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Technologies for neonatal care in LMICs

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Technologies for neonatal care in LMICs

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Editorial: Technologies for neonatal care in LMICs

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Editorial on the Research Topic
Technologies for neonatal care in LMICs

1 Introduction

Newborn babies are among the most vulnerable class of patients in any society. They are entirely incapable of surviving on their own without external help from caregivers and society. A poorly attended newborn will more likely die compared with another who received well-guided and knowledgeable care (1). Therefore, the neonatal mortality rate of any society represents a quick measure of the efficiency of its healthcare system, available technologies, and knowledge base. It is common knowledge that low- and middle-income countries (LMICs) disproportionately contribute over 98% of the global annual burden of neonatal deaths (2, 3). Limited access to sustainable affordable technologies for neonatal care is one of the major impediments in lowering neonatal mortality in LMICs (4). Expensive medical equipment that works well in high-income countries (HICs) may be unsustainable in LMICs due to poor operational infrastructure (5), thus making sophisticated technologies used in HICs unaffordable and unsustainable in LMICs. However, a well-crafted basic technology may be extremely affordable, easily maintainable by in-house technicians, and effective at saving lives.

Therefore, we encouraged researchers to submit their practical demonstrations of applicable LMIC innovations to enable a collection of hybridisable ideas for empowering the rest of the LMICs in neonatal care.

2 Outline of contributions

This Research Topic has showcased 10 rigorous studies from 64 collaborating authors across many continents, drawing from easy-to-apply innovative technologies to address a variety of neonatal conditions.

Singh et al. (an Indian–Australian collaboration), explored the "diagnostic utility of lung ultrasound" in predicting when surfactant therapy is needed during neonatal respiratory support. They noted that lung pathologies for respiratory distress at birth have overlapping symptomatology with other conditions, hence the need to research the

diagnostic accuracy of a cutoff for the lung ultrasound score (LUS) in predicting the need for surfactant therapy in neonatal respiratory distress. They correlated LUS and the corresponding SPO_2 to FiO_2 in 100 neonates and found that an LUS cutoff of 7 predicted the need for the first dose of surfactant.

In another randomised controlled trial, Singh et al. compared the effect of premature infant oral motor intervention (PIOMI) and routine oromotor stimulation (OMS) on oral feeding readiness. They concluded that PIOMI is a more effective oromotor stimulation method for improving oral feeding in preterm neonates.

In a British–Indian collaboration, Hagan et al. assessed the "feasibility of multimodal imaging in neonatal hypoxic-ischaemic encephalopathy (NHIE) from an ovine model." They argued that the classical "Sarnat staging scale" used in NHIE classification is compounded by difficulties in the clinical detection of seizures. Hence, they proposed a low-cost bedside continuous monitoring electroencephalogram (EEG) tool—functional near-infrared spectroscopy (fNIRS)—that non-invasively measures the electrical activity of the brain from the scalp, capturing the neurovascular coupling (NVC) status. They tested how the imaging system may differentiate between normal, hypoxic, and ictal states in perinatal ovine models. Their main finding was that EEG-fNIRS imaging results are feasible and may provide a biomarker of sepsis effects on the NVC in NHIE.

Rauschendorf et al. (an American–Filipino–British collaboration) presented the effectiveness of a novel bubble continuous positive airway pressure (CPAP) system—Vayu—for neonatal respiratory support in the Philippines, where they compared the clinical outcomes of 1,024 "control" neonates with 979 "test-cases" after the introduction of Vayu bubble Continuous Positive Airway Pressure (bCPAP) systems. They found that Vayu device usage in a neonatal unit resulted in significantly improved outcomes.

Reis et al. —in a Brazilian–Mozambican collaboration—presented a study for enhancing "respiratory distress syndrome (RDS) prediction at birth by optical skin maturity." They developed a handheld optical device that evaluates the photobiological properties of skin tissue, processing it with other variables to predict early prematurity-related neonatal prognosis and tested the device's ability to predict RDS. The test correctly discriminated RDS newborns with 82.3% accuracy and demonstrated a new way of assessing a newborn's lung maturity, providing potential opportunities for earlier detection and more effective care.

In a pilot preclinical study, Bluhm et al. (USA) demonstrated that their low-cost "self-warming" biomedical device—the NeoWarm—could comparatively assist the hypothermic recovery of six piglets (TEST animal models) when assessed against five other unrecovered piglets (CONTROL) in an induced hypothermia experimental setting. The self-warming "NeoWarm" promises to be potentially applicable—with additional validation—in humans as an alternative to the time-consuming Kangaroo Mother Care technique.

In the first study to identify the factors affecting perinatal and neonatal deaths in Sao Tome and Principe, with collaboration from Portugal, Vasconcelos et al. concluded that the high-risk pregnancy score, meconium-stained fluid, the prolonged rupture of membranes, the transfer from another unit, and instrumental vaginal delivery increased the risk of stillbirth and neonatal deaths by four- to nine-fold. Therefore, prompt intrapartum care is a key strategy that should be implemented in Sao Tome and Principe.

In another fascinating work by researchers from the USA and Cambodia to minimise CPAP-associated oxygen toxicity, Wu et al. conducted a clinical safety assessment of their novel "low-cost entrainment syringe" oxygen blender system for modified bubble CPAP circuits. Thirty-two Cambodian children were included, of which 31 were clinically successful in treatment, as determined by the monitoring of oxygen saturation, the carbon dioxide partial pressure, the fraction of inspired oxygen, the frequency of device adjustments, and the duration of support. The overall outcome declared the blender safe for clinical use.

From the Republic of Korea, Hwang and Lee conducted a cross-sectional study, in which safe-delivery kits were distributed to 534 mothers in rural Ethiopian communities to investigate their impact on preventing newborn and maternal infection. The outcome demonstrates that single-use delivery kits decrease the likelihood of maternal infection, emphasising the need for their adoption in vulnerable countries to improve hygienic birthing, especially for deliveries outside of healthcare facilities.

Finally, a team of Nigerian, British, and Canadian researchers —Amadi et al. —in their courtroom "jury-style systematic review of 32 years of literature without significant mortality reduction," wondered why high neonatal mortality rates had persisted in Nigeria and some LMICs since the days of "United Nations' Millennium Development Goals (MDG) target (4)". They reviewed 4,286 publications but only 19 had the potential to reduce neonatal mortality; however, these remained largely unutilised by policymakers. The recommendation from this article was that healthcare systems in LMICs may have to look inwards to strengthen identifiable game-changing discoveries they already possess.

3 Concluding remarks

We invite organisations and policymakers of relevant countries to avail themselves of the rich contents of this Research Topic to implement a far-reaching neonatal life-saving campaign across LMICs, inspiring further research for inclusion in our next edition.

Author contributions

HA: Writing – review & editing, Writing – original draft, Data curation. TS: Writing – review & editing, Data curation. OM: Writing – review & editing. JG: Writing – review & editing.

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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Technical feasibility of multimodal imaging in neonatal hypoxic-ischemic encephalopathy from an ovine model to a human case series

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Hypoxic-ischemic encephalopathy (HIE) secondary to perinatal asphyxia occurs when the brain does not receive enough oxygen and blood. A surrogate marker for "intact survival" is necessary for the successful management of HIE. The severity of HIE can be classified based on clinical presentation, including the presence of seizures, using a clinical classification scale called Sarnat staging; however, Sarnat staging is subjective, and the score changes over time. Furthermore, seizures are difficult to detect clinically and are associated with a poor prognosis. Therefore, a tool for continuous monitoring on the cot side is necessary, for example, an electroencephalogram (EEG) that noninvasively measures the electrical activity of the brain from the scalp. Then, multimodal brain imaging, when combined with functional near-infrared spectroscopy (fNIRS), can capture the neurovascular coupling (NVC) status. In this study, we first tested the feasibility of a low-cost EEG-fNIRS imaging system to differentiate between normal, hypoxic, and ictal states in a perinatal ovine hypoxia model. Here, the objective was to evaluate a portable cot-side device and perform autoregressive with extra input (ARX) modeling to capture the perinatal ovine brain states during a simulated HIE injury. So, ARX parameters were tested with a linear classifier using a single differential channel EEG, with varying states of tissue oxygenation detected using fNIRS, to label simulated HIE states in the ovine model. Then, we showed the technical feasibility of the low-cost EEG-fNIRS device and ARX modeling with support vector machine classification for a human HIE case series with and without sepsis. The classifier trained with the ovine hypoxia data labeled ten severe HIE human cases (with and without sepsis) as the "hypoxia" group and the four moderate HIE human cases as the "control" group. Furthermore, we showed the feasibility of experimental modal analysis (EMA) based on the ARX model to investigate the NVC dynamics using EEG-fNIRS joint-imaging data that differentiated six severe HIE human cases without sepsis from four severe HIE human cases with sepsis. In conclusion, our study showed the technical feasibility of EEG-fNIRS imaging, ARX modeling of NVC for HIE classification, and EMA that may provide a biomarker of sepsis effects on the NVC in HIE.

KEYWORDS

hypoxic-ischemic encephalopathy, electroencephalogram, near-infrared spectroscopy, neurovascular coupling, experimental modal analysis

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) is one of the most common causes of neonatal death worldwide, accounting for approximately 23% of all neonatal deaths (1). Worldwide, it is estimated to account for more than one million deaths annually. HIE also accounts for considerably higher numbers of chronic neurological deficits that create an economic burden, more so in developing countries. Despite having such an immense societal impact, an adequate rapid diagnostic method for HIE is lacking (2). In HIE, there is a prolonged lack of oxygen entering the brain, which causes serious neuronal damage within a very short window of time, approximately 2–3 min if complete lack of oxygen, and will lead to a cessation of any neuronal activity shortly thereafter. Due to the direct effect of HIE on the neuronal state, current monitoring and outcome prediction are predominantly based on the electroencephalogram (EEG), which measures neuronal activity in the cerebral cortex. Amplitude-integrated EEG (aEEG) is an effective prognostic method for long-term neurologic deficits induced by HIE with a 90% classification accuracy at 6 h after injury in both positive and negative predictions. Here, positive predictions dictate that a subject will have significant deficits caused by the hypoxic event and negative predictions characterize recovery of normal neuronal function after the injury. In most studies, the least time to obtain an accepted and accurate prediction of extended deficits was found to be around 6 h and the lowest acceptable was 3 h, where the positive prediction scores were below 80%, and prior to that time window, the method did not provide any consistent predictive value (3, 4). Other alternative methods for prognosis in HIE such as magnetic resonance imaging (MRI) have fallen out of favor as they lack prognostic ability or speed in the early stage of brain injury. For example, T1- and T2-weighted MRI takes approximately 1 week for an accurate prognosis resulting from brain swelling from the injury. Also, there is a lack of MRI facilities in resource-poor settings and it is often cost-prohibitive. According to a meta-analysis by van Laerhoven (5), the diagnosis is at best on par with the 6-h aEEG with a positive predictive score of 83% and a negative score of 90%. Then, Chalak et al. (6) presented a neurovascular coupling (NVC)-based approach in HIE using multimodal imaging with aEEG combined with functional near-infrared spectroscopy (fNIRS) and wavelet coherence analysis. Here, the challenge remains in the continuous monitoring of NVC, where Sood et al. (7) presented a Kalman filter-based method that allowed online autoregressive with extra input (ARX) parameter estimation using time-varying signals and could capture transients in the coupling relationship between EEG and fNIRS signals. Then, the availability of low-cost portable brain imaging devices, e.g., OpenBCI (https://openbci.com/) and M3BA (8), can be leveraged for clinical translation of continuous cot-side brain monitoring in limited resource settings that can potentially help for better management of neonates with perinatal asphyxia and improve the long-term neurodevelopmental outcome. In the current study, the overarching objective was to test the feasibility of a low-cost multimodal brain imaging device (8) and an ARX-based support vector machine (SVM) classifier for point-of-care HIE monitoring in limited resource settings.

