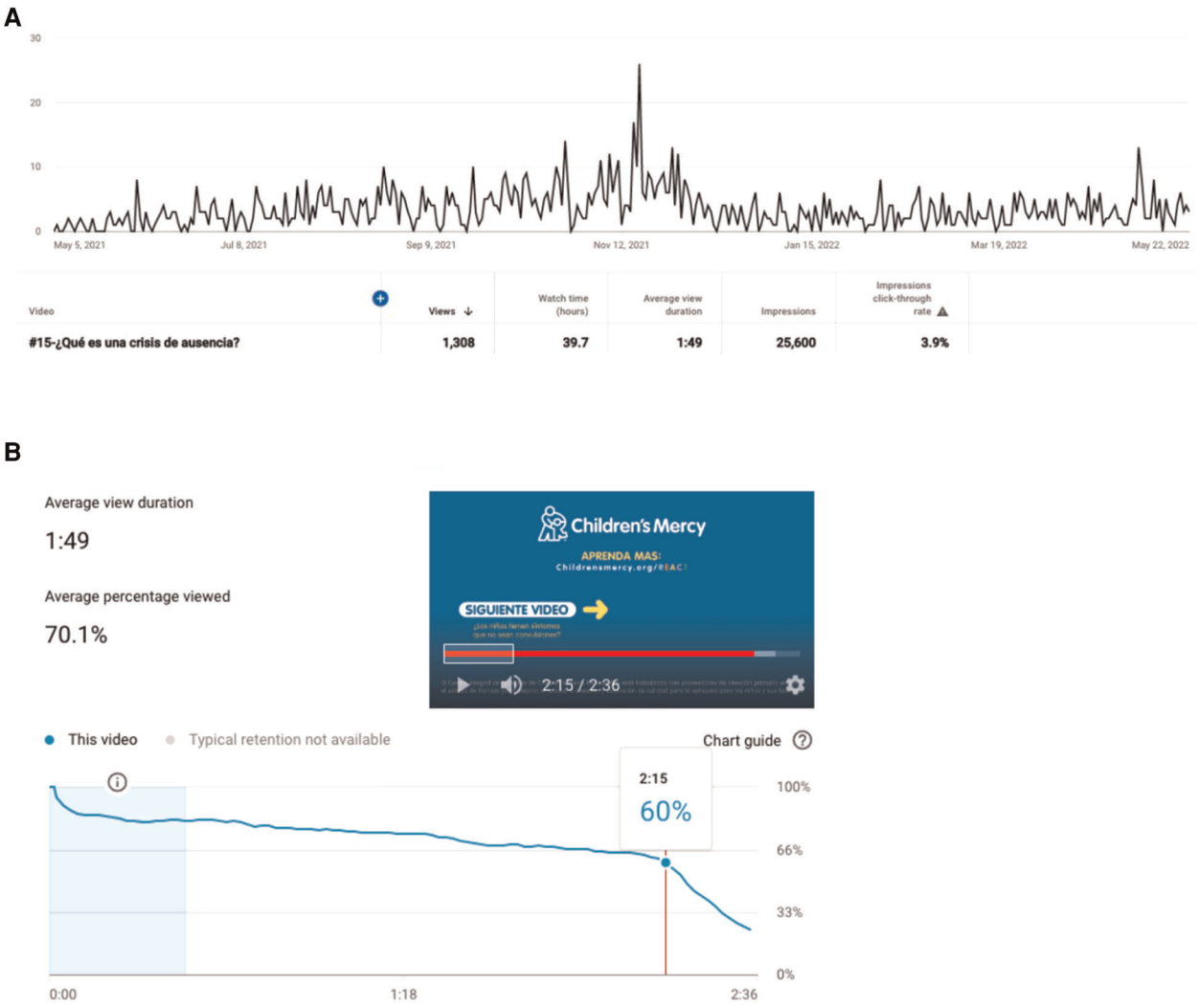

FIGURE 1
Example of a Spanish video analytics "¿Qué es una crisis de ausencia?" (What is an absence seizure?). (A) Views of top viewed video. The height of each peak represents the number of views during the indicated day. (B) Video audience retention. Average video viewing duration, red line marks beginning of the credits.

36 and 65 years old. The physicians represent two universities and five hospitals including a military hospital. Years of experience in neurology varied with 40% having 4–9 years of experience and 60% having 10 or more years ($n = 15$, Table 6). The survey was created to measure provider knowledge and comfort levels on a variety of topics related to neurology/epilepsy as a result of participating in the educational activities. The survey consisted of qualitative and quantitative items. The quantitative data collected included: demographic information, number of neurology and epilepsy or seizure patients seen per month, and educational activity participation. The qualitative data included impact of educational activities on patient care, general knowledge and comfort level in managing different aspects of epilepsy, and interest in other topics for future educational opportunities.

For the data analysis the teaching topics were categorized into four categories: treatment of epilepsy (11 sessions), epilepsy surgery (3), counseling (4) and routine management of epilepsy (4). The survey also included three open-ended questions. For each question, a conceptual analysis was conducted to quantify the presence of specific content categories through a process of selective reduction. The analysis was conducted based on these themes with flexibility to add categories as needed through the coding process (Table 7). Analysis revealed that participants in active learning activities (such as virtual case study sessions, workshops, in-person patient observations and direct contact for case-related inquiries) reported greater satisfaction than when engaging in passive learning activities ($M = 4.65$; SD = 0.46 compared to $M = 4.22$; SD = 0.82; Table 7, Figure 2A).

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TABLE 3 Educational video patient and family demographics.

Demographic characteristic	Full sample ($n = 40$)		No completed videos ($n = 16$)		Completed videos ($n = 24$)	
	Freq	%	Freq	%	Freq	%
Language preference						
English	40	100.0	16	100.0	24	100.0
Child with epilepsy						
No	8	20.0	2	12.5	6	25.0
Yes	32	80.0	14	87.5	18	75.0
Cargiver of child with epilepsy						
No	5	12.5	1	6.3	4	16.7
Yes	35	87.5	15	93.8	20	83.3
Gender identity						
Male	6	15.0	1	6.3	5	20.8
Female	34	85.0	15	93.8	19	79.2
Ethnicity						
Hispanic/latino	3	7.5	0	0.0	3	12.5
Non-hispanic/latino	33	82.5	16	100.0	17	70.8
Prefer not to answer	4	10.0	0	0.0	4	16.7
Race						
White	34	85.0	15	93.8	19	79.2
Black	3	7.5	1	6.3	2	8.3
Other	1	2.5	0	0.0	1	4.2
Prefer not to answer	2	5.0	0	0.0	2	8.3
Urban Status						
Urban	9	22.5	3	18.8	6	25.0
Suburban	22	55.0	12	75.0	10	41.7
Rural	9	22.5	1	6.3	8	33.3
Education						
Elementary school	1	2.5	0	0.0	1	4.2
Middle school	1	2.5	0	0.0	1	4.2
Some high school	1	2.5	0	0.0	1	4.2
High school or GED	14	35.0	5	31.3	9	37.5
Associate/technical degree	9	22.5	4	25.0	5	20.8
Bachelor's degree	10	25.0	7	43.8	3	12.5
Master's degree	4	10.0	0	0.0	4	16.7
Civil status						
Married	20	50.0	8	50.0	12	50.0
Single	16	40.0	6	37.5	10	41.7
Divorced	4	10.0	2	12.5	2	8.3

Demographic information for participants who completed the video and pre and post surveys.

Providers were then asked to rank their knowledge/comfort level in managing epilepsy patients on a 5-point Likert scale with 1 being "Extremely unknowledgeable/uncomfortable" to 5 being "Extremely knowledgeable/comfortable". Participants were also asked to rank their colleagues' overall knowledge regarding managing epilepsy patients. Interestingly, the participants generally ranked themselves higher than their colleagues (80% of physicians ranked themselves a 4 or 5 rating and only 20% ranked their colleagues a 4 or 5, Table 7). Overall, most providers reported that these activities resulted in significant changes in their practice, with over 90% of providers ranking the changes as "a lot" or "extremely" (Figure 2B, see also Table 7 for specific examples of practice changes following these training sessions).

TABLE 4 Patient/family educational video improvement scores.

Variable	N	Mean	Std Dev	Minimum	Maximum
Average improvement (% improvement)	24	0.28	0.28	−0.33	1.00
Average videos completed	24	2.63	2.24	1.00	9.00

Average improvement from the pre to post survey per video and average number of videos completed by each family/patient.

TABLE 5 Neurology provider activities.

Activities	Number of participants N (%)	Impact Mean (STD)
Neurology virtual lectures	12 (80)	4.17 (0.58)
Neurology in-person lectures	11 (73)	4.45 (0.93)
Symposia	4 (27)	4.25 (0.50)
Conference session	12 (80)	4.33 (0.98)
PASSIVE LEARNING ACTIVITIES		4.22 (0.82)
Virtual case study sessions	10 (67)	4.60 (0.70)
Workshops (eg., EEG)	8 (53)	4.63 (0.52)
In-person patient visit observations	7 (47)	4.57 (0.53)
Direct contact for case-related inquires	10 (67)	4.90 (0.32)
ACTIVE LEARNING ACTIVITIES		4.65 (0.46)
Changes based on impact of activities	**Freq (%)**	
Somewhat	1 (7)	
A lot	5 (33)	
Extremely	9 (60)	

Learning activities completed by providers in Egypt. The first group of activity falls in the category of didactic or passive learning, while the second group required active participation. The right column is the participants ranking on a five-point Likert scale, with 5 being "extremely impactful" and 0 "not at all impactful".

TABLE 6 Egypt provider demographics.

	Freq	%
Rank		
Resident	1	6.67
Assistant lecturer/specialist	5	33.33
Lecturer (MD)/consultant	3	20
Professor	6	40
Sex		
Male	7	46.67
Female	8	53.33
Age		
26–35	6	40
36–45	3	20
46–55	4	26.67
56–65	2	13.33
Practice location		
University affiliation only	3	20
Hospital-based only	5	33.33
University and hospital	7	46.67
Years in neurology		
4–6 years	2	13.33
7–9 years	4	26.67
10 or more years	9	60
Specialty		
Pediatric neurology	3	20
Neurology	9	60
Neurophysiology	1	6.67
Neurosurgery	2	13.33
Percent epilepsy/seizure patients		
0%–10%	1	6.67
11%–20%	1	6.67
21%–30%	4	26.67
31%–40%	2	13.33
41%–50%	1	6.67
51%–60%	2	13.33
61%–70%	2	13.33
71%–80%	2	13.33

TABLE 7 Qualitative data quotes from providers in Egypt.

What changes have you made in your practice from what you have learned? (Please specify. E.g., Is there a specific skill you gained?)
"I have better confidence at epilepsy practice"
"The whole way I dealt with EEG has change…it moved from being a diagnostic test into a complementary test for epilepsy patients"
"I became more skillful in EEG interpretation"
"Updated my knowledge of various epilepsy syndromes"
"Thorough understanding of the importance of data concordance in decision making in resective epilepsy surgery"
Why did you participate in the activities?
"Improve my skills, gain more experience and better practice"
"It is extremely helpful at practical and research levels"
"Because it was a rare opportunity to get such lectures from someone such as Dr. Ahmed"
What are you doing today in your practice that you didn't do prior? Please specify:
"Evaluation of drug resistant epilepsy patients"
"I look at epilepsy as a curable disease"
"Misdiagnosed typical absence as atypical"
"Improved EEG reading skills"
"Improved our battery for presurgical evaluation"
"Start to apply VNS and keto diet as treatment options for patients with DRE"

Examples of direct quotes from the qualitative data section of the survey.

Discussion

The ETG is a significant issue both in high- and LMIC. In the United States a retrospective study using a large database of almost 60,000 patients with a new epilepsy diagnosis revealed that up to one third of these patients remained untreated up to 3 years after epilepsy diagnosis (16). The situation with regards to access to care is exacerbated in rural areas. While the incidence of epilepsy in rural areas is similar to that of urban areas, access to care is not. In a study published by the Center for Disease Control in 2022, 7% of patients with active epilepsy reported not seeking care due to lack of transportation, and almost 6% had trouble finding a provider who would see them (17). These issues were exacerbated in lower income and underrepresented populations. Multiple other barriers prevent patients in rural areas from seeking care, including cultural perceptions and stigma, transportation, lack of access to services, and financial pressures (18). The situation in LMIC with respect to the ETG is much worse. In a report from the ILAE Epidemiology Commission the treatment gap was found to be as low as 5.6% in Norway and 10% in the USA, while it was greater than 50% in all of the LMIC examined (2). The COVID-19 pandemic resulted in a dramatic expansion of TH in the United States and around the world. This expansion in the practice of medicine seems to be here to stay and has resulted in a transformation of medical care (19). TH is a practical solution to reach patients with limited access to an epilepsy provider and is generally well accepted by both patients and providers (20). TH can be leveraged to address all aspects of care in epilepsy both in high- and LMIC (8). Kissani et al. set up a framework to reach both patients and providers using TH-based model called project ECHO (Extension for Community Healthcare Outcomes). The ECHO model has been adopted by the American Academy of Pediatrics for the treatment of epilepsy. Furthermore, the ECHO model has been applied successfully in 38 countries, in both high- and LMIC. In this paper we illustrate how this concept can be

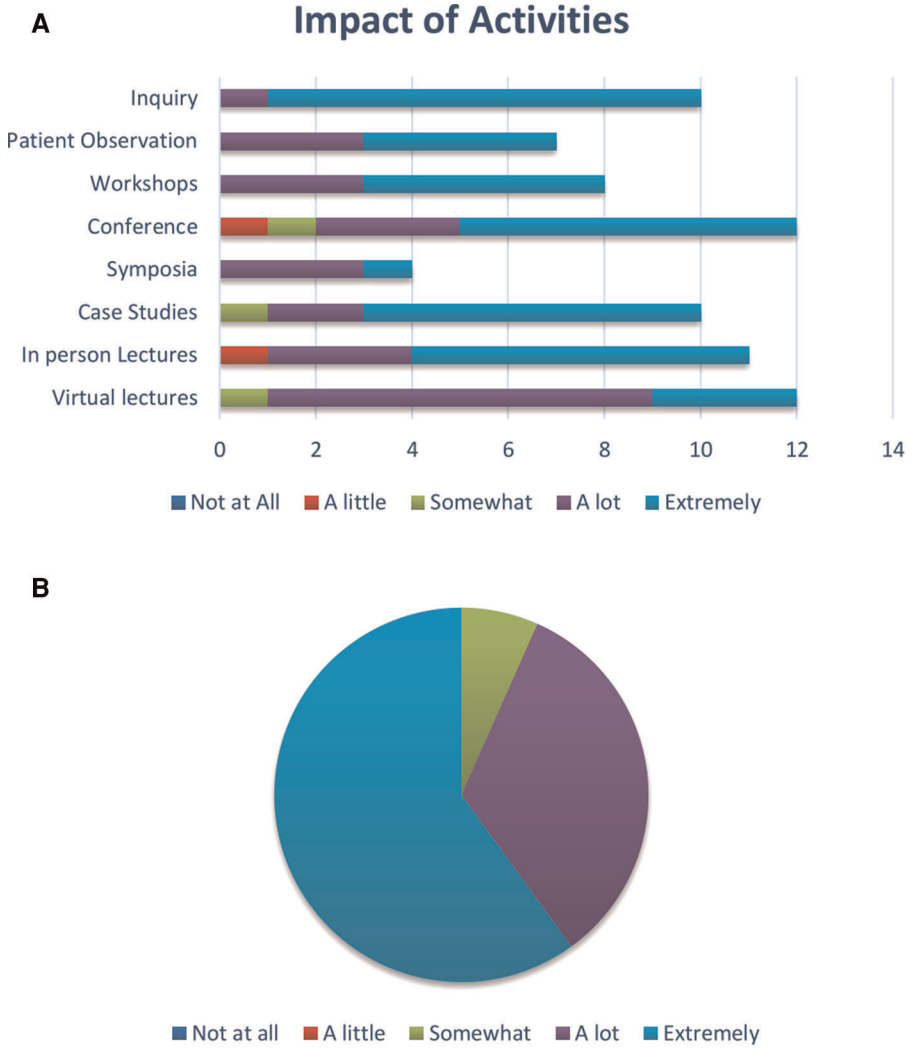

FIGURE 2
(A) Impact of activities on providers in Egypt. X axis is the number of physicians attending each activity. (B) Self-reported impact on clinical practice after participating in learning activities.

successfully applied, using three examples targeting different areas of need in the management of patients with epilepsy.