Continuous monitoring of neurovascular coupling may be superior to clinical scores for HIE classification (9). The hypoxic state can be rapidly detrimental for the brain neurons due to a large amount of oxygen needed in continuous supply (~10 ml/100 g tissue/min) and its low reserve, leading to large changes in neuronal firing during oxygen deficits that can affect the EEG power spectrum. Indeed, hypoxia effects on the EEG power spectrum have been extensively studied in both humans and animal models (10, 11). The spectral density, more commonly referred to as the power spectrum of the signal, makes the EEG signal easier to analyze based on rhythms that can be monitored over time as a spectrogram. The effect of hypoxia on the power spectrum has been studied using animal models (12); for example, Goel et al. (13) in an animal model of a neonatal piglet showed results from hypobaric hypoxia that was induced for 30 min using 10% oxygen concentration in air. Then, the airway was occluded for min, during which the piglet's neural firing ceased, and the piglet was resuscitated afterward. Throughout the protocol, the EEG was monitored while the piglet was anesthetized. The power spectrum was calculated at the end of both segments, airway occlusion and resuscitation, and one remarkable feature was spectral dispersion, where the low-frequency alpha and theta firings were most affected by hypoxia; also, there was a degree of disproportionality in the recovery of power of the three dominant frequency bands (1.0–5.5, 9.0–14.0, and 18.0–21.0 Hz) relative to their mean recovered power. Time domain features, such as Hjorth parameters, have also been used. The Hjorth parameters are simple statistical calculations on the EEG signal, with the first parameter known as the activity of the signal, which is the variance of the amplitude for a window of the signal in time, and the second Hjorth parameter known as the mobility of the signal. Mobility is defined as the square root of the ratio of the first parameter of the rate of change of the signal, divided by the actual first parameter of the signal, or the rate of change of the activity divided by the activity of the signal. The last of the Hjorth parameters is known as the complexity of the signal, which is the second derivative of the activity divided by the first derivative of the activity. Each of these Hjorth parameters changed during HIE and was found useful, especially in the classification of early partial seizure onset (14). Then, aEEG is a major clinical tool for the long-term prognosis of HIE; however, it uses 10-min windows for calculation and needs at least 6 h of data for accurate prognosis. Here, aEEG on its own needs prolonged data acquisition for an accurate prognosis that may outrun the early treatment window for HIE. Also, aEEG can be processed using Washington University-Neonatal EEG Analysis Toolbox (WU-NEAT) to estimate NVC in conjunction with fNIRS (9), which can be used for HIE classification (6). Another time series analysis is autoregressive (AR) modeling, which takes a segment of data and fits it to the current data point in a linear combination of previous data points multiplied by parameters that have a fixed value throughout the segment. The AR model requires matrix

calculations to acquire these parameter values and requires validation to ensure that it is adequately capturing the EEG signal properties and not the noise especially when detecting seizure activity (15). If the AR model adequately fits the data, the power spectrum trends are captured in the transfer function output of the system model and can be reconstructed. Then, operational modal analysis using AR with the eXogenous input (ARX) model can provide mechanistic insights from the NVC system model with the simultaneously acquired EEG-fNIRS data. We have extended published algorithms for online multimodal brain imaging using EEG and fNIRS in our prior work (7).

The current study is motivated by recent findings on the role of NVC in the prediction of brain abnormalities in neonatal encephalopathy (9). Das et al. (9) found NVC to be a promising biomarker in neonatal HIE that was superior to the total Sarnat score (16) for the prediction of abnormal brain MRI in the later stages. In estimating coherence, stationarity and ergodicity of the signal are assumed, which needs preprocessing of the raw EEG data to remove trends and low-frequency variations. Then, the modeling accuracy becomes more challenging when the spectra contain sharp peaks, e.g., during rhythmic activity (17). Therefore, an ictal classifier based on EEG spectral features was developed using the Children's Hospital of Boston and the Massachusetts Institute of Technology (CHB-MIT) dataset (18) to separately label seizure activity (19). Then, a SVM was used with the AR parameters to classify EEG (20) into various experimentally induced states in an ovine model of perinatal asphyxial arrest (21). Here, we applied AR modeling and assumed AR parameters being constant throughout the selected window size (22). Ahmed et al. (20) have used a multiclass SVM classifier for the best estimation of an outcome based on a commonly used clinical grade of one to four: a grade of one being non- to mild abnormalities, two being moderate, three being major EEG depression, and four being a severe EEG discontinuity. Their classifier overall had an 87% accuracy in classifying the recovery grade of newborns from HIE and was found to be one of the most effective such classifiers, while others were as accurate as 77% (23). Here, we also performed ARX modeling using EEG-fNIRS data from the ovine model of perinatal asphyxial arrest (21). The objective was to test the feasibility of a low-cost EEG-fNIRS device and the ARX-based linear classifier to label simulated HIE states in a perinatal ovine hypoxia model. Then, we applied the ARX-based linear classifier trained with perinatal ovine hypoxia model data to a human case series on perinatal HIE with and without sepsis. We also investigated experimental modal analysis (EMA) of the NVC system model that provided mechanistic insights from simultaneously acquired EEG-fNIRS data. Here, the ARX model allowed the estimation of the modal parameters and frequency response functions (FRFs) of the NVC system. Then, the FRFs of the EEG power as input and the hemodynamic (fNIRS) changes as output were used for the EMA of the NVC system dynamics for the mechanistic insights into the HIE (with vs. without sepsis).

2. Materials and methods

2.1. Animal model and data processing

The preparation of ovine subjects was carried out in accordance with the Institutional Animal Care and Use Committee at the State University of New York at Buffalo, United States (24–26). Term (140–147 days) pregnant ewes were obtained from New Pasteur Family Farms (Attica, NY, United States). After an overnight fast, the pregnant ewe was anesthetized with intravenous diazepam and ketamine. The ewe was continuously monitored using a pulse oximeter and an end-tidal carbon dioxide monitor. The ewe was intubated with a 10-mm cuffed endotracheal tube and ventilated with 21% oxygen and 2%–3% isoflurane at a breathing rate of 16 breaths per minute. The perinatal ovines were delivered by a cesarean section and partially exteriorized and intubated. Once the delivery process was completed, excess fluid that remained in the lungs of the newborn was removed via passive measures, by tilting the head back and forth for simulating the process by which fluid is removed during birth. Once the excess liquid was removed, the airway was occluded to prevent gas exchange. The catheters were then placed in the jugular vein and right carotid artery to sample blood and administer any necessary medication. A 2-mm flow probe (Transonic Systems Inc., Ithaca, NY, United States) was placed around the left carotid artery and a 4-mm flow probe was placed in the left pulmonary artery. The electrocardiogram electrodes were then placed in the right and left axilla and right inguinal area, a standard three-lead setup. The ECG100C (Biopac, Inc.) was used with Acknowledge software to record data from leads I, II, and III of the ECG. The saturation of preductal arterial oxygenated hemoglobin was monitored by a pulse oximeter placed on the right forelimb of the neonate. Low-cost wireless EEG-fNIRS (750 nm and 850 nm) sensors (OEM from Technische Universität Berlin) (8) were placed on the forehead for continuous measurement at 500 Hz for EEG and 10 Hz for fNIRS (see **Figure 1**). Our low-cost wireless EEG-fNIRS (750 nm and 850 nm) sensors (Bionics Institute, Australia) were validated using off-the-shelf EEG (Biopac Inc., United States) and fNIRS (Nonin Medical, United States) sensor data from the established perinatal asphyxiated lamb model experiments; see the experimental protocol by Vali et al. (26).

Following instrumentation, the umbilical cord was occluded until asystole, which is defined as the complete lack of carotid artery flow, arterial blood pressure, and heart rate. The lamb remained in the asystole for 5 min, and then resuscitation was started. Positive pressure ventilation (PPV) via an endotracheal tube was provided with 20% oxygen and was performed using a T piece at a rate of 40 breaths per minute (25). After 1 min of ventilation, chest compressions (CCs) were initiated and coordinated with CCs in the ratio of 3:1 (3 CC: 1 PPV). After 5 min of resuscitation, if the lambs did not have a spontaneous return of circulation (ROSC—defined as heart rate >60/m with systolic blood pressures >30 mmHg), medications (epinephrine or vasopressin) were administered through an umbilical venous

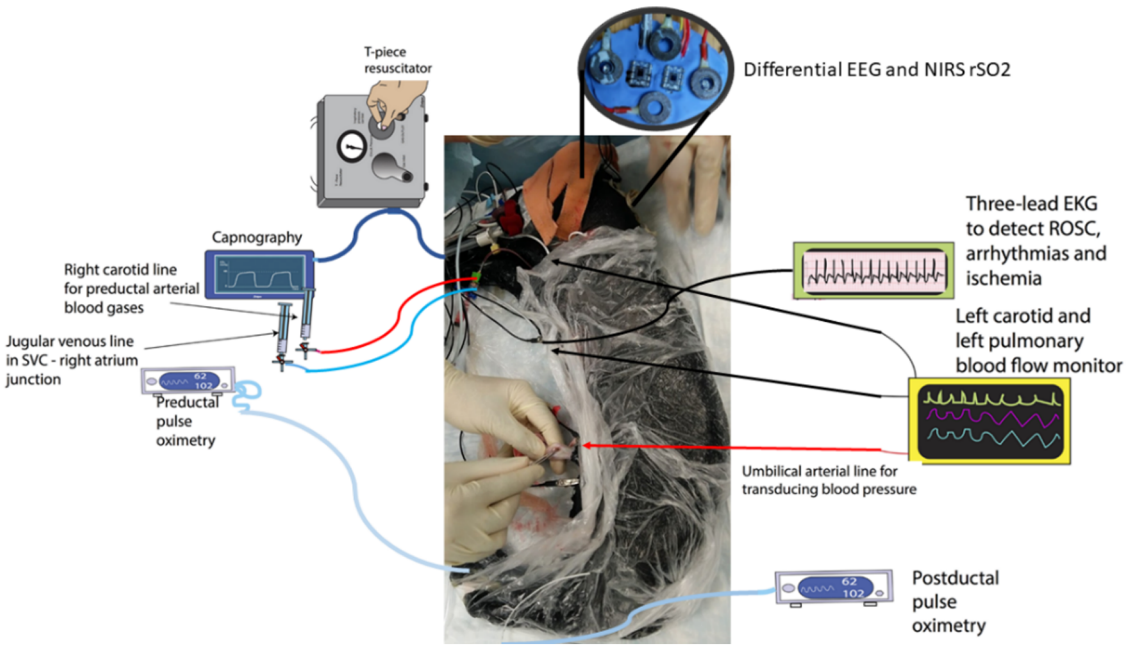

FIGURE 1
Differential EEG and the fNIRS sensors were added to the perinatal asphyxiated lamb model experiments (26). The figure was adapted from Figure 1 of Vali et al. (25). EEG, electroencephalogram; fNIRS, functional near-infrared spectroscopy.

catheter. Blood gases were obtained at intervals, and the lambs were ventilated after ROSC for 2–3 h. If the lambs had ROSC, resuscitation was stopped at 20 min. Data from five ovine subjects were analyzed in this study with a gestational time of 139–142 days, as shown in **Table 1**. The data analysis followed five major portions: raw data extraction, preprocessing, autoregressive modeling, classification, and validation. The workflow presented in **Figure 2** was used to obtain results from the EEG and fNIRS systems starting with the extraction of raw data.

2.1.1. Major events were labeled offline as follows

First, we start the EEG or initiate our experiment; then, neonate delivery was performed, followed by the asphyxiation of the subject. Here, from the beginning of EEG to the start of asphyxiation, the data were labeled as control or normal. The next major event was the point of no cardiovascular function, known as asystole. Data between the time of neonate delivery and asystole were labeled as ischemic data. The next event was the start of resuscitation. The data between the asystole and the start of resuscitation were labeled the asystole segment. The two portions consisting of ischemic and asystole data segments were combined into a more generalized hypoxia phase for our AR-SVM classifier testing. The last event was the recovery of spontaneous circulation or ROSC. So, the data segment between the start of resuscitation and the ROSC was labeled as the chest compression segment, and then, the last segment was the recovery segment in the case of ROSC of the subject.

TABLE 1 Five full-term ovine subjects used in the animal study.

Subjects	Gestational time (days)	Weight (lbs)	Sex
11/16-1	142	5.5	Male
12/13	141	3.05	Female
3/26	139	4	Male
11/16-2	142	5.5	Male
11/15	141	4.4	Male

2.1.1.1. Data preprocessing—removal of chest compression

As EEG is affected by the movement artifacts due to chest compressions, the data segment was completely removed during preprocessing.

2.1.1.2. Data preprocessing—removal of flat lines

The next stage of preprocessing was to remove sections of the data where electrode contact was lost or obstructed, which can appear as a flat-line artifact in the EEG. The EEG flat lines were removed by measuring the standard deviation of the signal in the sliding window after visual confirmation.

2.1.1.3. Data preprocessing—correcting for baseline drift

The removal of the baseline drift is the next step in the preprocessing pipeline. EEG is considered a zero mean signal; therefore, if the signal mean is not zero over time, then it was considered a baseline drift artifact. In the case of a baseline drift artifact, the EEG data were adjusted back to a zero mean using the "detrend" function in MATLAB (MathWorks, Inc.).

2.1.1.4. Data preprocessing—bandpass filtering of data

A bandpass filter was designed with cutoff frequencies set to 0.5–50 Hz [neonates rarely have high gamma activity (27)], thereby removing both low-frequency artifacts (common causes of

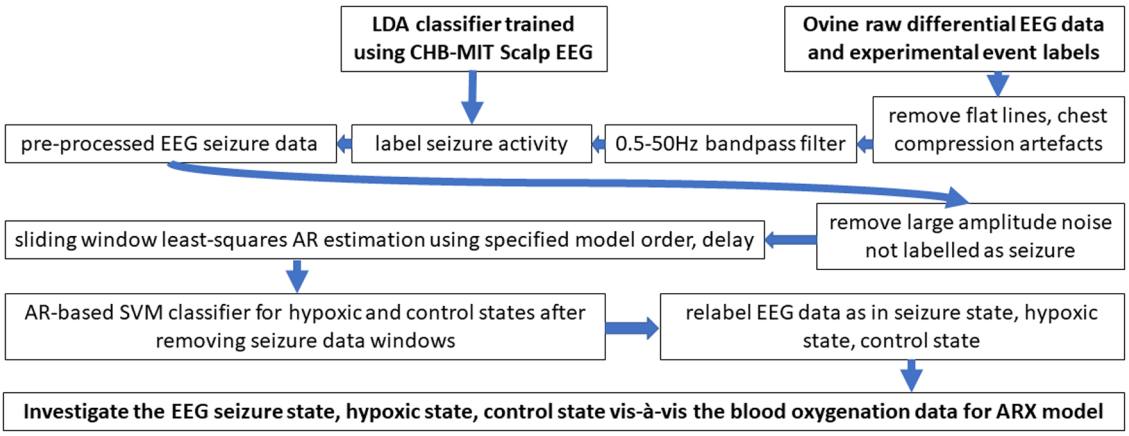

FIGURE 2
Algorithmic workflow for processing perinatal ovine EEG data. EEG, electroencephalogram.

nonstationarity) and high-frequency noise. We applied a fifth-order filter that provided a stable filter for our specific cutoff frequencies using the "butter" function in MATLAB (MathWorks, Inc.).

2.1.1.5. Data preprocessing—LDA binary classifier for seizure

The next stage of the preprocessing pipeline was to label ictal activity using a sliding window of the data (22) as seizure activity occurred frequently, and we aimed at hypoxia classification using background (nonseizure) EEG activity (28). Linear discriminant classifier (LDA) classifier training used the CHB-MIT dataset (18). The CHB-MIT scalp EEG dataset contains 22 subjects from children who have been removed from antiepileptic medication and suffered seizures. The sampling rate for all data was 256 Hz, and the international 10–20 standard montage was used for recording. A physician trained in EEG-based seizure detection manually labeled the occurrence of ictal activity in the CHB-MIT dataset. To maximize the scalability of the LDA classifier from the CHB-MIT dataset to our EEG measurement, only one channel of differential data was chosen for training the classifier, as described next.

The differential EEG channel used in our perinatal ovine study was comparable to the Fz-Cz electrode pair from the human 10–20 labels. Therefore, Fz-Cz electrode data were processed for differential EEG like our perinatal ovine data but we did not use their (19) SVM classifier that had several hyperparameters. We used a simpler LDA that was trained using the labeled CHB-MIT dataset [using 3.4-s sliding window that was longer than 2 s used in their SVM classifier (19)]. Our chosen features were alpha and low gamma band power (29). Here, LDA is a binary classifier that generates a linear decision plane to maximize the accuracy of binary classification. To avoid overfitting, a fivefold cross-validation was used, which divided the EEG data into five segments and used four-fifth of the data to train the classifier and one-fifth to test and performed this processing five different times, so all the EEG data can be used for both testing and training. This method is widely used in machine learning to avoid generating overfit classifiers. Once the LDA classifier was trained by the labeled CHB-MIT dataset, the Fz-Cz EEG ovine data in a 2-s sliding window was run through the binary classifier, and the windows with seizure were labeled.

2.1.1.6. Data preprocessing—removal of large-amplitude data segments

The last in the preprocessing was to remove data segments containing large activity (and not labeled as a seizure); this was done by finding the overall standard deviation of the EEG data and removing data segments that had a mean larger than two standard deviations of the whole EEG data.

2.1.1.7. Autoregressive (AR) modeling of the EEG data

The AR model is a linear model that fits the current output using a defined number of previous outputs, multiplied by the same number of coefficients, known as AR parameters. The AR parameters are optimized based on the linear algebra principle of least-squared estimate for the best fit, where the AR model yields higher resolution for spectral analysis than nonparametric approaches when the signal length is short. If an accurate AR model is constructed, then the spectral analysis of the signal can be solely described and reconstructed from AR parameters. AR model delay was included in our model, and the delay calculation was done using autocorrelation, which is a measure of mutual information shared between the signal and a time-shifted version of itself. The analysis of the data autocorrelation was performed for every possible positive delay. The maximum value denotes the time point when there is the most shared information. The delay was calculated for each ovine subject separately from the control phase of the EEG data. The AR model order is the other property of the model that must be optimized, which was done to make sure that the system is being accurately modeled while also being the least computationally expensive, e.g., using Akaike's information criterion (AIC). Prior work (13) also found an optimal AR model order of six for a similar kind of EEG data. After AR modeling the EEG data, these AR parameters were plotted in 3D to visualize clusters

from the nonictal background EEG activity. The ictal activity was labeled using a first-level LDA classifier—see section *Preprocessing—seizure binary classifier*. Then, AR parameters were used as features to visualize the clusters for all the three different experimental conditions in the 3D AR feature space; seizure state, hypoxia state, and normal/control state.

2.1.1.8. SVM classification using EEG AR parameters

Separation into the three experimentally induced states, normal/control, hypoxia, and seizure, was done using two different linear classifiers in the hierarchy. The first of the two linear classifiers in the hierarchy was the LDA seizure classifier that was trained using the CHB-MIT dataset—see section *Preprocessing—seizure binary classifier*. This binary classifier was applied to identify the data segments that contained ictal activity, which were removed before training and testing the second-level SVM classifier using the background EEG (3.4-s sliding window). The second-level SVM classifier was used to classify the AR parameters from the seizure-free (background) EEG data segments into the hypoxia state and the control (normal) state. Here, AR parameters were used as features (see **Supplementary material Figures S1–S3**), and the response variable used for training and validation were the event markers from the animal experiment. The SVM classifier was chosen for a more generalizable decision plane since this SVM classifier that was trained using perinatal ovine data was then applied to human perinatal case series. To avoid overfitting the SVM classifier, a fivefold cross-validation was used.