The first example is a case report of a patient with a mitochondrial disease and epilepsy living in the Kurdistan region of Iraq. By connecting experts in the United States and Iraq we were able to successfully start the patient on the ketogenic diet, resulting in a clinical improvement with reduced seizure burden, better weight gain, and improved cognition. This case shows that patients with complex diseases living in areas of the world with limited access to high level care can be successfully treated using telemedicine. This case is somewhat unique in that all the providers donated their time and expertise. Nevertheless, it serves to make the point that patients with drug resistant epilepsy can be successfully treated with the ketogenic diet.

In the second example of an application based on the ECHO model, we used virtual tools to provide education about epilepsy and seizures to families of CYE. Virtual tools can be synchronous (real-time), such as Zoom, or asynchronous (YouTube). Both are useful methods of TH that can be used for different necessities and audiences. Synchronous systems are very useful when a provider needs to communicate directly with patients, family members or fellow providers (as illustrated in the first example). When used to support remote locations, rural U.S. or international sites, these video systems may be limited by the technology infrastructure. Video resources describing clinical conditions can be a useful resource in support of TH. Educational videos can increase family engagement which will increase involvement in shared decision making with their providers,

giving them more confidence in managing their child's condition. Using a series of 17 short videos available both in English and in Spanish, we demonstrate that using a dedicated YouTube channel provides multiple benefits. First, viewers beyond those directly associated with the organization providing care may benefit from the video resources. Of the REACT channel views during the period evaluated, 229 originated from our institution, Childrensmercy.org (Traffic source -> External), less than 10% of total views. YouTube is the second most utilized search engine (21). We found that 38.6% of project REACT views originated from a YouTube search. Notably, we found that the video with the most traffic was the Spanish version of the "What is an absence seizure?". The majority of these views originated from YouTube search and users accessing the content from a mobile phone. The level of engagement was high, with most viewers watching the core content. The click-through rate for this video was nearly double that of the average for the entire channel, indicating a high level of interest in the content.

Designers of TH video content should consider using YouTube as a primary delivery platform as it expands the reach and impact of the content beyond the host organization. An investment in translating video content can result in meeting a need in under-served, under-represented communities in the U.S. and internationally. Examining a representative Spanish video demonstrated a high level of user engagement. Analysis of the search terms can guide the content designers to include key tags that may draw additional viewers to the content.

To further analyze the impact and applicability of including certain information in the educational videos, they were categorized into three groups and the average completion time per video was calculated for each group. Group 1 includes nine videos (1–7, 16 and 17) that provide general information regarding seizures and epilepsy. Of the $n = 24$ participants, 62 video surveys were completed and 50 of these came from the group 1. Therefore, each video in group 1 had an average of 5.6 completions. Group 2 includes six videos (8–13) that discuss the diagnosis or treatment plan options for epilepsy. Seven video completions came from group 2, meaning each video had an average of 1.2 completions. Group 3 includes two videos (14–15) that review *types* of seizures (tonic-clonic and absence). Six video completions came from group 3, meaning each video had an average of 3.0 completions.

There is a large variance in completion rates between the three groups of videos with group 1 having a higher completion rate. It is possible that these videos were viewed more frequently because the content is more generalized and applicable to CYE and their families. Group 2 covers videos that are more applicable to CYE with Drug Resistant Epilepsy (DRE), offering information on advanced treatment and non-pharmacological options such as: the Robotic Stereotactic Arm (ROSA), epilepsy surgery, ketogenic diet and neurostimulation. Approximately 7%–20% of CYE have DRE. It follows that a smaller portion of participants will view these videos as treatment options for their CYE (21). Finally, group 3 covers two specific types of seizures, absence and tonic-clonic seizures. Epidemiological studies have shown that 10% of CYE are diagnosed with absence seizures (22) and 50% of CYE and adults with epilepsy (23) are diagnosed with tonic-clonic seizures. Although the video on absence seizures had very few survey completions, this is the highest viewed video in Spanish according to our YouTube Analytics. This may be due to absence seizures being easily confused with other diseases such as ADHD, which may result in an apparent disproportionate interest in learning more about this topic.

For the third example of an application relying on virtual connections to address the ETG, we targeted epilepsy providers in a LMIC, Egypt. There are limited resources for neurology in most LMICs. For example, in Sub-Saharan Africa the median number of neurologists is 3 per 1 M population in comparison to 73 per 1 M in high-income countries. In addition, LMICs countries suffer from a lack of nurses and sub-specialized neurologic services, facilities for training, and struggle with access to treatments and antiepileptic drugs (22).

The survey shows providers ranked counseling patients and their families 3rd of 4 in comfort level, but paradoxically ranked it last of the topics they are interested in learning more about. Yet, proper counselling by the provider is a fundamental key in engaging patients and their families in effective treatment of CYE. It is an effective way to teach patients about their disease, introduce the risks associated with comorbidities, discuss sudden unexpected death in epilepsy (SUDEP), etc. We also found that providers are most comfortable with the routine management of epilepsy (ranked 1 in comfort level) but still, they expressed much interest in receiving more instruction on this topic, ranking second highest in the topics they want to hear more about. These findings reflect a greater interest in Egyptian providers to effectively treat epilepsy, and a much lower level of interest in addressing other psychosocial issues. There is clearly work to be done to emphasize the importance of addressing these issues for CYE. Not too surprisingly, we found that providers are the least comfortable with surgery related areas ranking it last, but they rank it first being the topic they are most interested in hearing more about. Surgery is the area with the largest gap but also the area that is the most "innovative" and "new" in a developing country. This opens real opportunities in a country ranked as a LMIC by the World Bank, to introduce new treatment modalities for epilepsy.

As part of the survey, providers were asked to rank both their own and their colleagues' knowledge and comfort level in managing epilepsy patients. As noted in **Table 8**, 12 of the 15 providers ranked their own knowledge in the top two categories (somewhat or extremely knowledgeable/comfortable). This is in contrast to how they ranked their

TABLE 8 Providers self-ratings and ratings of colleagues.

Knowledge/comfort managing epilepsy patients	My own	My colleagues
Extremely unknowledgeable	0	1
Somewhat unknowledgeable	1	7
Neutral	2	4
Somewhat knowledgeable	11	2
Extremely knowledgeable	1	1

Physician comfort/knowledge scale in managing epilepsy for self and colleagues.

colleague's knowledge level, with only three providers ranking their colleagues' knowledge as high, while 12 of the 15 providers ranked their colleague's knowledge as neural, somewhat or extremely unknowledgeable. There is no prior research regarding physician knowledge and comfort levels in managing epilepsy in Egypt. However, there was research conducted in neurosurgery training programs in Egypt. This study identified the three delivery models needed to improve effective neurosurgical treatment in Egypt: *Partnership or Twinning Model, On-Site Training Approach, and Online Neurosurgical Education*. It is reasonable to extend this model to neurology. The first approach, the *Partnership or Twinning Model*, relies on a longitudinal partnership between Egypt and high-income countries with a focus on a long-term collaboration between institutions in both countries, and regular site visits. The second practice model, the *On-Site Training Approach*, includes short-term visits, regular conferences, and workshops in the LMIC. The third practice model, the *Online Neurosurgical Education*, relies on virtual communication tools deepening the knowledge acquired in the first two practice models (14). We reprised these three practice models in the educational learning program we developed with Egypt, including developing long-term partnerships between institutions in both countries, brief onsite visits, and online neurological education.

Conclusion

While the ETG remains a problem both in high income countries, especially in rural areas, and in LMIC where it is anywhere from 5 to 10 times higher than in high income countries, the large increase in the use of TH is offering multiple opportunities to address this gap. In this paper we gave three examples of where TH was used to breach this gap. The first example showed that TH can be used effectively to treat patients with complex and rare disease in isolated regions. The second example illustrated the use of YouTube in asynchronous teaching to families of CYE located in rural areas. This model also illustrated that, given the wide availability of YouTube, these teaching videos were also effective at reaching patients well outside of our initial audience (this program was originally developed for CYE living in the state of Kansas), including many Spanish speakers. Finally, with the third example, we show that virtual tools can be effectively integrated within a comprehensive teaching program to reach providers in LMIC. There are many more similar programs with developing collaborations targeted to address the ETG both in underserved areas of the United States and in LMIC. With the marked use of TH that occurred following the COVID-19 pandemic, we are now in an ideal situation to aggressively address the ETG. It is our hope that this shift in how medical care is delivered will provide the foundation for more robust interventions worldwide, and subsequently result in a narrowing to the treatment gaps seen in most areas of medicine, including epilepsy.

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

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL, Stephanie Horton (SH), OA, MAH, and AA: contributed to project design, data analysis, and writing and editing the manuscript. EC: provided statistical expertise and contributed to writing and editing the manuscript. NK and Salah Hamada (SH): contributed to data gathering and editing the manuscript. All authors contributed to the article and approved the submitted version.

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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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Innovations and adaptations in neonatal and pediatric respiratory care for resource constrained settings

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Respiratory disease is a leading cause of death in children under 5 years of age worldwide, and most of these deaths occur in low- to middle-income countries (LMICs) where advanced respiratory care technology is often limited. Much of the equipment required to provide advanced respiratory care is unavailable in these areas due to high costs, the need for specialty trained personnel, and myriad other resource constraints that limit uptake and sustainable use of these devices, including reliable access to electricity, sensitive equipment needing frequent maintenance, single-patient-use supplies, and lack of access to sterilization equipment. Compounding the problem, pediatrics is uniquely challenging in that one size does not fit all, or even most patients. Despite these substantial barriers, numerous innovations in respiratory care technology have been made in recent years that have brought increasing access to high quality respiratory care in some of the most remote areas of the world. In this article, we intend to review the global burden of respiratory diseases for children, highlight the prototypical innovations that have been made in bringing respiratory care to LMICs, spotlight some of the technologies being actively developed to improve respiratory care in resource-constrained settings, and conclude with a discussion highlighting areas where further innovation is still needed.

KEYWORDS
global health, neonatology, respiratory support, innovations, medical devices, bubble CPAP

Introduction

Some of the leading causes of pediatric morbidity and mortality worldwide such as lower respiratory tract infections (LRTIs) and prematurity require advanced respiratory support as central components of their management. LRTIs are the leading cause of death in children under five years of age worldwide (1). Furthermore, nearly 45% of

all under-5 deaths occur in the neonatal period, with infections, birth complications and prematurity accounting for over 80% of these deaths (2). A disproportionate number of these deaths–approximately 80%–occur in low- to middle-income countries (LMICs) where the resources, skills, and technology required to adequately care for children being treated for LRTIs are often lacking (3). There are numerous reasons for this resource scarcity including high monetary costs, specialized training for personnel, unreliable access to electricity, and lack of sterilization (4). Therefore, a need exists to provide cost-conscious technologies and techniques that can effectively provide respiratory support for this vulnerable population.

Costs of respiratory support technology are high and not often realized by providers who primarily work at the bedside. A standard ventilator unit usually costs between $30,000 and $50,000 USD (5), while a typical continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) device typically costs between $1,000 and $10,000 USD (6). Oxygen blenders and flow meters often cost around $1,000 USD, as do some humidifiers (7) and these costs are beyond the budget for most health facilities. In 2019, the mean health expenditure of low income and low middle income countries was 5.4% of gross domestic product (GDP), in comparison to high income and upper middle-income countries, which had a mean expenditure of 7.2% of GDP. Given that the average GDP of a high-income country (HIC) was over 5.9 times that of an LMIC, this gap is even more profound (8). The spending burden is further compounded by the necessary purchase of multiple devices in addition to the cost of cleaning, maintenance, repairs and supplies. Other costs and barriers to operationalizing innovations in any low-resource setting (LRS) include the cost of time, including the time to build a device and/or time to deliver a product which can also impact how quickly the innovation can be made available, and labor costs, including any specially trained personnel for appropriate maintenance and repairs; this can impact the sustainability of a given technology and subsequently affect the overall cost-effectiveness of the innovation (9).

Additional barriers to providing adequate respiratory support in LMICs include but are not limited to dependence on electricity when reliable access is not guaranteed; limited supplies of oxygen and/or compressed air; limited tools or spare parts required for maintenance or repair; lack of access to sterilization techniques and technology; proprietary parts to equipment which limits options for replacement materials; and single use devices which ultimately add cost and increase medical waste (10). Therefore, innovations that do not rely on electricity and minimize utilization of consumables like oxygen can be beneficial. Devices that are reusable, low-cost, rugged, use materials with high durability, and/or operate through relatively simple and understandable mechanics are preferable.

Compounding these issues are unique challenges such as greater variability in size and physiology associated with caring for children. This significantly impacts the design of any given device and may influence the appropriate size of a breathing interface or the minimum respiratory support that the device can deliver (11). There are also specific clinical and physiologic targets that are different depending on age and disease process, to which the device should ideally be able to adapt. For example, the precision with which tidal volumes can be altered should ideally be greater for smaller children since small changes in volumes can have a greater impact in this population (12). Designing therapies intended to treat common pediatric conditions such as respiratory distress syndrome, pneumonia, asthma, and bronchiolitis should take these factors into account.

Once a device has been prototyped, it needs to be validated in a relevant clinical setting before it can be used confidently; however, designing and conducting such studies in LRS can be difficult. Monetary and time costs to research already exist as barriers in HICs and can be even more difficult to overcome in a LRS (13, 14). Uniquely, for any international exchange, the complexity of travel logistics is often part of the planning process which can further complicate the validation process. Once implementation occurs, ongoing training is a necessary step to optimizing sustainability.