2.1.1.9. SVM classification using EEG-fNIRS ARX parameters

We applied the ARX model to the EEG-fNIRS data (here, a 60-s sliding window was used due to a slower fNIRS signal) for the second-level SVM classifier using seizure-free data segments for labeling hypoxia and control (normal) states. We used the basic nirs-toolbox (30) script in MATLAB (MathWorks, Inc.) to process the fNIRS data (750 and 850 nm). Specifically, we used the following modules with default parameters: nirs.modules.OpticalDensity, nirs.modules.BeerLambertLaw, and nirs.modules.AR_IRLS. We used the AR-IRLS model (31) that employed both prewhitening and robust regression to remove noise from the data. The ARX model order of six from AIC was comparable to our previous work (7) that used the fNIRS oxyhemoglobin signal in the low-frequency (0.1 Hz) range as the output and the transformed EEG band power as the input (7). In this study, we used an EEG frequency band of 1.0–21.0 Hz due to the dominant frequencies found in a related prior work (13). Then, the ARX parameters ("arx" in MATLAB) were used as features in the SVM classifier, and the response variable used was the event markers from our animal experiment. To avoid overfitting the classifier, a fivefold cross-validation was used.

2.1.1.10. Hierarchical classifier outcome vis-à-vis carotid flow

After the hierarchical classifier was found from the perinatal ovine data, the classifier outcome was compared with the carotid blood flow data. Here, the objective was to compare the changes in the carotid flow rate (irrespective of the manually placed event boundaries) when the ovine subject physiologically entered the global hypoxia stage.

2.2. Human data acquisition and feasibility testing

The human perinatal study was conducted based on convenience sampling at the Department of Neonatology and approved by the Institutional Review Board (IRB) of the IMS & SUM Hospital, Bhubaneswar, India. The study objectives were to test the feasibility of the EEG-fNIRS joint imaging for the ARX-based SVM classifier that was trained with the perinatal ovine data to detect the severity of human perinatal HIE. The study was a prospective observational study. Ten newborns with moderate to severe HIE and four severe HIE cases with sepsis were recruited for the feasibility study. Sepsis screening was performed according to the clinical guidelines at the IMS & SUM Hospital, Bhubaneswar, India. Specifically, sepsis was suspected when there was a history of lethargy, poor feeding, fever, hypothermia, or temperature instability, abdominal distension, feeding intolerance, and tachypnea. The suspicion was corroborated with a positive sepsis screen (total leukocyte count < 5,000/cmm or absolute neutrophil count < 1,800/cmm, micro-ESR > 15 mm in the first hour, immature-to-total neutrophil ratio > 0.2, CRP > 10 mg/dl, any two of the four positive parameters meant sepsis screen positive). Sepsis was also confirmed if the blood culture was positive. Here, the physical and neurological examination was performed by neonatologists trained with Sarnat and Sarnat scoring criteria (32).

The inclusion and exclusion criteria were the following:

- Inclusion criteria: Neonates with gestation >35 weeks and >1,800 g admitted to the neonatal intensive care unit (NICU) for the treatment of perinatal asphyxia.
- Exclusion criteria: Premature babies <35 weeks, babies with multiple congenital anomalies, and not giving consent for inclusion in the study.

The experimental setup is shown in **Figure 3**, where the parietal EEG channels were averaged and subtracted from the averaged frontal channels to get a single channel EEG data. The bilateral frontal–parietal fNIRS channels were also averaged to get a single channel of fNIRS data. The preprocessing used in the perinatal ovine model study was applied to the human EEG-fNIRS data. The first-level LDA classifier [trained using human perinatal EEG data from the CHB-MIT dataset (19)—see section *Preprocessing—seizure binary classifier*] was applied to label the seizure segments in the EEG data. Then, the second-level SVM classifier in the hierarchical classifier, trained using the ovine EEG-fNIRS data, was applied to 60-s sliding windows of the human EEG-fNIRS data to label the hypoxia and the control (normal) states. Then, for mechanistic investigation of the NVC system using modal analysis (33), we applied EMA using the ARX system model ("arx", System Identification Toolbox). Here,

FIGURE 3
Experimental setup for perinatal human study in the NICU using the low-cost EEG-fNIRS device (OEM from Technische Universität Berlin)—see the bottom left inset. The eight EEG electrodes were distributed bilaterally in the frontal and the parietal areas—see the top right inset. The two fNIRS sources were placed bilaterally in the frontal area, while the two fNIRS detectors were placed bilaterally in the parietal area in the cap (using a black cloth headband). NICU, neonatal intensive care unit; EEG, electroencephalogram; fNIRS, functional near-infrared spectroscopy.

we performed EMA of the estimated NVC system that was estimated from the EEG-fNIRS data. Input and output time series were stored using a data object in the time domain ("iddata" in MATLAB). We used the modal analysis functions "modalfrf" to determine the FRFs, "modalfit" to determine the modal parameters of the FRF, and "modalsd" to generate a stabilization diagram for the modal analysis in MATLAB (MathWorks, Inc.). A single set of modal parameters was generated using the least-squares complex exponential (LSCE) algorithm in MATLAB (MathWorks, Inc.) by analyzing multiple response signals simultaneously in "modalsd". Then, a stabilization diagram was used to identify the physical modes by examining the stability of the poles as the number of modes increased. Here, the given pole was considered stable in frequency if its natural frequency changes by less than 1% and stable in damping if the damping ratio changes by less than 2% as the model order increases in the stabilization diagram.

3. Results

3.1. Results from the perinatal ovine study—classification based on autoregressive parameters

Clustering of the AR parameters for the experimentally induced HIE states in the ovine model (see the upper panel of Figure 4) allowed binary decision planes for the first level (seizure vs. nonseizure EEG data) and the second level (hypoxia vs. control EEG data) in the hierarchical linear classifier using a sliding window of 3.4 s for the EEG data. Here, a sliding window of 3.4 s [longer than 2 s used in the prior work with the SVM classifier (19)] was found to be adequate for the estimation of AR parameters for the reconstruction of the EEG power spectrum (22)—more details are in the thesis (24). The first level of the hierarchical linear classifier determined the seizure state using the LDA classifier applied to EEG data in sliding windows of 3.4 s, where the confusion matrix of the binary classifier trained with the human CHB-MIT dataset is shown in Table 2. Here, the accuracy is 92.68%, sensitivity is 76.88%, and specificity is 93%, which are comparable to those in the prior work (19). Then, the decision plane of the LDA seizure classifier was used to identify and label the seizure data segments (=3.4 s) in the perinatal ovine EEG data. Then, the second-level classifier was trained to separate the control (normal) segment from the hypoxia segment using either the AR parameters from EEG data (with a 3.4-s sliding window) or the ARX parameters from the EEG-fNIRS (with a 60-s sliding window). AR parameters performed moderately well to separate the control (normal) segment from the hypoxia segment (see Table 3), where the accuracy was 98.44%, sensitivity was 70.75%, and specificity was 81.78%. However, with ARX parameters from EEG-fNIRS data, the classifier performance to separate the control (normal) segment from the hypoxia segment (see Table 4) (also

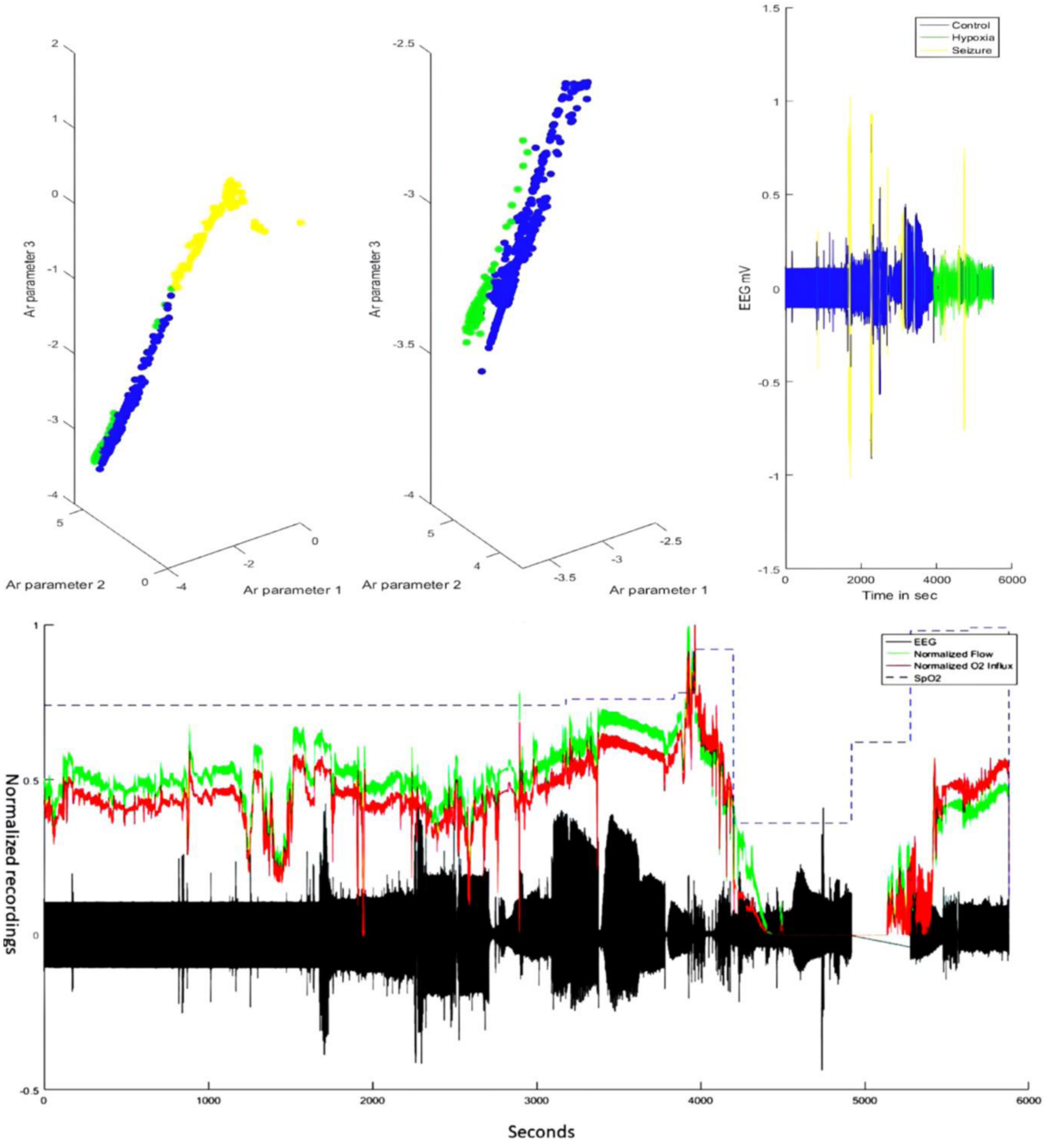

FIGURE 4
Illustrative example of subject 11/16-1—comparing EEG classifier labels vis-à-vis carotid blood flow and oxygen influx data. The top panel shows the labeling by the hierarchical classifier in the AR feature space that could discriminate the brain state—control or normal (blue), hypoxia (green), and seizure (yellow). The bottom panel shows the corresponding carotid flow and oxygen (O_2) influx from the oxygen saturation (SpO_2) data. Note that around the 4,000-s timepoint, the carotid blood flow increase is followed by a steep decrease—the response of the neonate to asphyxial arrest (21). The chest compression and resuscitation data sections were removed (around 5,000 seconds), which was followed by ROSC with the return of the carotid flow and oxygen influx. Here, the gap in the EEG data (in black) before ROSC and after the asphyxial arrest is due to the removal of the artifactual (due to chest compression) EEG data. EEG, electroencephalogram; AR, autoregressive; ROSC, spontaneous return of circulation.

Supplementary material Figures S1–S3) improved sensitivity and specificity, with the accuracy at 95.30%, sensitivity at 91.95%, and specificity at 96.75%. Figure 4 shows an illustrative example of the correspondence of the classification of the control (normal) segment from the hypoxia segment vis-à-vis normalized carotid flow recordings and global hypoxia (oxygen influx based on oxygen saturation).

3.2. Results from the human feasibility study

A nontechnical staff was trained to conduct cot-side continuous EEG-fNIRS data acquisition in NICU that was established in a limited resource setting with 1 day of shadowing of a technical expert to learn the experimental protocol—the setup is shown in Figure 3. The two-level hierarchical classifier developed using the

TABLE 2 Confusion matrix of the ictal state classification using the LDA classifier.

N = 8,670	Predicted class		
	8,670	*P*	*N*
Actual Class	P	143	43
	N	592	7,892

LDA, linear discriminant classifier.

TABLE 3 Confusion matrix of the hypoxia classification based on AR parameters from EEG using the SVM classifier.

N = 8,484	Predicted class		
	8,484	*P*	*N*
Actual class	P	1,819	752
	N	1,077	4,836

EEG, electroencephalogram; AR, autoregressive; SVM, support vector machine.

TABLE 4 Confusion matrix of the hypoxia classification based on ARX parameters from EEG-fNIRS using the SVM classifier.

N = 8,484	Predicted class		
	8,484	*P*	*N*
Actual class	P	2,364	207
	N	192	5,721

EEG, electroencephalogram; fNIRS, functional near-infrared spectroscopy.

ovine EEG-fNIRS data (see **Figure 4**) was applied to the human EEG-fNIRS data. The hierarchical classifier labeled the six severe HIE cases and four severe HIE cases with sepsis as "hypoxia" and the four moderate HIE cases as the "control"—hypoxia and control labels are based on the perinatal ovine experiment (see **Figure 4**). Here, EMA provided insights into the NVC modes (33), where the severe HIE and the severe HIE with sepsis cases were found to be different in the stabilization diagram.

3.3. Results from the EMA of the human NVC

Figure 5 shows the stabilization diagrams of the NVC system estimated from the EEG-fNIRS signals (60-s sliding window) from six severe HIE human perinatal cases, four severe HIE human perinatal cases with sepsis, and four moderate HIE human perinatal cases. Here, the stabilization diagrams of the four moderate HIE human perinatal cases did not show a dip at around 1 Hz in the averaged frequency response function; however, the four severe HIE human perinatal cases with sepsis had a dip at around 1 Hz and a stable pole mainly in the frequency between 0.5 and 1 Hz—is this related to respirocardiac dysfunction?

4. Discussion

Our study showed the feasibility of training an SVM classifier with the ARX parameters from the perinatal ovine model EEG-fNIRS data and then applying the SVM classifier to the human data to detect HIE severity. The SVM classifier was at the second level of our hierarchical classifier, where the first level was an LDA seizure classifier that was trained using the human CHB-MIT dataset (18). The LDA seizure classifier had an accuracy of 92.68%, a sensitivity of 76.88%, and a specificity of 93%, which were comparable to those in the published prior work using the CHB-MIT dataset (19). Then, the trained LDA seizure classifier was used to label the seizure data segments (=3.4 s) in the perinatal ovine model EEG data and the human EEG data. ARX parameters from the EEG-fNIRS seizure-free data segments (in 60-s windows) from the perinatal ovine model achieved an accuracy of 95.30%, a sensitivity of 91.95%, and a specificity of 96.75%. The perinatal ovine model-trained hierarchical classifier was applied to the human data, where it labeled the six severe HIE cases and four severe HIE cases with sepsis as "hypoxia" and the four moderate HIE cases as the "control." Therefore, we showed the technical feasibility of our two-level hierarchical classifier in differentiating severe HIE from moderate HIE, which is feasible for hardware implementation (34).

Prolonged hypoxic events in the ovine model led to substantial seizure activity when the neonates were inherently susceptible to seizures with many more excitatory synapses than inhibitory synapses. So, the seizure data segments (=3.4 s) were removed using the LDA classifier trained with the CHB-MIT dataset (18) before second-level HIE classification. Here, the LDA classifier used only EEG data for the classification of the seizure data segments since the manually labeled CHB-MIT dataset did not provide simultaneous fNIRS data. Then, our second-level SVM classifier using ARX parameters from the EEG-fNIRS seizure-free data segments (in 60 s windows) performed better in terms of sensitivity and specificity than the SVM classifier using AR parameters from the EEG seizure-free data segments—see **Tables 3**, **4**. Indeed, tissue oxygenation and hemodynamics can provide additional information (35) including seizure effects on the neurovascular tissue (36), as shown by our perinatal ovine model data (see that bottom panel of **Figure 4**), that may guide the hemodynamic care (37), especially in severe HIE cases with seizure load, which is time-critical (38). Under oxygen starvation, an extracellular increase in the gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter, can help in metabolic suppression (39), which correlates with the hemodynamics and neurovascular coupling (40)—the excitation/inhibition (E/I) ratio can be estimated with EEG-fNIRS (41). Importantly, the neurodevelopmental circuits in neonates under HIE insults may maladaptively coordinate their excitatory and inhibitory inputs to establish an E/I ratio (42), where neuroenergetics may play a crucial role (43). For example, hypoglycemia may reduce GABA levels due to ATP depletion in the hypoxia state (44). Also, the HIE effects on the cerebellum (45) may be underestimated (46), which needs future development of whole head fNIRS technology (47, 48) for neonates as the thin skin and skull allow deep penetration of the NIR light. Cerebellar Purkinje fibers are sensitive to hypoxic injury and can show damage even in the mild cases of HIE (49). Indeed, HIE accounts for chronic cerebellar deficits, including

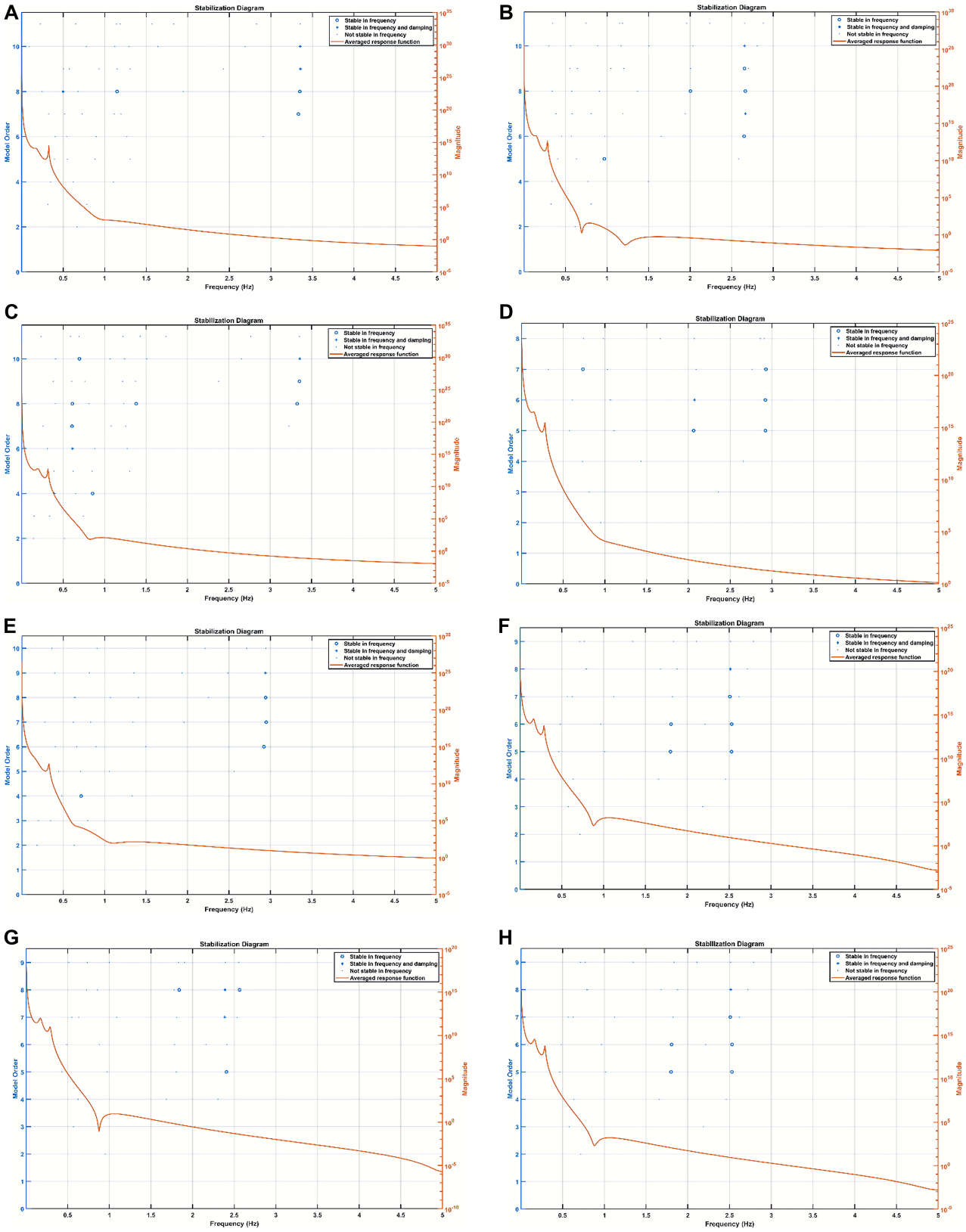

FIGURE 5
Stabilization diagram of the ARX model of the neurovascular coupling system. (**A**) Subj 1: moderate HIE, (**B**) subj 2: severe HIE with sepsis, (**C**) subj 3: severe HIE with sepsis, (**D**) subj 4: moderate HIE, (**E**) subj 5: severe HIE with sepsis, (**F**) subj 6: severe HIE, (**G**) subj 7: severe HIE, (**H**) subj 8: severe HIE, (**I**) subj 9: severe HIE, (**J**) subj 10: severe HIE, (**K**) subj 11: moderate HIE, (**L**) subj 12: severe HIE with sepsis, (**M**) subj 13: severe HIE, and (**N**) subj 14: moderate HIE. ARX, autoregressive with extra input; HIE, hypoxic-ischemic encephalopathy. (continued)