Finally, the technology sector has historically been motivated by intellectual property, marketability, and revenue, which is not often central to the motivation behind low-cost device development and frugal innovation (15). Global health work is often collaborative in nature and aims to find mutually beneficial ground for all parties. In this way, innovations are ideally generated out of and exist within a partnership that is also mutually beneficial, as opposed to the more competitive spirit that exists in traditional technology development and industry. As an example, open-source devices represent a field of innovation that focuses more on providing a service to a large audience than owning particular property or benefiting from profit (16).

Given all these barriers, it comes as no surprise that development, implementation, and maintenance of innovations to support child health in LRS have made slow progress. Nonetheless, progress has been made, and in this review, we will highlight several innovations that aim to lessen the burden of respiratory diseases in children living in LRS.

Innovations in respiratory care for LMICs

For new medical devices to be successfully implemented in LMICs, they need to satisfy certain criteria (**Table 1**). The prototypical example of a successful adaptation of medical technology, and one that has a substantial body of evidence to support its efficacy, is the home-made spacer for metered dose inhalers (17), which can be easily constructed from a disposable plastic water bottle, and modified to be used as a

TABLE 1 Criteria for medical equipment for resource limited settings.

Criteria for Medical Equipment for Resource Constrained Settings
Affordable
Not dependent on continuous electricity
Easy to set up, monitor and troubleshoot
Spare parts available
Easy to disassemble and clean
Optimized for pediatric patients
Robust design without sensitive materials that can break

face-mask, or mouth-piece interface. This simple intervention is implementable around the world at almost no cost. Most medical devices developed for LMICs will not be quite as cost-effective as this example. However, this example is worth mentioning because adaptation can be a powerful tool. In this section, we will highlight some of the ongoing innovations being developed and implemented around the world to improve the care of children with respiratory illnesses. It is important to note, that the many of the highlighted innovations are from our group of authors. There are many other innovations that are being developed globally that are not described in detail here but have similar concepts and aims of improved access to care. Examples of these include other CPAP device such the Pumani CPAP device which was described in the 2013 article by Brown et al. and the Diamedica baby CPAP device as well as low cost ventilator such as the MADVent developed for patients with COVID-19 and the noninvasive pressure support ventilator described by Garmendia et al. in their 2020 article (18–21).

Low-cost bubble CPAP

Devices that support breathing through the delivery of CPAP have long been recognized as important therapeutic interventions decreasing mortality from respiratory illness in all age groups (22–24). CPAP helps maintain lung volumes during exhalation, improves oxygenation, and decreases respiratory muscle fatigue. In children with respiratory distress, CPAP has become a standard intervention utilized to attempt stabilization prior to advancing to invasive mechanical ventilation and has decreased mortality in high-income countries (24–26). One means of delivering CPAP, ventilator-derived CPAP, is costly, relies on a reliable source of electricity, and requires intensive expert monitoring and advanced biomedical support, some or all of which are often lacking in hospitals in LMICs (27).

"Bubble CPAP" (bCPAP) is another type of CPAP that has been successfully implemented in low and high resource settings. The bCPAP circuit generates CPAP by submerging the distal aperture of the expiratory limb under water (**Figure 1**). The depth of the tube in the water determines the positive end expiratory pressure that is generated within the tubing. The water bubbles as exhaled air escapes against the pressure (28). Commercial bCPAP devices are still very costly ($3,000–$6,000 USD) (29); however, less expensive versions such as the Pumani and Vayu devices have been designed (18, 30) and simplified versions, as published by the WHO, can be constructed even more inexpensively ($4–5 USD) with easy to obtain supplies (31). Some of these simplified versions can function with compressed air and/or cylinder supplied oxygen and therefore do not require electricity. Because they use a nasal prong or mask interface, less intensive monitoring is required than with mechanical ventilation (32, 33).

There is a growing body of literature supporting bCPAP use, including low-cost versions, in neonatal respiratory distress in both high and low-income settings (28, 33, 34). A study in 2007 showed a 33% reduction in mortality using commercial bCPAP compared to conventional CPAP in premature infants (35). In 2014, a systematic review of 14 studies observing commercial bCPAP use in neonates in LMICs showed a reduction in the need for mechanical ventilation by 30%–50% when using bCPAP compared to oxygen therapy. The analysis also found a lower clinical failure rate when using bCPAP compared to conventional CPAP in low-resource settings (36). Reported complications associated with bCPAP are similar to those seen with all forms of non-invasive ventilation, including nasal tissue irritation (10%–13%) (35, 37) and aerophagia resulting in gastric distension (5%–15%) (38), with less frequently reported serious complications of aspiration (<1%), nasal septal necrosis (<1%), and pneumothorax (<1%) (36, 39). Overall, bCPAP is considered a safe treatment option in neonates and is endorsed by the World Health Organization (WHO) for this purpose (31).

While the evidence that bCPAP is effective in neonates is clear, much less is known about its use in older infants and children. The efficacy, safety, and feasibility of bCPAP for use in children beyond the neonatal age group has yet to be conclusively demonstrated. High-income countries use ventilator-derived CPAP in older children. In LRSs, there have been five small observational clinical studies evaluating bCPAP use in older infants and children (22, 40–43). These studies provide preliminary evidence that bCPAP appears to be safe and feasible, but efficacy has not been conclusively demonstrated possibly due to issues with nasal seal and leak in older children. A low-cost (~$5 USD) modified bCPAP circuit (Simplified Earplug Adapted-bCPAP, "SEAL-bCPAP," (**Figure 1A**), has been developed and tested for safety for use in children (32). SEAL-bCPAP is constructed with easy-to-obtain and inexpensive materials. The addition of commercial earplug material around the nasal prong produces an improved fit at the nasal interface to decrease leak by creating a soft seal. This modification has been shown to be safe, and there was a trend toward improved efficacy, but further study is needed of the modification and use in children.

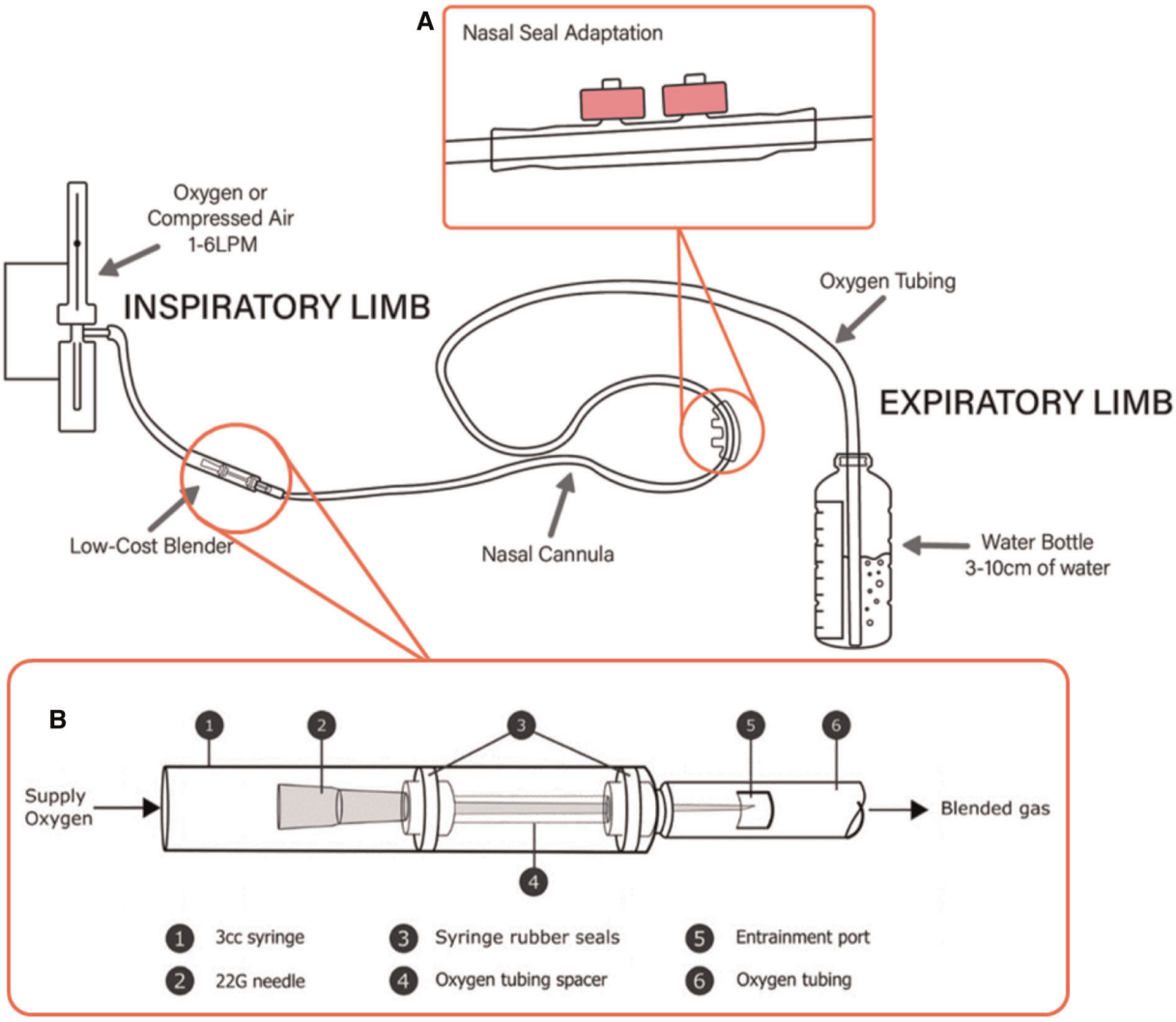

FIGURE 1
A low-cost bCPAP circuit with SEAL-bCPAP modification and low-cost blender modification. (A) SEAL-bCPAP Modification. (B) Low-cost Oxygen Blender Graphic credit: Mara T. Halvorson.

TABLE 2 The BCPAP score for effectiveness of bubble CPAP delivery.

	0	1	2	Total
Bubbles	Not present	Intermittent	Continuous	
Circuit	Contaminated (e.g. mold, biofilm, dirt)	Clean but small diameter (<10 mm)	Clean and wide diameter (≥10 mm)	
Prongs	Too small	Too large	Occlusive fit	
Airway	Blocked	Partially blocked	Open with bilateral breath sounds	
Pressure	Air leak	Intermittent	Maintained at set level	

Table re-used with permission from Oxford Press. "Contaminated" refers to the presence of mold, biofilm, dirt, etc.

bCPAP efficacy scoring

As previously noted, higher cost bCPAP setups are widely used in high resource settings with good results (44). Hospitals in resource constrained settings often use "home-made" bCPAP setups with varying results (45, 46). To ensure that these are safe and effective, a simple scale has been developed based on the fluid mechanics of constant positive pressure delivery (47). If the expiratory limb is clean, wide (≥10 mm) and continuously bubbling, there is a similar pressure at the bubbling air/water interface and in the respiratory circuit proximal to the patient interface. If nasal prongs are occlusive of the nares, this pressure is adequately transmitted to the patient's nasopharynx. If bubbling is

auscultated in both lungs, the pressure has been transmitted to both lungs. As a quick spot check, the clinician can also measure the pressures proximal to the prongs to ensure that the patient is receiving the prescribed CPAP treatment. Taken together, all these components can be utilized to calculate a score to assess the effectiveness of delivery of bCPAP. A score of 0–5 indicates ineffective bCPAP, 6–9 inconsistent bCPAP and a score of 10 suggests likely effective bCPAP (**Table 2**).

By regularly using a stepwise approach from the bubbler through the circuit and nasal interface to the patient's lungs, clinicians can ensure safe and effective delivery of positive airway pressure therapy. Deviating from this protocol to use of narrow bore tubing in the expiratory limb should be approached with caution as this could result in the delivery of higher pressures depending on the air flow rate and the degree of occlusion at the nasal prongs (48). Because of the discordance between increased pressure seen in laboratory models of home-made bCPAP setups with a narrow bore expiratory limb (<10 mm) and the very few documented clinical concerns with these low-cost versions of bCPAP the authors are conducting a study to further investigate actual clinical problems seen with various forms of CPAP used in LMICs.

Low-cost oxygen blender

Low-cost, constructible oxygen blenders are another example of a bCPAP modification which increase the feasibility of implementing these devices in LRS (49). As described above, bCPAP is an invaluable tool for treating pediatric respiratory disease in LRS. However, it is very common in these settings for low-cost bCPAP to be powered by pressurized 100% oxygen from a tank. As multiple studies have demonstrated, providing 100% oxygen introduces the risk of hyperoxia, and thus has deleterious effects on all ages, particularly neonates and critically ill children (50–52). In HICs, oxygen blenders are commonly employed to titrate oxygen concentrations between 21% and 100%, but these devices often cost several hundred U.S. dollars per unit, making them cost prohibitive for many LRS.

In the same way bCPAP is inexpensive and constructible, a novel oxygen blender that can be readily made using two 3 ml syringes with rubber stoppers, a 22G hypodermic needle, oxygen supply tubing, a nasal cannula circuit, tape, and a sharp cutting edge (scalpel or razor blade are preferred) has been designed and tested in the laboratory (49). The blender is currently being evaluated for use in children. The blender is positioned in-line with the bCPAP circuit between the oxygen source and the patient (**Figure 1B**). The mechanism utilizes the Venturi effect to entrain ambient air (21% oxygen) into the 100% oxygen stream, diluting the oxygen concentration to less than 100%. Similar principles have been utilized for other low-cost blender designs prototyped with 3D printing (53).

Preliminary studies have shown that use of this device can be taught to new English-speaking users in the span of about an hour and can be constructed in about 15 min once proficient (49). The blender can be built using one of two different sized entrainment ports which allows for two options of oxygen concentrations: 40%–50% or 60%–70%. The device also has a built-in safety check whereby the bubbling decreases when if the entrainment port is covered, often with a finger, which indicates that the device is working properly.

There are many advantages to this design. This is a cost-effective intervention, as the materials required for assembly total approximately $5USD. Furthermore, access to these materials is commonplace, even in the most resource-restricted hospitals. Therefore, spare parts are readily available in most healthcare settings. We have found that workshops including live demonstration, video, and guided instruction over the course of 1–2 h are sufficient to begin use. Monitoring of the device function is easily seen by the presence or absence of bubbling in the water bottle, as loss of flow or entrainment usually results in loss of bubbling. Lastly, the blender is powered by compressed oxygen and therefore does not rely on a stable source of electricity or medical air to function.

While there are many benefits to this blender, there are some notable limitations. Because of the design of the blender, it is not easily cleaned and therefore intended to be a single patient-use device, which contributes to increased medical waste. However, as many respiratory support circuits are designed to be single use, this is not a unique phenomenon. Another potential downside is that the syringe chamber is operating under high pressure and therefore prone to fragmenting if used with higher oxygen flows, which limits its usability to CPAP levels of 10 cm H2O or less and flow rates of 6 liters per minute or less. Fortunately, the entrainment of air allows for appropriate flows that reach the patient, however attempting to provide higher levels of CPAP remains a limitation of the blender circuit.