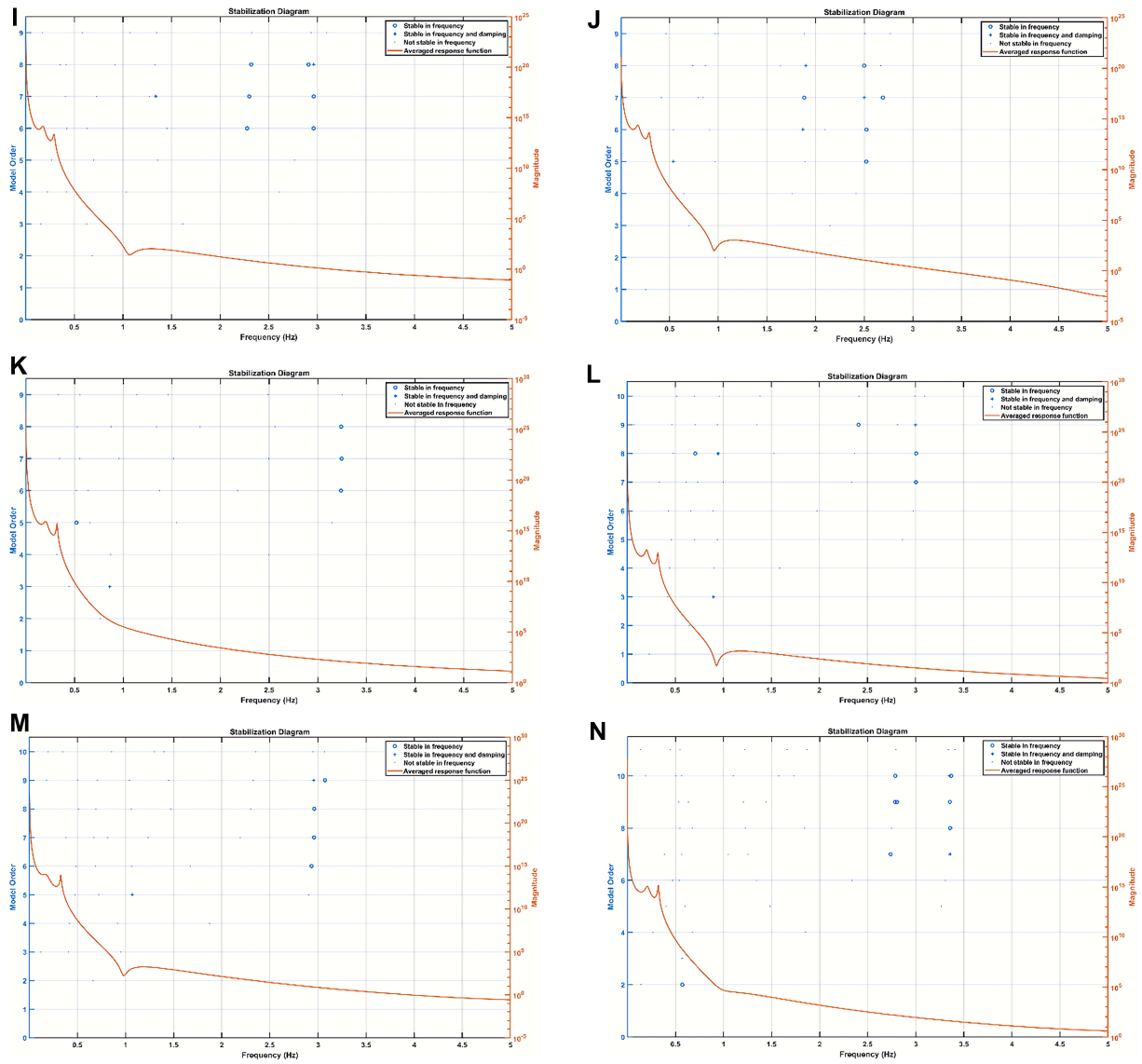

FIGURE 5
Continued.

schizophrenia and other nonaffective psychoses (50), which create an economic burden; hence, low-cost technological innovations are crucial (51).

Our perinatal ovine hypoxia model benefited from previous studies on hypoxia-ischemia animal models for a mechanistic understanding of the SVM classifier results. In the study by Bjorkman et al. (52), the ictal activity was subclassified into two subgroups, clinical and subclinical. Clinical seizures had some visual effect on movement, limb jerks, or mouth quivering, while subclinical seizures can only be detected by abnormalities in the EEG with the absence of movement. In this study on 28 piglets with 77% ictal activity, the background EEG showed lower amplitude compared to that of the nonseizure ischemic state. This supports our SVM classifier approach, where we analyzed the background EEG after removing seizure data segments (using the first-level LDA seizure classifier). Here, a lower amplitude background EEG activity can be a marker of increased neurological damage, where the importance of a lower amplitude background EEG activity was shown by histological analysis after euthanasia (52). Then, fast oscillations (>40 Hz) in neonatal EEG are rare, and high gamma frequencies (27) evaded our first-level LDA classifier. More advanced seizure detection methods are available to identify fast oscillations (>40 Hz) (27); for example, in previous publications (53, 54), researchers have used backpropagation neural networks (53) with an input layer of 9 neurons, a hidden layer of 2–3 neurons, and an output layer containing 1 neuron. The input layer was trained on statistical measures of the ictal waveform itself. Researchers used this classifier to identify the differences between EEG activity and obtained a 93.75% accuracy. Another group (54) attempted to identify all ictal activity with one classifier by dividing peaks that are separated enough to be

considered seizures, that is, at least 100 ms. Then, the researchers analyzed the portions of the wave before and after the peak with the amplitude difference and the duration of the wave. These parameters of each half-wave were used to train an SVM with a high sensitivity of 97%. Many advanced machine learning algorithms are under development; however, their clinical utility beyond conventional EEG needs further investigation, especially in limited resource settings (55).

In the current study, we showed the importance of EMA of the NVC system estimated from the seizure-free background EEG and fNIRS data that provided insights. Here, stabilization diagrams with and without stable poles were found for the different cases of severe HIE, severe HIE with sepsis, and moderate HIE. However, the clinical and physiological significance of the dip at around 1 Hz and a stable pole mainly in the frequency between 0.5 and 1 Hz in the four severe HIE human perinatal cases with sepsis (see **Figure 5**) needs a larger clinical study with another control group with depressed neonates without HIE. Here, changes in the NVC due to HIE have been demonstrated by previous works by Chalak's group (6, 9); however, our system analysis using EMA may provide further insights into the neurovascular (and neurometabolic) dynamics. Neurovascular (and neurometabolic) dynamics is also relevant to adult acute brain injury cases, where normalization of neurovascular coupling may herald recovery of consciousness (56). Here, the effects of seizure activity on the coupling dynamics of the neural activity (measured with EEG) with the cerebral metabolism, oxygen delivery, and blood volume may be crucial to guide medication (36, 57), especially by leveraging optical monitoring in neonates (58). Other relevant chromophores, cytochrome c oxidase (CCO) and water, can also be investigated with optical monitoring in the neonates (58), which was developed in another study by adding four different wavelengths (780, 810, 820, and 840 nm) to the low-cost EEG-fNIRS sensor (https://neuromodec.org/nyc-neuromodulation-online-2020/P18.html) (59). In that case series (59), we found that neurometabolic coupling was specifically affected in HIE with sepsis, which may be related to the differences in the stabilization diagrams (see **Figure 5**) between the six severe HIE human perinatal cases and the four severe HIE human perinatal cases with sepsis. Howard et al. (58) highlighted the importance of the estimation of the oxidation state of the CCO (oxCCO) concentration changes in HIE. Here, CCO is essential to generate ATP efficiently during aerobic respiration, so the effects of seizure activity on the background EEG and oxCCO will be important to study its metabolic effects (58). Then, Howard et al. (58) reviewed the literature that showed preictal changes in the cerebral hemodynamics that aligns with our perinatal ovine data (24)—see **Figure 4**. **Figure 4** shows a small increase in the preictal carotid artery flow that was also detected with fNIRS and may improve the latency [or even predict (60)] of ictal period classification when fNIRS is added to EEG monitoring of seizure activity. Also, the accuracy of the ictal period classification may be improved with multimodal EEG-fNIRS data due to the primarily biphasic response of oxyhemoglobin and deoxyhemoglobin concentration changes (58). Nevertheless, the hemodynamic responses to seizures are not uniform across the literature (58), and the individual differences in the neurovascular and neurometabolic coupling may subserve the effects of seizures on the brain tissue (57). For example, any progressive decrease in oxCCO baseline with sequential seizures (61) needs future investigation vis-à-vis clinical outcomes including exacerbation of epileptogenesis following HIE (62).

Hypoglycemia is a common metabolic problem among malnourished newborn babies (63), which can also disturb brain metabolism in HIE. A multiscale model will be needed for the mechanistic understanding of the hypoglycemia effects on the outcome from HIE and sequential seizure events. Sepsis is characterized by systemic changes in the metabolism (64) that can further disturb brain metabolism in HIE where optical monitoring can provide insights (58). Prior work by Jolivet et al. (65) provided a detailed neurometabolic model that captured the concentration of lactate in the neuronal, astrocytic, and extracellular compartments that was coupled as modulatory feedback (66, 67) with the voltage of the neuronal membrane. Such mechanistic investigation is crucial since oxygen and glucose deprivation can lead to an increase in the extracellular concentrations of excitatory amino acid neurotransmitters (68), leading to an E-I imbalance in the brain tissue (at the level of neuronal circuits) (43). Then, neuronal circuits may try to self-organize toward E-I balance (69) via changes in the connectivity that can be dysfunctional when there is a genetic risk (70, 71). Also, hypoxia-ischemia-induced gene transcription effects are possible (72). Previous work on patient-derived cerebral organoids has revealed gene expression patterns suggesting dysregulation of mitochondrial function (73) that can lead to long-term deficits in synaptic E-I balance in susceptible individuals. Such gene–environment interactions can be investigated mechanistically using a subject-specific brain organoid model from human-induced pluripotent stem cells (iPSCs) to test optical theranostics (59). Then, oxygen–glucose deprivation can be implemented in an *in vitro* subject-specific brain organoid model (59) for mechanistic studies. Notably, our *in vitro* subject-specific brain organoid study (https://neuromodec.org/nyc-neuromodulation-online-2020/P18.html) (59) showed an increase in the CCO activity and pH in the organoid tissue and a decrease in the electrophysiological spectral exponent [related to the E-I balance (74)] following photobiomodulation. These preliminary results are important for future works on nonpharmacological therapeutics since histogenous hypoxia and acid retention are closely related to glucose metabolism (71) that may be photobiomodulated (https://neuromodec.org/nyc-neuromodulation-online-2020/P18.html) (59), which needs future investigation. In phase zero studies (43), the brain organoid platform (59) can use a dual-polymer sensor in the Matrigel matrix to provide real-time glucose and oxygen monitoring (75) during mitochondrial photobiomodulation to capture the neurometabolic dose/response relationship for individualized delivery (33). However, our brain organoid platform (59) cannot currently model neurovascular coupling, which may be feasible with vascularized organoids (76).

In conclusion, the current study showed the feasibility of multimodal EEG-fNIRS data acquisition and the EMA approach

for the systems analysis of NVC that may provide biomarkers of the sepsis effects on the neurovascular brain tissue in human HIE. Here, the EMA approach to the NVC dynamics using EEG-fNIRS data is novel in our knowledge; however, the systems analysis may need to be extended beyond the neurovascular bundle (77) to include noninvasive measurements of blood pressure and cardiac output (e.g., electrocardiogram of the heart rate) in the human studies [see **Figure 1** and the published results from the perinatal asphyxiated lamb model experiments (26)]. Then, cerebral blood flow (CBF) is regulated by cerebral autoregulation, cerebral vasoreactivity, and neurometabolic coupling (78, 79), which can be monitored using cerebral near-infrared spectroscopy (35). Also, seizure-induced autonomic dysfunction is possible (80), which requires systems analysis beyond EEG and fNIRS with the inclusion of simultaneous blood pressure and cardiac monitoring. Here, the effect of the preictal increase in the CBF during a severe metabolic deficit in HIE (e.g., slowing of background EEG) may be physiologically important (52, 81–83)—see **Supplementary material Figure S4** from the perinatal asphyxiated lamb model experiments in the **Supplementary Material**. So, a unified theory of seizure-induced brain state abnormalities including the effects of sepsis in HIE, which may share a common point of origin with hypoperfusion/hypoxia (57), needs future investigation for the development of a robust biomarker amenable to optical brain tissue monitoring in the neonates (58).

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 the Institutional Review Board (IRB) of the IMS & SUM Hospital, Bhubaneswar, India. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. The animal study was reviewed and approved by the Institutional Animal Care and Use Committee at the State University of New York at Buffalo, United States.

Author contributions

AnD developed the multimodal neuroimaging and systems analysis of the neurovascular coupling concept, supervised BH and RM on hardware development, computational modeling, and supporting human and animal studies. AbD was the principal investigator for the Bill and Melinda Gates Foundation & IKP Knowledge Park, Department of Biotechnology (DBT), Government of India for human neonatal studies in India. AnD was the principal investigator for the Global Health Equity Seed Funding, University at Buffalo, United States, for supporting the preclinical animal studies in the United States and the clinical human studies in India. JPS was the lead for the neonatal study in IMS & SUM Hospital, Bhubaneswar, India. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1072663/full#supplementary-material.

SUPPLEMENTARY FIGURE S1
AR parameter 1 in the three cases: control, hypoxic, and ictal states. The control and hypoxic clusters have average separation but are not completely separated, while the ictal activity is clearly separated.

SUPPLEMENTARY FIGURE S2
AR parameter 2 in the three cases: control, hypoxic, and ictal states. The control and hypoxic clusters have average separation but are not completely separated, while the ictal activity is clearly separated.

SUPPLEMENTARY FIGURE S3
AR parameter 3 in the three cases: control, hypoxic, and ictal states. The control and hypoxic clusters have average separation but are not completely separated, while the ictal activity is clearly separated.

SUPPLEMENTARY FIGURE S4
Reduction in the amplitude of the discharges in EEG (black line) during an increase in the normalized flow (green line) and normalized oxygen (O_2, red line) delivery (based on constant oxygen saturation, SpO_2, dashed black line).

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Respiratory distress syndrome prediction at birth by optical skin maturity assessment and machine learning models for limited-resource settings: a development and validation study

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Background: A handheld optical device was developed to evaluate a newborn's skin maturity by assessing the photobiological properties of the tissue and processing it with other variables to predict early neonatal prognosis related to prematurity. This study assessed the device's ability to predict respiratory distress syndrome (RDS).

Methods: To assess the device's utility we enrolled newborns at childbirth in six urban perinatal centers from two multicenter single-blinded clinical trials. All newborns had inpatient follow-up until 72 h of life. We trained supervised machine learning models with data from 780 newborns in a Brazilian trial and provided external validation with data from 305 low-birth-weight newborns from another trial that assessed Brazilian and Mozambican newborns. The index test measured skin optical reflection with an optical sensor and adjusted acquired values with clinical variables such as birth weight and prenatal corticoid exposition for lung maturity, maternal diabetes, and hypertensive disturbances. The performance of the models was evaluated using intrasample k-parts cross-validation and external validation in an independent sample.

Results: Models adjusting three predictors (skin reflection, birth weight, and antenatal corticoid exposure) or five predictors had a similar performance, including or not maternal diabetes and hypertensive diseases. The best global accuracy was 89.7 (95% CI: 87.4 to 91.8, with a high sensitivity of 85.6% (80.2 to 90.0) and specificity of 91.3% (95% CI: 88.7 to 93.5). The test correctly discriminated RDS newborns in external validation, with 82.3% (95% CI: 77.5 to 86.4) accuracy. Our findings demonstrate a new way to assess a newborn's lung maturity, providing potential opportunities for earlier and more effective care.

Abbreviations

LMICs, low- and middle-income countries; ACU, accuracy; ACTFM, antenatal corticosteroid therapy for fetal maturation; CI, confidence interval; CPAP, continuous positive airway pressure; DB, diabetes; HD, hypertensive disease; IQR, interquartile range; LBW, low birth weight; LR+, likelihood ratio positive; LR, likelihood ratio negative; NICU, neonatal intensive care unit; NPV, negative predictive value; RDS, respiratory distress syndrome; SEN, sensibility; SPE, specificity; TTN, transient tachypnea of the newborn; PPV, positive-pressure ventilation; PPV, positive predictive value.

Trial registration: RBR-3f5bm5 (online access: http://www.ensaiosclinicos.gov.br/rg/RBR-3f5bm5/), and RBR-33mjf (online access: https://ensaiosclinicos.gov.br/rg/RBR-33rnjf/).

KEYWORDS

respiratory distress syndrome, newborn, prematurity, childbirth, skin physiological phenomena, machine learning, equipment and supplies, medical device

Introduction

Infant mortality is a critical human development indicator since it reflects the quality of assistance, and social, economic, and environmental factors (1). Most child deaths occur due to prematurity meeting lung immaturity as the main bare reason (2). Approximately 11% of newborns worldwide are preterm, born earlier than 37 weeks of gestational age, and of whom 6% are late preterm, born between 34 and 37 weeks of gestational age (3) and require specialized care (4). Respiratory distress syndrome (RDS) is a common reason for neonatal intensive care unit (NICU) admission and neonatal mortality. Since lung immaturity due to surfactant deficiency is the cause of the disease, respiratory failure occurs soon after birth. However, most respiratory insufficiency at birth is not accurately evaluated, leading to poor outcomes because of delays in appropriate treatment (4, 5). Indeed, on many occasions, the respiratory picture at birth can be confused with an adaptive syndrome such as transient tachypnea of the newborn (TTN), as well as non-respiratory reasons, which may be cardiac, neurological, metabolic, or hematological, among others (6). Clinical history, lung image assessment, and blood lab tests are clues to discriminate between RDS and other respiratory distress, pointing newborns at higher risks of severe complications (7). Beyond clinical manifestation, assessing lung maturity is supported by biochemical and biophysical tests on amniotic fluid, genetic approaches, and microbubble evaluation in gastric aspirates (8). Unfortunately, the lack of healthcare technologies increases exponentially in low- and middle-income countries (LMICs) in scenarios with limited neonatal assistance, where the burden of preterm birth is higher than in other countries (4).

To achieve lower infant morbidity and mortality rates focused on the day of birth, early identification of lung maturity risk enhances chances of survival even based on referral safe transportation among facilities. Nevertheless, very often, especially late preterm infants are inappropriately classified as full-term newborns, delaying care for the former (9). This way, improvements centered on equity of technology access and quality of antenatal and childbirth care can reduce neonatal health disparities among birth scenarios with or without full support for preterm children identification and treatment (1, 10). The search for an affordable approach to quickly identify premature infants according to the degree of lung maturity remains a relevant target for health systems. Early intervention to manage respiratory distress in a newborn could mean the difference between survival and, possibly, a reduction in mortality (11).

Lungs develop linearly before childbirth; however, the maturational competence for extrauterine breathing occurs later in pregnancy or under stressful influences such as maternal disease, placental dysfunction, and drug exposition (12). Under the scientific basis, evidence is extensive concerning the influence of corticosteroid exposition during the prenatal period to prepare fetuses for after-birth life (13). At the same time, the skin is a tissue with late maturation, postponing the protective external barrier to near-term and term gestation (14, 15). Meanwhile, there is a direct relationship between epidermal layer competence and neonatal survival, facing risks of hypothermia, water loss, and infections (16, 17). Likewise, in this organ, antenatal corticotherapy induces cytodifferentiation and keratinization, enhancing the chances of survival (13). Beyond visual inspection of skin appearance, which characterizes preterm newborns (18), an objective measure of skin reflectance with a photometer was correlated with gestational age (19). Based on a multicenter clinical trial, a new medical device was able to assess the gestational age by adjusting a machine learning model for optical skin maturity to antenatal corticosteroid therapy for fetal maturation (ACTFM) and birth weight, discriminating preterm from term newborns, with 37 weeks of gestational age or more, with an area under ROC curve of 0.970, [95% CI: 0.959–0.981] (20). The present study explored new machine learning algorithms on the same optical device, to evaluate its ability to predict RDS in the first 72 h of life, even in places with scarce resources.

Methods

Cohorts

We analyzed two birth scenarios, one to provide predictive models and the other to apply them to a more realistic picture of the usage of the model. Accordingly, both studies were multicenter prospective, concurrent cohorts comprised of six urban referral perinatal centers. Five Brazilian urban referral centers for high-complexity perinatal care took part in the study: Clinical Hospital—Universidade Federal de Minas Gerais (as coordinator), Minas Gerais State; Sofia Feldman Hospital—Minas Gerais State; Hospital da Universidade Luterana do Brasil—Rio Grande do Sul State; Hospital Materno-infantil de Brasília—Federal District; and Hospital Universitário da Universidade Federal do Maranhão—Maranhão State. One referral center in Mozambique, the Maputo Central Hospital, the largest in the country, is headquartered in its capital.