Taken together, the blender is an extremely low-cost method of delivering CPAP and appropriate levels of oxygen therapy when the only alternatives may be CPAP with 100% oxygen or no CPAP at all. While ideally all hospitals treating children with respiratory distress should have bCPAP machines with titratable oxygen levels available, not all do, thereby creating an environment where this low-cost blender can prove useful. A clinical trial to test its feasibility and safety in a LRS is currently underway.

NeoVent—bubble NIPPV

While bCPAP is effective for infants in mild to moderate respiratory distress, infants with worsening or more severe respiratory failure can benefit from additional support such as Nasal Intermittent Positive Pressure Ventilation (NIPPV). NIPPV consists of a constant baseline pressure with

intermittent positive pressure ventilation to reduce the patient's work of breathing (54). The clinician can set a peak inspiratory pressure (PIP) above a set positive end expiratory pressure (PEEP) with a cycling rate to additionally support oxygenation and ventilation. NIPPV has been used to prevent intubation and decrease post extubation failure, with particular benefit in premature infants or those with apnea (55, 56). Conventionally, in HRS, NIPPV has been delivered using expensive, complex electric ventilators in a noninvasive ventilation mode. In many LRS, NIPPV is often delivered with manual bag mask ventilation, which is only sustainable for a few hours.

A novel bubble NIPPV device (NeoVent) has been developed which attempts to preserve the simple, non-electric design of bCPAP while providing additional support for infants in respiratory distress (57, 58). As previously described, with bCPAP, the delivered pressure is set hydrostatically by the submerged depth of bubbling. By altering the submerged depth of bubbling between two levels (e.g., 5 cm H2O and 20 cm H2O), bubble NIPPV can be delivered. This is achieved with a variable buoyancy float. Bubbles emerge from the submerged expiratory limb and the low pressure is delivered. The float collects these bubbles, becomes buoyant and rises. In the process, the float moves an attached sleeve which occludes the bubbling holes of the expiratory limb, so that a high pressure is delivered. The float then vents the air, becomes heavy and falls, reopening the bubbling holes and causing the pressure to return to the lower level. This process cyclically repeats, affecting a dual pressure waveform (**Figure 2**). The device has been designed to limit the time at *P* high to approximately one half of a second to prevent breath stacking. As in the case of bCPAP, bubble NIPPV is non-electric with a few components that can easily be set up, monitored, taken apart and cleaned. The delivered pressures and volumes have been optimized for supporting infants. Physicians, nurses, and family members can easily assess the device's function: when the float is "up", pressure is "up" and when the float is "down", pressure is "down". As with bCPAP, if there is a significant leak, the bubbling will cease. The technology is currently undergoing clinical studies of safety.

Implementation of new devices and techniques

When developing any new device or treatment it is essential to work together in a true partnership with a multidisciplinary

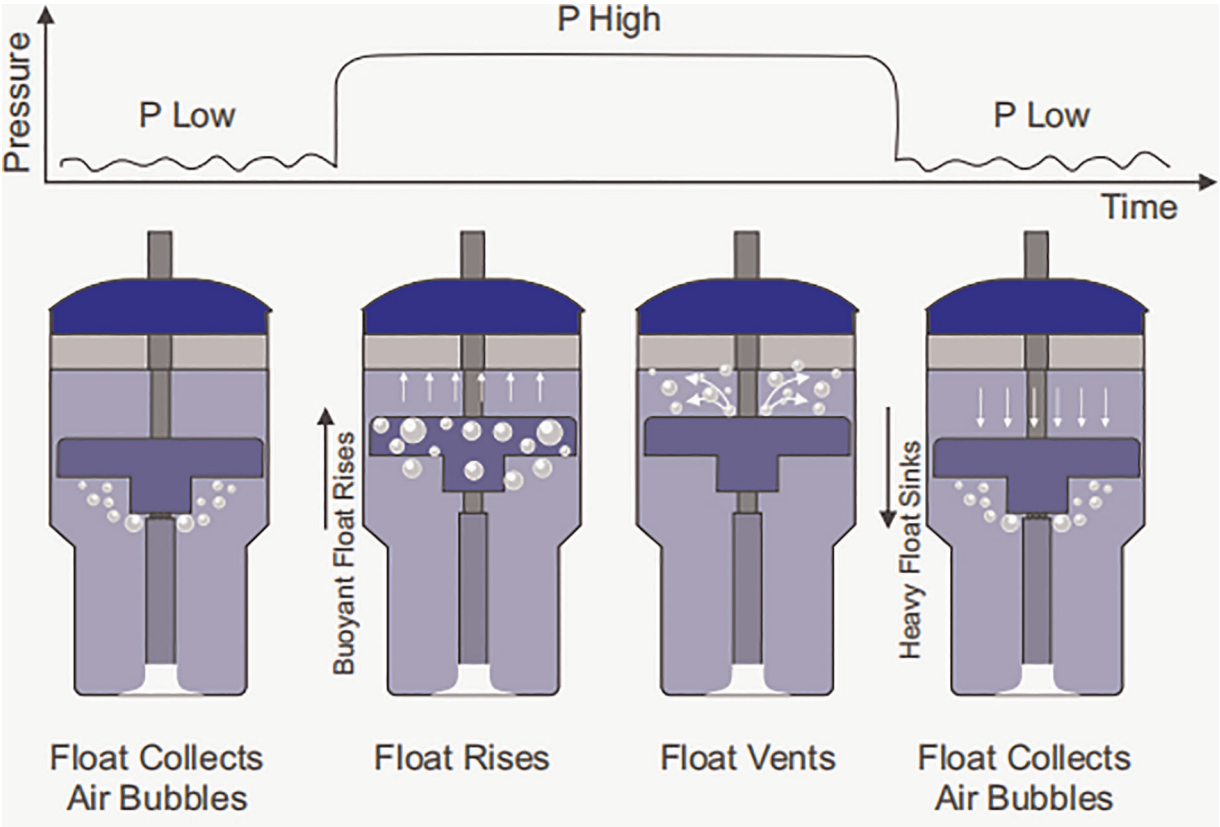

FIGURE 2
the NeoVent Bubble-NIPPV device. Figure used with permission from AIM Tech.

team in the LMIC including clinicians, biomedical engineers, and technicians, allowing them to describe to the HIC partners what they actually need. The team should work together to determine the needs and ensure that on the ground providers understand how the innovation actually works. This collaboration will help with buy-in from the local providers, increasing its use and ultimately building the capacity for that facility to care for sicker patients, decreasing the need to transfer patients to higher-level facilities, and all the costs that are associated with that process. It is also important to recognize the challenges of conducting research in settings where research is not routinely conducted. It may be quite difficult to get staff buy-in about new studies when they are already very busy with patient care responsibilities. An on-the-ground champion for the study who is knowledgeable about the study protocol as well as the device being tested is vital for success, however this places substantial pressure on that individual. These responsibilities are best served by a dedicated research team whenever feasible.

As we move many of these treatments and devices from research into clinical practice, the implementation process is essential for ensuring that these devices are utilized as a means of decreasing morbidity and mortality. Challenges already being addressed by programs such as NEST-360 (59) and others include implementing proven therapies like bCPAP for neonates into the lower acuity health centers responsible for delivering, stabilizing and then referring sick neonates to higher levels of care.

Successful implementation of any technology requires trained biomedical engineers and/or technicians in addition to trained clinicians. Multiple sources including the WHO (60) highlight the "equipment graveyards" which litter hospital and healthcare facilities in LRS. These are filled with donated equipment and supplies that came broken or need a voltage step down, had missing critical parts or single use essential pieces not available in the LMIC, and equipment that was never appropriate for the specific facility to which it was donated because of the level of care they were able to provide (i.e., ventilator with no source of piped gas in the facility). Similarly, it is often seen that equipment that worked well for a time but then later malfunctioned is unable to be repaired due to lack of a specialist with the appropriate skills, and the equipment is ultimately discarded. Appropriately trained local biomedical engineers, technicians and their teams can be empowered to maintain and repair life-saving equipment vital to their healthcare facility. The appropriate maintenance of equipment is also facilitated by having service agreements coupled with the purchase of each piece of equipment. This helps hold the companies responsible for supporting high quality, durable equipment as well as recycling all equipment that can no longer be used or repaired.

Implementation and sustainability also require training of the entire healthcare team, including not just physicians but also nurses, respiratory therapists, and everyone responsible for caring for infants and children. This training must be appropriate for the given tasks of each team member and must include an ongoing plan of refresher courses. Examples of successful training packages include the Helping Babies Survive program which is now being rolled into the WHO's Essential Newborn Care package (61), the Fundamentals of Critical Care from the Society of Critical Care Medicine (with an adapted version for adults in LRS) (62).

Sometimes the best option for training is retraining existing staff for another task, such as training a nurse working in a pediatric or neonatal intensive care unit to function as a respiratory therapist in the same unit. While this can be an effective option that leverages existing resources, ensuring that retraining will lead to long-term reassignment is essential. Working with administrators so that trained staff are not constantly moved to other units shortly after they are appropriately trained for a given unit is critical. To stop this practice, administrators must be engaged and supportive, ensuring that they understand why it is important to develop staff and allow them to remain in their newly assigned units to enable successful implementation. Training works best when it is stepwise and building on previous skill sets and trainings. For example, it is often useful to first provide training on the basics of intensive care nursing and respiratory therapy such as the use of low-flow nasal cannulas, suctioning techniques, setting up and responding to monitors. Thereafter training can be advanced to non-invasive respiratory support, recording vital signs and using critical care flowsheets, with subsequent introduction to invasive ventilation only when both personnel and infrastructure support for using it safely and effectively is established. This stepwise and thoughtful progression allows the development of high-quality special care units.

Future directions for research and development

Looking to the future, there remains a significant need for development, adaptation, and refinement of advanced respiratory support equipment for resource constrained settings. Areas of ongoing need include further development of ways to blend, warm, and humidify oxygen and air, low-cost but durable battery (or solar) powered oxygen concentrators, low-cost ventilators and video laryngoscopes for facilities that can support such technology, and reusable laryngeal-mask airways of appropriate sizes. Sustainable sources of items that are essential but cannot be reused, such as testing strips, or cartridges for point of care machines, are also necessary. Teams should also be encouraged to develop low-cost monitoring devices including multi-mode monitors with as many reusable pieces as possible. Additional needs include laboratory investigations such as point-of-care blood

gas machines, durable reusable end-tidal carbon dioxide monitors and micro-sample tubes.

Countries should be prompted to include support medications such as vasopressors, sedation, pain medications, caffeine citrate and surfactant in their essential medication lists. Sustainability and appropriate local adaptations would be improved greatly if local entrepreneurs and companies were encouraged to participate using locally available resources to develop and manufacture these supplies and equipment. Biomedical engineers must be brought into the team, and subsequently empowered, trained, and given an enabling environment to be creative and innovative. There are many examples of this being successfully done in countries such as India (63) but far fewer examples in sub-Saharan Africa where it is often difficult for to import critical supplies and equipment. The more each country can be encouraged to develop their own high quality durable products, equipment, and resources, the more sustainable these products and processes become.

LMICs must also be supported in their efforts to develop, sustain, and improve local training programs to ensure that their healthcare providers are equipped to provide excellent care in their LRS. Whenever possible, high-income partners should support local training to help slow down the ongoing depletion of vital healthcare staff who often leave their home countries in pursuit of opportunities in higher resourced settings—the so-called "brain drain". Efforts should be made to provide adequate remuneration, training and retraining as well as access to supplies and equipment needed to provide excellent care in an environment where well-trained local providers are encouraged, supported, and valued to encourage local staff retention. When striving for excellence, there should be collaboration between HIC provider teams and LMIC teams to share best practices and lessons learned as may be applicable and acceptable to that locale.

When providing increasingly more complex and intensive care, all team members must factor in the cultural, environmental, religious, and social implications of the suggested care. This will include weighing in practical points such as "who will take care of the other children when a neonate is hospitalized for months"; "how many other children in the family will miss school this year because their sibling in the pediatric intensive care used all the family funding for school fees"; and "what are the long-term implications of keeping a neonate or child separated from their family for extended periods of time or on the siblings when the parents are unavailable to meet the needs of the whole family while providing skin-to-skin care and breast milk to their extremely premature neonate".

Lastly, provision of intensive care is globally expensive, in many settings in LMICs healthcare costs are paid out of pocket and thus unaffordable. Governments at every level have the power to invest in health insurance systems especially for the most vulnerable populations.

Conclusion

Children living in LMICs continue to suffer from the highest proportion of childhood mortality in the world. Most of this burden is associated with respiratory diseases. Therefore, increasing access to therapies that are specifically targeted for these diseases and are adapted for this population are vital to reducing this mortality burden. Put another way, an ideal therapy or product should not only be effective in supporting the child's physiology, but also be affordable; easy to monitor, setup, clean, and repair; not rely on unstable energy sources (i.e., continuous electricity); and be durable. As above, SEAL-bCPAP, the syringe oxygen blender, and NeoVent bubble NIPPV are all examples of innovations that have taken these characteristics into consideration and have been successfully implemented to various degrees. However, more work remains to be done in all sectors of this work, including needs assessment, conceptualization, development, implementation, and maintenance. Altogether, this requires a collaborative effort between interprofessional HIC and LMIC teams to generate and disseminate the tools necessary to decrease the burden of respiratory diseases worldwide. Ultimately, we invite a global, unified, and collaborative effort to invest in the development of more accessible tools, technologies, and techniques such as those highlighted here.

Author contributions

AW, MM-Y, LS, SJ, BRA, TS, AB, JW and CE all contributed equally to the writing and development of this manuscript. CB assisted with literature review and served as primary copy-editor for the publication. JW assisted with writing, coordination and editing of this manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

Stephen John has filed for patent-protection for a bubble NIPPV device, and serves as CEO of AIM Tech which is developing this technology.

Publisher's note

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Management challenges in the treatment of severe hyperbilirubinemia in low- and middle-income countries: Encouraging advancements, remaining gaps, and future opportunities

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Neonatal jaundice (NJ) is common in newborn infants. Severe NJ (SNJ) has potentially negative neurological sequelae that are largely preventable in high resource settings if timely diagnosis and treatment are provided. Advancements in NJ care in low- and middle-income countries (LMIC) have been made over recent years, especially with respect to an emphasis on parental education about the disease and technological advancements for improved diagnosis and treatment. Challenges remain, however, due to lack of routine screening for SNJ risk factors, fragmented medical infrastructure, and lack of culturally appropriate and regionally specific treatment guidelines. This article highlights both encouraging advancements in NJ care as well as remaining gaps. Opportunities are identified for future work in eliminating the gaps in NJ care and preventing death and disability related to SNJ around the globe.

KEYWORDS
hyperbilirubinemia, neonatal jaundice, phototherapy, G6PD deficiency, low- and middle-income countries (LMIC), kernicterus

Introduction

Neonatal jaundice (NJ) is common among all newborn infants, with as many as 80% of infants experiencing some amount of hyperbilirubinemia (1–3). Neonatal jaundice results from the accumulation of unconjugated bilirubin in the blood, due to increased production (i.e., hemolysis) and/or decreased enterohepatic clearance (4, 5). For many, the clinical course is benign and self-limited, but for some can require hospitalization and treatment with phototherapy and/or exchange blood transfusion. A subset of infants is at risk for severe neonatal jaundice (SNJ) often defined as a total serum bilirubin (TSB) level >20–25 mg/dl (6). SNJ can result in acute bilirubin encephalopathy (ABE) and chronic bilirubin encephalopathy (CBE) also referred to as Kernicterus or Kernicterus Spectrum Disorder (KSD) (7). SNJ and the resulting neurodevelopmental impairments can include a wide range of motor (choreoathetoid cerebral palsy), hearing, and cognitive challenges although intelligence is often not affected (7–9). These morbidities are largely preventable with appropriate diagnosis, treatment, and follow-up.

Long-term complications from SNJ rarely occur in high-income countries (HIC) (10–15) but remain a challenge in low- and middle-income countries (LMIC) due to lack of resources for appropriate prevention, diagnosis, and treatment of the condition (16). Accurate population-based studies are lacking, but one report based on mathematical models estimated that 1.1 million infants develop SNJ globally each year (17). A systematic review of the literature from 2017 estimated a pooled incidence of SNJ at 244 per 100,000 live births (6). These studies and others highlight the African and Asian regions having a disproportionate burden of SNJ-related disease (6, 17, 18).

There have been noteworthy improvements in the care of infants with NJ over the last years and decades. Significant effort has been made in the prevention of SNJ through parental and healthcare provider education (19, 20) and improved diagnosis with more accessible bilirubin measurement tools (21–25). The advent of phototherapy over sixty years ago (26) with improved quality of devices including the introduction to light emitting diode (LED) based units (27, 28), and subsequent upscaling and distribution of this treatment has reduced the need for exchange transfusions and therefore likely improved outcomes (29–31). Although large-scale studies are lacking, there is evidence from local LMIC institutions that demonstrate improving NJ management and outcomes. For example, the mortality rate from NJ in Taiwan decreased from 0.51% to 0.26% in the years 2000 to 2010 due to a combination of increased screening for risk factors like G6PDD, family and provider education, and improving hospital discharge follow-up. Similarly, on the Thai-Myanmar border, mortality from NJ decreased from 10% to 2% from the years 2009–2011 after the implementation of standardized guidelines and LED PT devices (32). At the Cairo University NICU in Egypt, mortality from NJ decreased from 25% in 2008 to 10% in 2015, again attributable to the combination of several interventions including protocols, training of personnel, and innovative technology (33). Lastly, NJ as a cause of neonatal death at a teaching hospital in Lagos, Nigeria, decreased from 23.3% in 2001 (34) to 11.5% in 2020 (35).

Elaboration on these improvements and others will be discussed in more detail in the coming sections. Despite these encouragements, there remain significant gaps in care across the world with SNJ as its devastating consequences disproportionately affect LMICs. These gaps highlight opportunities for improved and more equitable SNJ management (36, 37). This article based on expert cross-cultural opinion will highlight the areas of advancement in NJ care, the remaining gaps, and will suggest opportunities for future work.

Advancements

Prevention: emphasis on parental education

Serum bilirubin levels usually peak between three and five days after birth (5). However, most infants born in a hospital have been discharged before this peak, and many mothers in LMICs deliver at home or at a birthing center without skilled attendants (19). The American Academy of Pediatrics recommends that all newborn infants have at least one bilirubin measurement (serum or transcutaneous, TcB) before discharge (38), but this is not feasible in most LMICs due to cost and infrequent hospital births (37, 39). Therefore, the education of parents, especially mothers, can be an important aspect of the primary prevention of SNJ. This importance has been recognized in the past several years, with a few interesting developments for educational programs to empower parents to seek care in a timely way (40–42). Some strategies, highlighted in the next paragraphs, include oral presentations, pamphlets and posters, radio jingles, and the use of ictometers. Many of these educational materials can be accessed on the internet [Bilimetrixusa.org (43)].

A recent multicenter, cross-sectional study in Nigeria implemented antenatal and postnatal maternal instruction programs. This study demonstrated a decreased incidence of ABE in the group of mothers that received the intervention (maternal instruction) compared to those that received no instruction (40). This educational program, which is still in use, taught proper identification of jaundice through blanching the skin, the need to avoid hemolytic triggers due to high prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in the population, warnings against ineffective treatments and home remedies, and instructions on how to pursue additional evaluation and medical care for NJ (40). This instruction was delivered in multiple formats including antenatal group classes and question and answer sessions, postnatal one-on-one teaching, and written materials. This study found that delayed care-seeking for NJ was the strongest predictor of ABE and the group's maternal instruction program decreased delayed care-seeking from 49% to 17% (40).

Although general visual assessment of jaundice by family members has been encouraged in parental education efforts, by itself it is an unreliable method for detecting significant jaundice (44, 45). Icterometers can be used as a visual reference and are simple and effective tools that can be used at home by parents and at the community level by traditional birth attendants and community health workers. Harry Gosset in 1954 invented the icterometer using a Perspex glass as a non-invasive tool to assess the total bilirubin (46). It is still used as a screening tool for jaundice in LMICs. Since then, icterometers have been studied as a possible predictor of significantly elevated serum bilirubin and thus risk for SNJ (47, 48). A two-color icterometer was studied in Lagos, Nigeria, with mothers assessing the color of their newborns nose (blanched skin) and comparing to either light yellow (non-significant jaundice) vs. dark yellow (significant jaundice) and validating these assessments against either a TcB or TSB (49). This study found the two-color icterometer (Bilistrip™) to have a high sensitivity (95.8%) in detecting infants requiring phototherapy and a strong negative predictive value (91%–99%) in identifying infants at low risk of severe NJ when compared with a range of TcB thresholds (49). A similar study was conducted in China using a color card, "JCard" with eight hues of yellow, ranging from light to dark/severe and were tested on different areas of the infant's body (forehead, cheek, sternum). The cheek was found to be the most accurate location for assessment, with an area under the curve (AUC) of 0.985 when correlated with TSB > 13 mg/dl (50). Yet another example of an ictometer is the Bili-ruler which was created using advanced digital color processing and visual design to improve color matching (51). This product was developed through a collaboration between Sylhet Osamni Medical College Hospital in Bangladesh and Brigham and Women's Hospital in Boston. Its performance was similarly strong, with AUC values for identifying

TcB ≥ 13 and TSB ≥ 13 mg/dl reported as 0.93 and 0.87 respectively, with an interrater reliability with 97% of measurements by two readers performing within 1 point of each other (51).

The combination of formal maternal instruction programs with simple detection tools has the potential to prevent the development of SNJ by decreasing delay in seeking appropriate medical care.

Diagnosis: point of care bilirubin measurement

Accurate and timely measurement of bilirubin in an infant is essential to provide appropriate treatment and prevent neurological sequelae. Serum bilirubin measurement with total and direct fractions are the gold standard for diagnosing NJ but can be time intensive and require expensive equipment and trained personnel. High performance liquid chromatography is the gold standard laboratory technique, but not an option for many LMIC settings (52). Other methods used for serum measurement are Diazo reaction method and direct spectrophotometry (24, 25, 53, 54), although these still require equipment and reagents that aren't always available.

Advancements in point-of-care bilirubin determination have been very important in improving jaundice care in LMICs. TcB devices are non-invasive screening tools that have become widely used in both HIC and LMICs in the past several years. These devices use reflectance densitometry to quantify yellow skin color (21). They are user-friendly, fast, and relatively low cost. These devices are especially helpful at screening low-risk infants and determining which patients should have a serum bilirubin level measured (55). TcB is generally not recommended for use in making treatment decisions, as there can be variability among devices, different ethnic populations, gestational ages, and a limited reporting scale (56, 57). Also, the accuracy of TcB decreases with increasing TSB levels (both over and underestimation), so caution must be used and validating a high TcB (≥12–15) with a serum level is advised (58–60).

There are also emerging technologies for point-of-care (POC) devices to measure serum bilirubin. The advantages of these POC devices are their low cost, need for only a small amount of blood, the ability to use during treatment with phototherapy, and the potential to use in a field environment. **Table 1** outlines the characteristics of two such POC devices (Bilistick® (22, 61) and BiliSpec (23)) and how they compare to TcB devices in general. Although these technologies hold promise to offer low-cost, accurate, and timely diagnosis of NJ, they have not been used broadly yet in LMICs partly due to concern for high failure rate in certain environmental conditions (62), questions regarding accuracy (63), paucity of testing in severe range TSB levels (23), and lack of assurance regarding long-term storage and durability.

In settings where serum bilirubin cannot be easily or accurately assessed even by POC methods in a timely manner, the Bilirubin-Induced Neurologic Dysfunction (BIND) score is a clinical algorithm with associated web-based application (66), that has been found to predict bilirubin encephalopathy with high sensitivity and specificity (67). Although this is not a true diagnostic method, as a clinical screening tool it can be used to initiate phototherapy and exchange transfusions ahead of obtaining serum bilirubin levels in the LMIC setting if laboratory resources are immediately lacking. How widely this algorithm is currently implemented remains to be assessed. The routine use of these described methods, despite their limitations, including emerging technologies such as smartphone or artificial intelligence-based systems to be discussed later in this article, will likely improve early and prompt diagnosis of NJ.

Treatment: phototherapy technology

Phototherapy (PT) as a treatment for NJ was first discovered over sixty years ago (26) and has since reduced the need for exchange transfusions and likely has prevented death and disability for possibly millions of neonates (29–31, 68–70). The ongoing

TABLE 1 Comparison of currently available point-of-care bilirubin measurement devices.

Characteristics	Transcutaneous (56, 64, 65) (Bilicheck, BiliMed, JM-103)	BiliSpec (23)	Bilistick® (22, 61)
LMIC Locations Studied	Many	Malawi	Egypt, Nigeria, Indonesia, Vietnam
Invasiveness	Non-invasive	50 µl whole blood	25 µl whole blood
Time to result	Immediate	120 s	100 s
Gold standard comparison	Clinical laboratories	UNISTAT	Clinical laboratories
Pearson's Correlation	$r = 0.70–0.86$	$r = 0.973$	$r = 0.961$
Bland-Altman (mean difference)	Varies	0.3 mg/dl	0.58 mg/dl
Calibration	Varies	Daily	Per sample
Power source	Rechargeable Battery	Battery	Rechargeable Battery
Approximate Cost (USD)	$2,000–$6,000	$150 USD Lateral flow card: $0.05	$500–$1500 Calibration kit: $250
Disadvantages	- Cannot be used to monitor response to PT - Decreased accuracy in dark skin patients and preterm infants	- Unknown performance at TSB >25 mg/dl - Long-term storage needs are unknown	- Recalibration with each sample - Need to measure sample immediately - Errors and high variability under humid conditions, high hematocrit

innovation and implementation of PT in low-resource settings has improved over the recent years, making this treatment more widely available to at-risk infants in LMICs.

The main types of PT lights used in practice are halogen light sources, fluorescent tubes (regular and special), LED, and fiberoptic pads. The ideal light source has a wavelength that includes the optimal blue to blue-green range (including peak absorption for bilirubin isomerization (458 nm) (29). The PT device should have an irradiance of at least 30 $\mu W/cm^2/nm$ for intensive PT (71). Halogen spotlights produce heat, which can be dangerous for the infant and thus are not preferred but are sometimes still used in LMICs. Fluorescent lights have a wavelength range of 400–520 nm with special blue fluorescent tubes offering higher irradiance. Fluorescent lights don't produce much heat compared to halogen bulbs (72) but do lose irradiance over time and need to be monitored for efficacy regularly (73). The combination of regular (not special blue) fluorescent and white lights have been used successfully in LMICs to achieve effective irradiance levels while still being relatively low cost and accessible (74). Modifications to PT devices in LMICs such as white reflecting bassinets or blankets to optimize irradiance and exposed surface area, have become more standard practice (75, 76).

LED light sources have been shown to be effective in lowering TSB levels (77), are replacing fluorescent and halogen bulbs in high-income countries, and are becoming more widely used in LMICs as well. LEDs are advantageous because they emit a narrow bandwidth of light (450–470 nm), produce little heat, and last much longer than other types of bulbs. LED bulbs have a lifespan over double that of fluorescent lights (20,000 + h) (29). The price of these light sources has declined over recent years, making it more affordable in LMICs without the need for frequent replacements (27). Local fabrication of LED devices has been demonstrated to be low-cost and effective (28).

Lastly, innovative technology to meet the specific needs and resources of LMICs has been a welcome addition over the past several years. Filtered sunlight phototherapy (FS-PT) is one such example. Slusher and colleagues published their novel FS-PT canopy that uses commercial tinting films to remove ultraviolet and infrared light and allows multiple mother/infant dyads to sit together under the canopy (78). This method proved to be a feasible, safe, efficacious, and affordable treatment strategy for areas of the world where conventional PT is not available (79). This method is now in the process of being implemented in other LMICs such as Ethiopia, Uganda, other regions in Nigeria, and though these findings are not yet published, there is potential for future upscaling and distribution.

Remaining gaps

Prevention: gaps in routine screening for risk factors

The recognition of infants who are at particular risk for SNJ is paramount so that proper diagnosis and treatment can be implemented. Prematurity, postnatal bruising, and macrosomia are common postnatal risk factors that are often identified (38). One of the biggest risk factors for SNJ, however, is hemolysis, with isoimmune hemolytic disease (blood group incompatibility i.e., Rh and ABO) and G6PD deficiency being major contributors. The prevalence of Rh disease and G6PD deficiency vary among regions in the world and recognizing these important influences on SNJ requires further improvement.

Rh disease has been almost entirely prevented in HICs through universal prenatal blood type and antibody screening, Rh immunoprophylaxis, and the diagnosis and management of fetal anemia (80). The prevalence of Rh disease in these countries is estimated to be 2.5/100,000 live births, thanks to universal and coordinated perinatal care for most all pregnancies (17). In contrast, the global prevalence of Rh disease is approximately 276 per 100,000 live births, ranging widely among regions with Southeast Asia/Pacific countries at 57 and Eastern Europe at 529/100,000 live births, per 2010 data (17). This gap between HIC and LMIC care is largely attributed to the lack of routine blood group testing for both mothers and infants (which also identifies ABO incompatibility, another contributor to SNJ), as well as the high cost of immunoprophylaxis for Rh negative mothers (17, 36).

G6PD deficiency is another risk factor for hemolysis in the neonatal period and contributes substantially to the global burden of SNJ (17, 81). G6PD deficiency, an X-linked inherited condition, is the most prevalent enzyme deficiency in the world, with varying prevalence by geography and ethnicity (82). The G6PD enzyme is needed to prevent oxidative stress in the red blood cell, and thus with impaired enzymatic activity, the red blood cell is susceptible to lysis under conditions of stress (infections, medications, fava beans, traditional remedies, etc.) (82). The World Health Organization (WHO) recommends that regions of the world with a G6PD deficiency prevalence of more than 3%–5% in males should adopt universal neonatal screening and also education of healthcare workers and parents (83). Now decades later after this 1989 recommendation, routine G6PD deficiency screening programs have not been adopted in many regions, even those with a significant burden of G6PD deficiency and SNJ (81). A recent survey of healthcare providers in Nigeria, one such high risk country, illustrated gaps in knowledge of the common prevalence and need for screening of G6PD deficiency at their local hospital (20). The combination of routine screening and education of both healthcare workers and parents is needed to reduce the contribution of G6PD deficiency to SNJ globally.

Diagnosis: gaps in infrastructure for timely diagnosis

Although there have been encouraging advancements in the diagnosis of SNJ over the past years to decades, there remains a delay in accessing care and thus timely diagnosis due to fragmented medical infrastructure. With the high rate of births happening outside of hospitals in LMICs, most infants develop SNJ at home, thus too late for any of the state-of-the-art diagnostic techniques or treatments to have full effect (37). Delays in seeking and receiving appropriate care for NJ have been reviewed as important contributors to the higher rates of SNJ in LMICs (37).

Cultural and socioeconomic barriers often contribute to a delay in diagnosis of SNJ. Families may delay seeking care due to a cultural expectation to stay home during the postpartum period, for a traditional naming ceremony, for instance (37). The advice from

other family members to use traditional remedies or other treatments prior to seeking medical help can also contribute to a delay. Iskander and colleagues asked parents of infants with SNJ a series of questions to better understand reasons for late presentation to the hospital (84). None of the parents in the study received any education or follow-up instructions about NJ. Although the majority of these infants were delivered at a health care facility, once home, almost 50% of parents did not seek medical advice due to the belief that NJ was normal and self-resolving. Many families reported from this and other studies the use of herbal supplements, vitamins, antibiotics, and/or direct sunlight to treat the infant at home prior to seeking care (84–86). Once the decision has been made to seek medical attention, often the most convenient or accessible medical health center is not equipped to measure bilirubin or provide appropriate advice (37, 84). Iskander et al. reported that over 30% of parents tried 2 or 3 healthcare facilities prior to reaching the appropriate location and many traveled over 5 h to do so (84). Thus, although there have been new technologies for user-friendly bilirubin measurement and diagnosis of NJ, there remains a significant gap in actually getting the infant to a healthcare provider that has the resources to do so in a timely way.

Treatment: need for culturally appropriate and locally specific treatment guidelines

Kernicterus happens infrequently in HICs likely due to the presence of national guidelines (71, 87, 88) and healthcare systems in place that facilitate appropriate treatment and timely follow-up (89). As mentioned above, in LMICs, healthcare is more fragmented, many infants are born at home, and arranging follow-up care is difficult (90). Because there is regional variation of risk factors of SNJ, guidelines must be locally specific to effectively prevent SNJ. Olusanya and colleagues conducted a review of existing NJ guidelines worldwide and found that very few were from LMICs and many were not high quality, according to the group's grading system (91). We do have evidence that implementing a local NJ guideline can improve outcomes, for example Thielemans et al. published a 8% decrease in mortality from SNJ after implementing a protocol at their institution (32).

Local guidelines should be specific to the region's population including prevalence of top risk factors. For example, local guidelines should recommend G6PD deficiency screening in high prevalence areas (83), unlike the US, for example, that only recommends G6PD deficiency screening when the family history of ethnic origin suggests it as a possibility or for an infant without an appropriate response to PT treatment (71). The American Academy of Pediatrics recommends pre-discharge screening for NJ with either TcB or TSB (38, 92), however this is not possible in regions where more births occur at home. In many LMIC regions, it is not common to have a routine newborn follow-up visit to assess for NJ. A neonate is typically seen during the first week of life for vaccination, however, often that visit happens after the natural bilirubin peak and other health concerns beyond vaccines are not always addressed (93). Alternative measures for follow-up that may include the role of a traditional birth attendant, midwife, or visit by a community healthcare worker with a visual screening tool, may be an alternative approach.

Local guidelines should also include reference to the use traditional remedies or practices that may delay proper treatment or lead to worsening NJ. For example, hemolytic agents, such as methylated spirits, eucalyptus oil, and henna are used in some regions to care for the umbilical cord after birth but may promote hemolysis and exaggerated NJ in infants with G6PD deficiency. To demonstrate a more direct relationship between exposure to traditional remedies and hemolysis, a zebrafish model of G6PDD was used to test the effects of traditional compounds on hemolysis. Arogbokun et al. reported that eucalyptus oil induced a 13.4% increase in hemolysis and methylated spirit showed a 39.7% increase in hemolysis in the zebrafish model (94). A survey of healthcare workers and trainees in Southwest Nigeria demonstrated that even these medical professionals often recommended hemolytic agents for the umbilical cord (82% recommended methylated spirit) (95). Other regional practices may delay proper care. For example, exposing infants to unfiltered sunlight and using antibiotics or herbal medicine are often identified in surveys of mothers when asked about care practices and beliefs related to NJ (37, 93, 96–98). Familusi and Dawodu, for example, published an association between a positive history of naphthalene exposure in the home and SNJ (need for exchange transfusion or death of the infant) (99). Because these practices vary by culture and region, they should be included in a local NJ guideline in a culturally sensitive and appropriate way.

Lastly, local treatment guidelines must include monitoring and maintenance of PT devices through routine irradiance measurements (100). Irradiance meters are used to assess the quality (dose or strength of lights) of PT delivered to infants with NJ, as the irradiance of PT devices decay with use and time (73). Florescent light bulbs decay faster than LED lights (73). In LMICs, the quality of PT is rarely monitored and a significant proportion of available PT devices may be producing suboptimal irradiances (75, 101, 102). This is because irradiance meters are expensive and not readily available (103). Recently, Powell et. al. tested an inexpensive mobile phone based irradiance meter suitable for resource constraint settings (104). Although it is ideal that the irradiance meter used it one that was specifically developed by the PT device manufacturer to measure the specific characteristics of the particular device, these are often not purchased, therefore independent low-cost meters may be a reasonable alternative. Further work into making irradiance meters affordable, accessible, and user-friendly is needed.

Opportunities for future steps

Prevention: emphasis on prenatal care and education

The future of prevention of SNJ needs to include an emphasis on prenatal counseling and identification of SNJ risk factors during pregnancy. Although advancements have been made in an effort to educate mothers and families as described above (40), this has largely taken place during the postpartum time frame. By identifying a fetus who is at risk for SNJ prior to birth, a birth plan can be made to ensure timely diagnosis and treatment, if needed. Delivery at a hospital or care center equipped with the laboratory technology and access to PT may be recommended so that diagnosis and

treatment can be escalated in a timely and organized way. Education against hemolytic agents or other traditional remedies can take place weeks to months ahead of birth, rather than in the postpartum time when mothers may be exhausted and overwhelmed.

An emphasis on prenatal prevention must include education of the maternal providers, including obstetric physicians, traditional birth attendants, or nurse midwives. A survey of healthcare providers and trainees identified significant gaps in provider knowledge related to prevention of and possible sequela of SNJ (20). For example only 53% of healthcare providers reported seeing a case of neonatal jaundice and very few traditional birth attendants recognized risk factors for SNJ (G6PD deficiency, Rh incompatibility, preterm birth) (20). Risk factors of SNJ that should be identified during pregnancy include a family history of SNJ, Rh negative blood type, family history of G6PD deficiency or other risk factor for hemolysis.

One randomized controlled study from China demonstrated that antenatal education about jaundice led to mothers being more likely to recognize jaundice in their infants (71% in education group vs. 41% of controls) and were less likely to use traditional medicines and exposure their infants to the sun compared with control infants (105). 95% of mothers in the intervention arm knew that NJ can lead to brain damage vs. 38% of mothers in the control group. This is one example of effective antenatal counseling, although there has not been a study comparing antenatal to postnatal education, as a previously mentioned study on maternal instruction did not have an adequate sample size to compare antenatal vs. postnatal effectiveness (40).

Diagnosis: harnessing telehealth for timely diagnosis and appropriate referral

Advancements in technology, improved access to the internet, and availability of smart phones, together can work to provide more timely and accurate diagnosis of SNJ and therefore lead to expedited treatment. The healthcare systems' recent experiences with the COVID-19 pandemic have led to more progress with telehealth in an effort to reduce in-person exposures to potential infections, when possible. As outlined previously, delayed care for neonates with SNJ is a major contributor to the development of negative outcomes. One contributor to delay is poor advice from physicians and other healthcare providers and seeking medical care at a facility that is not equipped to diagnose or treatment SNJ (19, 37).

Teleconsultation may be an efficient way to ensure proper treatment for NJ is being implemented and that a transfer to another medical facility can be coordinated if needed (106). Smartphone technology has recently been harnessed to diagnose NJ in a point-of-care manner. Taylor et al. published their BiliCam technique that used a camera with specialized software and machine learning to identify and predict bilirubin levels (107). The BiliCam had a correlation of 0.91 with TSB levels and a relatively high sensitivity (85%–100%) (107). Another study in China demonstrated decreased neonatal readmission rate and decreased maternal anxiety scores for mother-infant dyads that used a smartphone app to monitor for neonatal jaundice at home under web-based guidance of pediatricians compared to the control group that received routine care (108). Similar smartphone-based detection tools are being studied in other regions of the world, including Singapore (109), Ghana (110), and Saudi Arabia (111), and Nigeria (112), just to name a few. Although these tools are best suited as screening devices, as with the TcB, they are encouraging uses of state-of-the-art technology to improve the recognition and diagnosis of NJ. This smartphone technology could also help connect the local provider and family with a facility that is capable of next steps in care, as to avoid seeking care at a facility that is ill-equipped, thus providing efficiency in treatment.

Treatment: improving long-term medical care for those affected by severe neonatal jaundice

Lastly, long-term medical care and support is needed to improve the quality of life for those affected by SNJ. The WHO introduced the term disability-adjusted life year (DALY) as a measure of population health taking into account the whole burden of disease (113). DALY takes into account years lost due to premature death and years of healthy life lost due to disability (113). This measurement is important to consider when it comes to disability and impairment as a result of SNJ and its neurological sequelae. For example, the DALY for SNJ would include both premature death for neonates that died due to SNJ as well as years lived with disability, including cerebral palsy, hearing loss, and cognitive challenges for survivors (18). NJ accounted for 113,401 DALYs globally in 2016 in the neonatal period and was the 15th leading cause of DALYs among children under five years of age (114, 115). One recent analysis estimated the contribution of G6PDD to SNJ and its associated burdens to be 54,251 DALYs with related economic deficits to be $309–584 million (116).

Assisted technologies such as hearing aids, cochlear implants, communication boards, eye tracking devices, and simple aids to daily living such as wheelchairs and grab bars are not readily available in many LMICs (117, 118). Early intervention with physical and occupational therapies, as early as infancy, have the potential to improve developmental opportunities for at-risk patients (117, 119). Developmental clinics with multidisciplinary care teams should be in place to follow these children over time in an organized fashion. Finally, as noted in a 2017 article in African Business "*Too many disabled Africans are excluded from the labour market. More must be done to include them*" (120). While advocacy work in Africa is increasing, much more needs to be done to assure that adults living with KSD are equipped and encouraged to contribute to their societies.

Conclusion

In conclusion, when reviewing the past years of NJ literature, there have been encouraging progress to the way SNJ is prevented, diagnosed, and treated in LMICs. A focus on education and harnessing emerging technologies are common themes for these advancements. Remaining challenges in LMICs are related to fragmented medical care, traditional birth and postpartum practices, and the lack of locally specific and culturally appropriate management guidelines. Large scale implementation of small-scale

projects noted above would be a giant step in the prevention and treatment of SNJ. Having buy-in from policy makers, as well as embracing innovative technologies such as smartphone enabled detection of NJ and filtered sunlight PT devices, should make the scourge of SNJ yet another disease relegated to the history books together with diseases such as smallpox and poliomyelitis.

Author contributions

KS, TS, and ZF devised the contents and themes to be included in the manuscript. KS drafted the manuscript and TS and ZF provided critical review. All authors contributed to the article and approved the submitted version.

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.

Publisher's note

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Case report: Managing multisystem inflammatory syndrome in children (MIS-C) in Lao People's Democratic Republic, a success story

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Introduction: Multisystem inflammatory syndrome in children (MIS-C) is believed to be one of the most important life-threatening complications of COVID-19 infection among children. In any setting, early recognition, investigations, and management of MIS-C is crucial, but it is particularly difficult in resource-limited settings (RLS). This is the first case report of MIS-C in Lao People's Democratic Republic (Lao PDR) that was promptly recognized, treated, and resulted in full recovery with no known complications despite the resource limitations.

Case presentation: A healthy 9-year-old boy presented to a central teaching hospital fulfilling the World Health's Organization's MIS-C criteria. The patient had never received a COVID-19 vaccine and had a history of COVID-19 contact. The diagnosis was based upon the history, changes in the patient's clinical status, and response to treatment and negative testing and response to treatment for alternative diagnoses. Despite management challenges relating to limited access to an intensive care bed and the high cost of IVIG; the patient received a full course of treatment and appropriate follow-up cares post discharge. There were several aspects to this case that may not hold true for other children in Lao PDR. First, the family lived in the capital city, close to the central hospitals. Second, the family was able to afford repeated visits to private clinics, and the cost of IVIG, and other treatments. Third, the physicians involved in his care promptly recognized a new diagnosis.

Conclusions: MIS-C is a rare but life-threatening complication of COVID-19 infection among children. The management of MIS-C requires early recognition, investigations, and interventions which may be difficult to access, cost-prohibitive, and further increase demand on healthcare services that are already limited in RLS. Nevertheless, clinicians must consider means for improving access, determine which tests and interventions are worth the cost, and establishing local clinical guidelines for working within resource constraints while awaiting additional assistance from local and international public health systems. Additionally, using COVID-19 vaccination to prevent MIS-C and its complication for children may be cost-effective.

KEYWORDS

MIS-C multisystem inflammatory syndrome in children, low- and lower-middle-income countries, children, hospitalized, low resource areas, COVID-19, SARS-CoV-2

Introduction

As of December 15th, 2022, there were 646,740,524 confirmed COVID-19 cases and 6,637,512 total deaths from COVID-19 worldwide (1). As of December 15, 2022, Lao People's Democratic Republic (Lao PDR) reported 217,304 cases and 746 deaths (2). Of the total reported cases, 48% (104,938/217,304) were in those less-than-16-years-old (2). Eleven-to-15-

year-olds accounted for 61% of children infected (63,630/104,938) followed by 5-to-10-year-olds (22%, 23,364/104,938), < 2 (9%, 9,780/104,938), and 2-to-5-year-olds (8%, 8,164/104,938) (2). The total number of deaths in children under 16 years old in Lao PDR was 18 (2).

Globally multisystem inflammatory syndrome in children (MIS-C) is a life-threatening inflammatory response (3) resulting from COVID-19 (4–6). It is caused by an abnormal immune response to the SARS-CoV-2 virus (7). It presents as a post-infectious complication of the virus rather than acute infection (8). Characteristics of MIS-C include persistent fever, systemic hyperinflammation, and multisystem organ dysfunction (9). Severe MIS-C patients usually have significant multisystem damage, including cardiac involvement and shock (8). MIS-C is rare and arose in less than 1% of confirmed SARS-CoV-2 cases in children with disproportionately lower reported cases in Asian children (8). There was a higher risk among males (7), older children (8–11-years-old) (8), and children with comorbidities (obesity and asthma) (8). The reasons why MIS-C affects different populations of children at different rates remains unclear. It may be due to different rates of exposure to SARS-CoV-2 in different populations. MIS-C is usually curable and/or transient, but its cardiac manifestations are immense and life-threatening (9).

Due to limited knowledge and experience with MIS-C, the wide spectrum of clinical presentations, and limited resources, families may present late, and diagnosis and treatment may be delayed in resource-limited settings (RLS) (10, 11). Many challenges including access to health care facilities and the availability of costly immunomodulatory drugs may be more difficult in RLS (12). Limited laboratory and radiologic studies in RLS are additional challenges for prompt diagnosis, appropriate follow-up, and appropriately excluding other diagnoses. These challenges may affect the morbidity and mortality of MIS-C patients in Lao PDR.

We report the first known MIS-C case in Lao PDR, a 9-year-old previously healthy boy with an 8-day-history of fever, 5-to-6-days of gastrointestinal symptoms and anorexia, 3-days of mucocutaneous symptoms and lethargy which rapidly improved after IVIG administration. This case report demonstrated that prompt recognition, diagnosis, and treatment can result in positive outcomes, even in RLS. This case also highlights what resources were available to this child but may not be available to other children in Lao PDR.

Case presentation

Patient information

A 9-year-old ethnically Lao boy was referred from a private clinic to a central hospital's emergency department (ED) in Vientiane, the capital city of Lao PDR, on December 20th, 2021, with a typical presentation of MIS-C. He had an 8-day-history of fever and a 5-day-history of abdominal pain in the setting of having family members recently test positive by PCR for COVID-19 on November 23rd, 2021.

His first symptom (day 0) was an intermittent "high grade" fever (the mother did not measure his temperature) associated with chills and daily intermittent mild sore throat, relieved with paracetamol. On days 2–4, he developed mild intermittent periumbilical cramping pain and yellow watery stools without melena/hematochezia which progressed to vomiting with anorexia. He was found to have a 1–2 cm swollen area on his left posterior neck that spread to the right side over 2–3 days. This area was not red nor warm nor tender. His parent brought him to a private clinic (PC1) where he was diagnosed with tonsillitis and given amoxicillin without improvement. On day 5, he was more fatigued and developed bilateral nonexudative conjunctival injections, red lips, and increased anorexia. On day 6, the fever became persistent despite antipyretics. His abdominal pain, vomiting, and diarrhea worsened. His family brought him to an emergency department (ED) at a central hospital (CH1). He was diagnosed with acute gastroenteritis without dehydration and was discharged with oral rehydration solution and analgesia/antipyretics. On day 7, he returned to PC1, with no change in diagnosis nor treatment (timeline in **Figure 1**).

On the day of admission (day 8), his symptoms had not improved, and his family brought him to a new private clinic (PC2) where he was diagnosed with suspected severe sepsis with concerns for typhoid fever. At PC2, he had lymphopenia of 0.6×10^9/L–5%, granulocytosis of 11.8×10^9/L–91.8%, slightly raised CRP, negative dengue, and scrub typhus antigen testing, as well as a normal abdominal ultrasound. Subsequently, he was referred to the ED. His fever, fatigue, anorexia, and decreased urination continued, but the diarrhea decreased to once a day. He developed an occasional dry cough.

He did not have any flank pain, urinary symptoms, other upper respiratory tract infection symptoms, chest pain, shortness of breath, hypogeusia/ageusia, change in senses of smell/anosmia, altered level of consciousness, headache, dizziness, visual disturbances, focal neurological symptoms, joint/muscle/bone pain or swelling, rash/eschar.

His mother and youngest sister had positive PCR results for COVID-19 three weeks prior. During that time, he had a low-grade fever and mild respiratory symptoms (runny nose and cough), but he was not tested for COVID-19. Two weeks prior to his illness, he travelled to Vang Vieng, a vacation area, where he swam in a shallow river. The family denied other recent travel.

The patient was previously healthy with normal development. He had completed the basic Lao national immunization schedule but had no COVID-19 immunization. He did not take any regular medications and had no known allergies, nor surgical history. There was no family history of allergy and auto-immune diseases. Based on his family's report of the average nominal monthly consumption per capita (KIP) (13), the child's family wealth quintile was reported to be at the 5th quintile (most wealthy).

Clinical findings

At admission his vital signs were: temperature = 39.4 °C; respiratory rate = 50 bpm, heart rate = 150 bpm (regular), SpO2 = 95% on room air. His blood pressure was not recorded. His weight was 28.3 kg (weight for age = −0.4 SD) and height was 124 cm (height for age = −1.9 SD). The patient was fatigued, but alert, orientated and cooperative. He had warm pink skin, capillary refill

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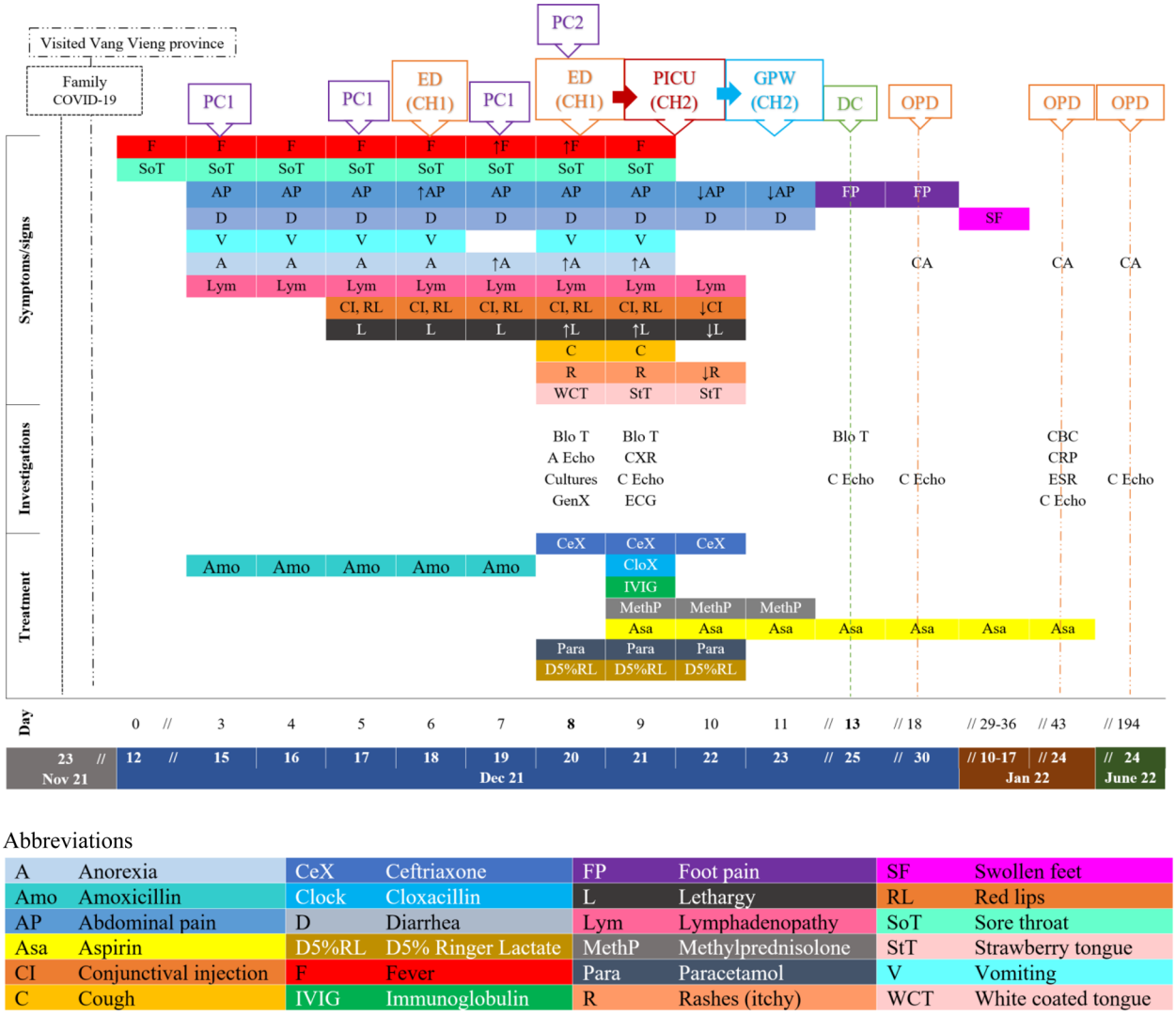

FIGURE 1
Timeline (dates and days of illnesses) with patient's clinical symptoms and signs in relation to health care services sought, investigations, treatment, and outcomes since the period of possible COVID-19 exposure, to the day of symptoms onset (12 December 2021), the discharged date (25 December 2021), and three follow-up dates (30 Dec 21, 24 Jan, and 24 June 22). (A Echo = Abdominal echography, Blo T = blood test, CA = Clinical assessment, C Echo = Cardiac echography, CH = Central hospital, CBC = complete blood counts, CXR = Chest x-ray, D = discharged, ECG = electrocardiogram, ED = Emergency department, ESR = Erythrocyte sedimentation rate, GPW = General Pediatric Ward, GenX = GeneXpert COVID-19, OPD = Outpatient department, PC = private clinic, PICU = Pediatric Intensive Care, PIDW = Pediatric infectious disease ward, ↑/↓ = Increasing/decreasing, → = Transfer/admit).

of < 2 s, and normal skin turgor. He had non-exudative conjunctival injection, red full lips, a white coating on his tongue, and itchy pink blanching maculopapular rashes at his palms, soles, and left knee (Figure 2). Non-tender smooth mobile enlarged lymph nodes were present in the bilateral posterior cervical chain (1.5–2 cm) and bilateral posterior triangles (left: 2 × 3 cm, right: 1.5–2 cm). There were no eschars, bruises, petechiae, desquamations, calf/muscle/joint/bone pain nor edema.

He had mild intercostal retractions. His apical impulse was palpated at the 4–5th intercostal space in the midclavicular line. He had normal S1 and S2, but with reduced heart sounds. We heard no murmur nor additional heart sounds. His lung sounds were normal. He had mild abdominal distension with generalized tenderness on palpation, especially in the right upper quadrant with mild to moderate guarding. There was no rebound, percussion, nor flank tenderness. Bowel sounds were normal with no hepatosplenomegaly. The genital examination was not remarkable. He had no meningismus and the neurological examination was grossly normal.

Diagnostic assessment

Based on the history and findings on the physical examination, MIS-C was thought to be the likely diagnosis. Cultures (blood, throat swab, urine, and stool) were sent (see Figure 1) and returned negative. COVID-19 rapid test and COVID-19 GeneXpert were also negative. Within three hours of admission, the patient's mental status changed from "A (alert)" to "V (responsive to voice)". He maintained his blood pressure at 90/60 and was able to walk to the toilet to pass urine with minimal assistance. He had a high fever (39–40 °C), tachycardia

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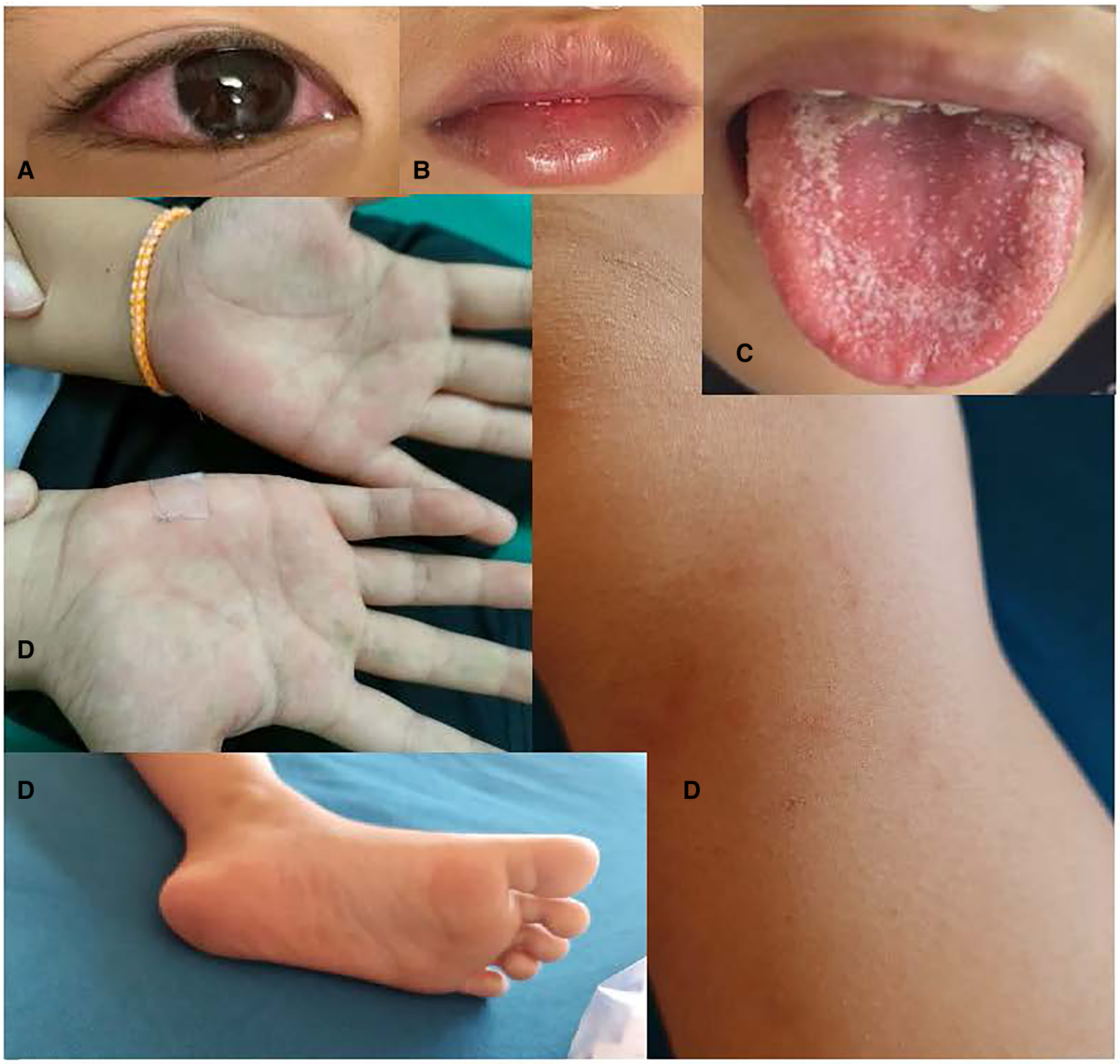

FIGURE 2
(A) Non-exudative conjunctival infection, (B) red lips, (C) strawberry tongue (onset day 9: 21/12/21), (D) itchy pink branching maculopapular rashes on palms, feet & left knee.

(150s), tachypnea (50–58), and desaturated (93% on room air) requiring oxygen (1-liter per minute) by nasal cannula to maintain his SpO2 at 97%. The patient was admitted late in the evening therefore, inflammatory markers (CRP, ESR, ferritin, LDH, albumin), liver and renal function tests, chest x-ray (CXR), electrocardiogram (ECG) and echocardiogram were unavailable and planned to be carried out after transfer and consultation with the pediatric cardiologist at CH2. Upon admission to CH2, COVID-19 RT-PCR was again negative. CXR showed mild cardiomegaly with normal lung fields. The initial echocardiography revealed mild impaired left ventricular function (ejection fraction of 45%–51%) with no dilatation of coronary arteries. His electrocardiogram was normal. In our region, dengue and scrub typhus are common and antigen testing for these illnesses were done and were negative. His urine analysis was unremarkable. The COVID-19 IgG was tested later as an outpatient in follow up and was found to be positive (**Figure 1**).

Therapeutic interventions

The patient had previously received five days of amoxicillin without improvement. On day 9 of illness, he clinically worsened and the following were started: intravenous immunoglobulin (IVIG at 2 g/kg in a single infusion over 12 h), methylprednisolone (2 mg/kg/day for 3 consecutive days), aspirin (3.5 mg/kg/day) ceftriaxone (100 mg/kg/day) for four total doses and cloxacillin (50 mg/kg/dose) for one dose. Cloxacillin was started for concern for toxic shock syndrome and stopped as patient stabilized. Rest, oral nutrition, and oral hydration were also encouraged.

Follow-up and outcomes

Twenty-four to 48 h after initiating IVIG and methylprednisolone, his clinical symptoms and fever improved. His heart and respiratory

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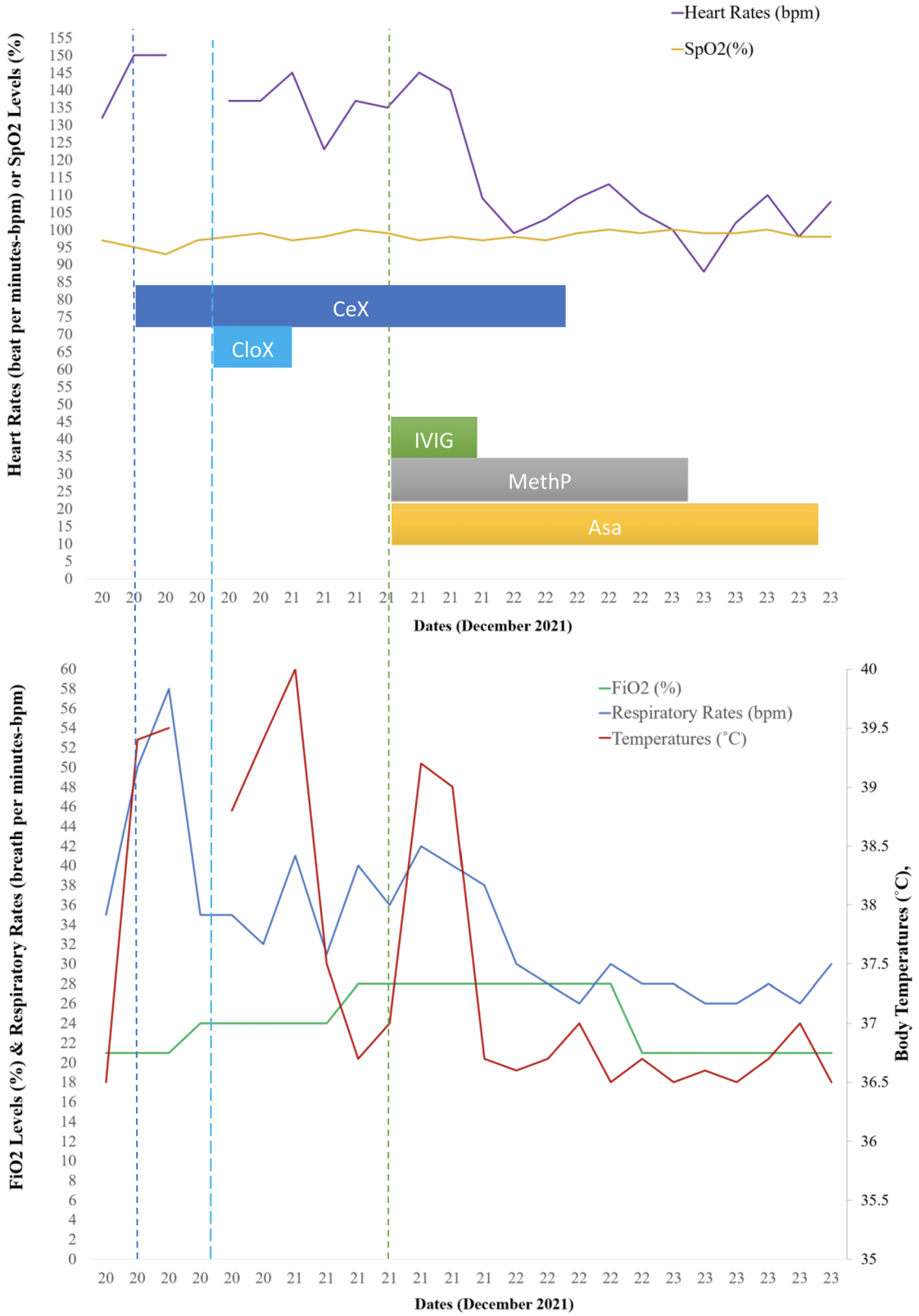

FIGURE 3
Cardiovascular and respiratory situations in relation to pharmacological therapy.

rates normalized, and oxygen therapy was no longer required (Figure 3). The lymphopenia and mild impaired cardiac function resolved (Figure 1). He was discharged from the hospital after 5 days with aspirin. He reported mild bilateral knee pain without swelling, warmth nor redness on the date of discharge, lasting for approximately one week. He later developed bilateral feet swelling for

one week, which also spontaneously resolved. On the second follow-up visit, complete blood counts (CBC) and CRP had completely normalized, while ESR significantly improved from ten times upper normal limit to five times the upper normal limit. During these visits, he had repeated echocardiograms which were normal (**Figure 1**).

Health care expenses

The patient's family did not have health insurance, which is available in Lao PDR. The family paid around US$ 1,185 for the management of the patient during hospital admissions and the follow-up visits (July 6, 2022: US$ 1 = 17,750 Lao kips), which consisted of services/equipment (6%), medications (86%), and investigations (8%). The IVIG and methylprednisolone costs were around US$ 949 (~US$15 per gram) and US$ 42 respectively, which constituted about 80% and 3.6% of the total treatment cost. The price the family paid at the government hospital is equivalent to the cost of the service, however, the price at the private clinics is higher. At the time of his hospitalization the test for IgG for SARS-CoV-2 was not available in the public hospital and this needed to be sent to a private laboratory which was the most expensive investigation costing US$29 (2% of total treatment cost).

Discussion

This is the first ever known MIS-C case report in Lao PDR with moderate to severe symptoms in a previously healthy 9-year-old boy. The diagnosis was based on the epidemiologic link to COVID-19 infection (8). Later, serology testing supported this diagnosis. This case report raised many important areas for consideration: delayed diagnosis, importance of ruling out other causes, diagnostic challenges associated with health care access and low-resources.

This child's diagnosis was made on day 8 of his illness after visiting two private clinics, and one ED twice. His delayed diagnosis unnecessarily increased his exposure to antibiotic therapy at the beginning of his illness. This is concerning as antimicrobial resistance is accelerated by the overuse of antibiotics and causes severe infections, complications, longer hospital stays, and increased mortality (14).

Though early recognition and diagnosis of MIS-C are necessary, it is also important to rule out other causes. The patient was first diagnosed and treated for tonsillitis, gastroenteritis, and a suspected typhoid fever bacteremia. At presentation to the hospital alternative diagnoses to MIS-C included Kawasaki disease, bacterial sepsis, staphylococcal toxic shock syndrome, dengue fever, typhoid fever, and severe acute COVID-19.

Though the patient presented with moderate MIS-C symptoms, compared to higher-resourced settings very limited investigations were performed initially. D-dimer, fibrinogen, procalcitonin, interleukin-6, coagulation studies, and cardiac markers were not carried out. Currently all these tests are available at higher prices in private clinics in Lao PDR. At the public hospitals D-dimer, fibrinogen, coagulation studies and cardiac markers are available before 10 am Monday through Friday. While it is well known that suboptimal health care access can lead to diagnostic and treatment delay, worsening disease, and higher disease complications (15), the speed with which the investigations were completed is faster in Vientiane Capital than in most rural areas, while still slower than in many high resource areas. In our opinion, the most useful laboratory tests in this case include full blood counts (FBC), quantitative CRP or ESR, liver function tests (LFTs), dengue rapid diagnosis test (Den RDTs), scrub typhus test, SARS-CoV-2 tests, and cultures. Raised inflammatory markers tend to be associated with illness severity (8); this could potentially assist in the decision to transfer to a more resourced health care facility.

In rural Lao PDR physicians may have access to FBC, LFTs, Den RDT, scrub typhus test, and SARS-CoV-2 RDTs. They will likely have less access to quantitative CRP and ESR, SARS-CoV-2 GeneXpert and PCR, or cultures. Tests such as a procalcitonin or interleukin-6 are not available. Therefore, in these settings the decisions to start, stop, or complete a course of antibiotics must include an assessment of likeliness of MIS-C and the inability to rule out alternative diagnoses.

The most expensive investigation for MIS-C was IgG SARS-CoV-2, followed by ferritin level and cultures. Son (8) suggested that all suspected MIS-C cases be tested for SARS-CoV-2 serology and reverse transcription PCR (RT-PCR). SARS-CoV-2 GeneXpert is no longer available in Lao PDR. Development of lower cost serology and PCR testing would facilitate faster diagnoses in RLS. Son additionally recommends that blood, urine, throat, stool cultures, respiratory viral panel, Epstein-Barr virus serology and PCR, cytomegalovirus serology and PCR, Enterovirus PCR, and Adenovirus PCR should all be carried out for moderate to severe MIS-C (8). Even in our central teaching hospitals, the last five could not be carried out. While it is important to rule out other diagnoses, it may be most prudent to focus on diseases with high prevalence locally with locally affordable and accurate testing. Investing in accurate low-cost testing for disease with high local prevalence will help facilitate faster diagnoses in general, as well as for MIS-C. Inflammatory markers, such as ferritin, are also nonspecific and therefore not testing all the inflammatory markers may be a means for cost savings.

As in most RLS, it was impossible to rule out all alternative diagnoses and therefore it was also important that we monitored this child for response to antibiotics and provided antibiotics that appropriately treated the bacterial infections which were alternative diagnoses while awaiting culture results. Though we did not complete the antibiotic course of the bacterial infections, it may be prudent to complete antibiotic treatment for common illnesses that may be endemic in each area that cannot be satisfactorily ruled out with the available laboratory testing.

CXR and echocardiograms also may not be available in remote settings. Echocardiograms require equipment and experts to perform, however, it is particularly useful to assess and predict levels of MIS-C severity as well as to follow up the cardiac outcomes. The ability to get patients in low and middle-income countries (LMICs) urgent quality echocardiographic evaluation remains difficult in most areas (16).

There was a significant expense related to the management of this patient's MIS-C. This family paid more for treatment than would be possible for most families in Lao PDR. IVIG was the most expensive single item in this patient's care and in Lao PDR it was only available in CH2 and would not be affordable for many patients in LMICs

(10). The limited availability and cost of immunomodulatory drugs likely affects the outcome of MIS-C in RLS (12). Currently there is inadequate evidence showing differences in the efficacy and safety of glucocorticoid or IVIG vs. combination treatment (17), international recommendations tend to recommend IVIG or IVIG plus glucocorticoids in the setting of hypotension, unless IVIG is not available or contraindicated (8, 18). When IVIG is unavailable, the first line treatment with pulse methylprednisolone was associated with favorable immediate and short term follow up outcomes (19). This led to considerable deliberation in our circumstance when IVIG is technically available but is cost prohibitive. Fortunately, the parents' financial status facilitated getting this patient all recommended treatment including IVIG, methylprednisolone, and antibiotics. Additionally, the family was able to return for additional investigations, including the costly SARS-CoV-2 IgG and completed all follow-up.

Additionally, at the time of admission to the CH1, there was limited pediatric intensive care unit beds, therefore the patient was transferred to CH2. Many MIS-C patients required ICU admission for cardiac or respiratory support (9). There are many places in Laos where an intensive care bed with appropriate staffing would not be available in a timely manner.

Regardless of the observed low incidence of MIS-C, caution is necessary and pediatric incidence rates of MIS-C and COVID-19 should continue to be monitored aggressively (9). The country's COVID-19 surveillance should be continued, and MIS-C surveillance systems should be established to monitor the impact of COVID-19 on the health of Lao children. As demonstrated above, due to the various clinical presentations, essential emergency/critical care, and possible fatal complications, it is essential to raise MIS-C awareness (10). Improving ability to appropriately identify, rule out, and treat diseases that can present similarly and with similar severity regardless of the patients' location is essential in improving the equity of care for children around the world and in RLS. Lastly, expanded access to a SARS-CoV-2's vaccine for children may be the best solution for decreasing this deadly illness.

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

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

VD, KN, BS, and DT were involved in the data collection, data verification, case analysis, and design of the paper's concept. VD wrote the first draft of the manuscript, designed, and created the figures. KN, BS, and DT read and verify the information. KK coordinated manuscript writing, read and revise multiple versions of the paper. All authors worked closely together to respond to reviewers' comments and complete the final version. All authors contributed to the article and approved the submitted version.

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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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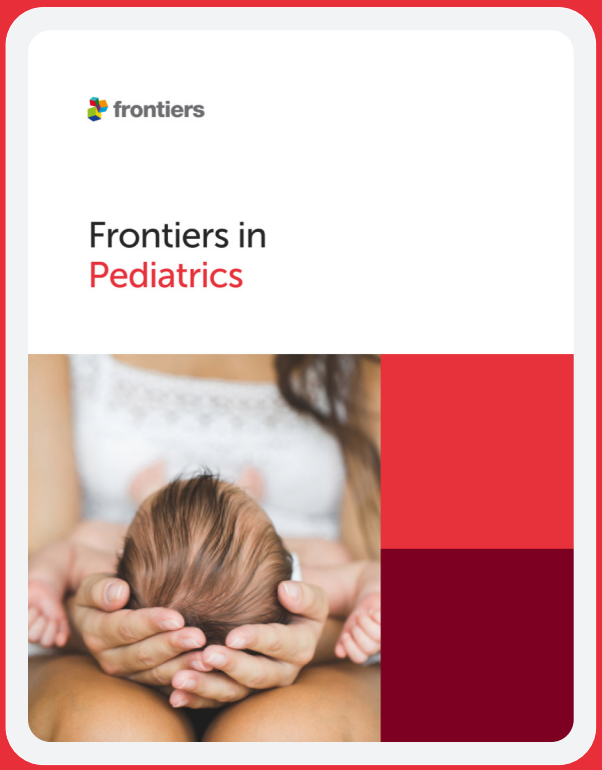

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