Both cohorts shared inclusion criteria for live newborns enrolled within the first day of life, with the available reference

standard gestational age, and childbirth after 24 weeks of gestation. Combining the last menstrual period with obstetric ultrasound assessment, we assessed gestational age at birth following international consensus for the due date (21). Anhydramnios, edema, congenital skin diseases, or chorioamnionitis were the exclusion criteria because they could modify skin structure, affecting the optical properties of the tissues. Teams of trained and certified health professionals and health professionals' research assistants enrolled and evaluated skin optical reflectance and clinical data at birth. All newborns had inpatient follow-up within the first 72 h of life to monitor immediate neonatal outcomes, with an early ending when discharge or death occurred, according to clinical trial protocols deposited in protocolos.IO (22). However, differences between the clinical characteristics of the newborns express different realities provided by birth weight eligibility criteria below 2.5 kg in the validation cohort (**Figure 1**).

For transparency, the clinical trials register and details of enrollment remain public. From clinical trial 1, registered under the number RBR-3f5bm5 (23), we evaluated Brazilian newborns with a gestational age of 24 weeks, and with any birth weight. The enrollment occurred from 2 January 2019 to 30 May 2021. Data from this study grounded the modeling process of machine learning prediction, thus being the baseline cohort. From clinical trial 2, registered under the number RBR-33rnjf (24), we assessed only newborns with birth weights under 2.5 kg in Brazil and Mozambique. The enrollment occurred from 15 February 2019 to 11 December 2021, and the dataset was used as the validation cohort. Most of the newborns were Mozambican ($n = 177$, 58.0%).

Primary outcome

The primary outcome was to predict the RDS. The reference standard for RDS diagnosis has a basis in clinical, laboratory, and radiological findings and respiratory outcomes (7). However, concerning the reference standard in the scenario of LBW Mozambican newborns, when a radiological exam was absent, the diagnosis was based on clinical evaluations such as tachypnea, nasal flaring, retractions, and grunting with the possibility of progress to respiratory failure (24). In such a scenario where propaedeutics and other resources are unavailable, maternal and delivery context and clinical progress of respiratory failure were considered, based on clinical priority in 72 h of follow-up. Transient tachypnea of the newborn (TTN) was a differential diagnosis of respiratory complications at birth. Despite RDS being the target outcome, we introduced an exploratory modeling step by discriminating between RDS, TTN, or none. The diagnosis had a basis in clinical findings and respiratory outcomes (7). Again, TTN was diagnosed for exclusion in the Mozambican center, typically with clinical evidence of tachypnea shortly after birth, grunting, nasal flaring, retractions, and occasionally cyanosis (24). The procedures for clinical evaluation, complementary exams of the newborn, and RDS diagnosis are available in the **Supplementary Material**. Subgroups of analysis, according to LBW and very-LBW newborns, with a birth weight of less than 2.5 Kg and 1.5 Kg, respectively, provided a potential picture of the application according to ranges of birth weight.

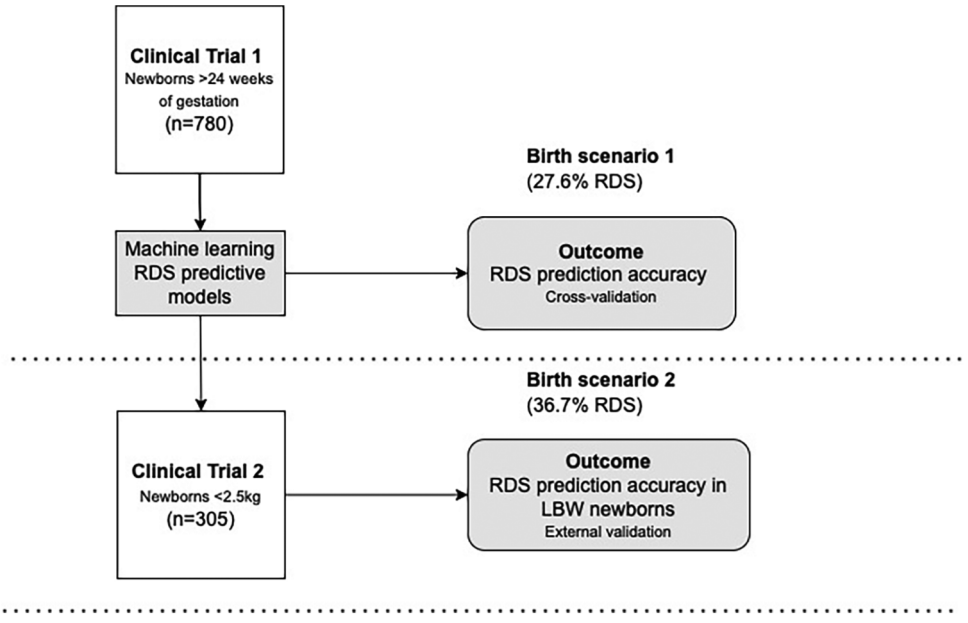

FIGURE 1
Database, birth scenarios, and index test (outcomes). LBW, low birth weight; RDS, respiratory distress syndrome.

The index test

The assessment of newborns' skin maturity with the optical device was possible with the development of the equipment. We already noticed a high agreement between gestational age calculated by this device with the best available gestational age as a reference, as well the accuracy for discrimination of preterm against term infants (24). The error of the optical component had a prior evaluation, resulting in an intraobserver error of 1.97% (95% CI: 1.84–2.11) and an interobserver error of 2.6% (95% CI: 2.1–3.1) (24). The present analysis focused on RDS prediction as an additional value beyond the gestational age. Here, the index test was intended to analyze newborn lung maturity, clinically represented by RDS, as an unprecedented association with the optical skin maturity measurement in a machine learning algorithm.

In this study, data temporality of predictors was the first day of life, a moment when the user did not receive the result of RDS prediction to provide test blinding. Alongside skin reflectance, automatically acquired with the device when it touches the sole of the newborn, clinical variables were added by the user, and machine learning algorithms delivered the RDS prediction and were stored in the processor (**Figure 2**). In the future, the RDS prediction will be available on the device's screen.

The testing steps were standardized and supported by the prior proof of concept publications. The sole was the site of the newborn's body with a higher correlation between the skin reflection and pregnancy dating than other body sites, with the advantage of fulfilling the patient security recommendation for minimum manipulation of newborns (19). The influence of skin color and environmental conditions such as humidity, temperature, and ambient light were reasons for enhanced sensor design, achieving a prediction model without its adjustments (19, 25). This approach to newborns attended to requirements of patient security, including disinfection of the device with alcohol 70, and minimum manipulation of the child anywhere they were: inside incubators, warm crib, or in the mother's lap.

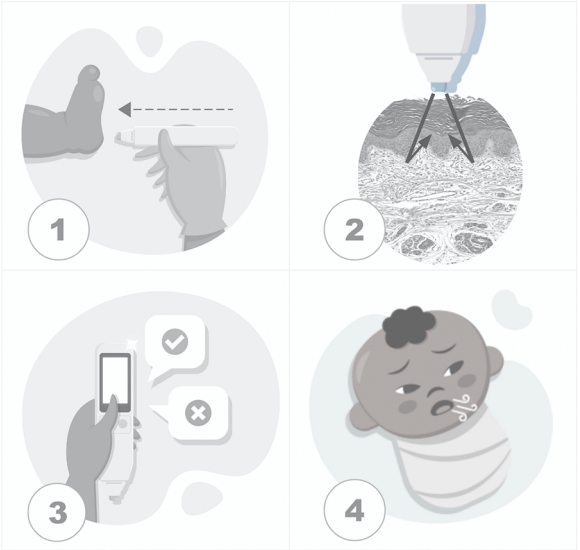

FIGURE 2
Steps of the testing process. (1) The device touches the skin over the sole of a newborn. (2) The sensor acquires skin maturity by assessing the photobiological properties of the tissue when measuring the reflection portions of the light beam incident on the skin. (3) The user inputs clinical data. (4) The data processor uses machine learning algorithms to predict respiratory distress syndrome.

Standard and data collection

According to recommendations for good clinical practices involving human research with medical devices, and according to the International Organization for Standardization (ISO 14155:2011), trained research assistants collected data on 65 demographic and clinical features and 25 skin variables. The framework of variables is available in a previous report (20). Clinical information was collected through structured questionnaires using software developed for the clinical trials, and, simultaneously, in paper formularies containing the exact requests. The data curation process double-checked the data from paper and electronic collection conducted by senior researchers, before opening the outcome blinding. Data consistency and completeness resulted in only one exclusion.

Data availability

Data is available upon reasonable request and after anonymization to ensure ethical and legal data sharing, thus preserving the confidentiality of the persons who participated in this study.

Ethics and dissemination

The studies involving humans had independent ethical board approval at each hospital. The Brazilian National Research Council approved the clinical trials under numbers 81347817.6.1001.5149 and 91134218.4.0000.5149. In Mozambique, ethical approval was under the number IRB00002657, according to the National Bioethics Council. Parents signed an informed consent form on behalf of the newborns as recommended by the Regulatory Bodies for Good Clinical Research Practice, and copies were retained in case they should be needed. Patients were not involved in the design of clinical trials. However, participants' parents received oral explanations and a press-illustrated folder with the proposal of the studies. Besides scientific articles, the results are continuously disseminated by non-scientific publications in media and on the project website: http://skinage.medicina.ufmg.br.

Methods for estimating or comparing measures of diagnostic accuracy

Model development

We trained the models to binary prediction of RDS occurrence until 72 h of life with the five variables, and, additionally, for RDS, TTN, or none. The variables were: skin reflection, birth weight, ACTMF, diabetes, and hypertensive disturbances. The choice of independent variables took into account the easy access to data in the delivery scenario, the biological plausibility, and the importance-feature graphic analysis. Furthermore, we compared models based on three or five independent variables, including or not including maternal diseases. A wide range of models was tested, and the best results were obtained by the XGBoost Regressor model (26).

Model validation

The model was created using data from Clinical Trial 1. Two experiments were performed. In the first one, a ten-fold cross-validation procedure was used to assess the robustness of the model. This procedure was repeated 30 times, generating a total of 300 models that had their metrics of accuracy averaged and reported together with confidence intervals. The second experiment used data from Clinical Trial 1 to generate the model and from Clinical Trial 2 to validate the model.

Statistical analysis

For descriptive analysis of variables, we used average (SD) and median (IQR) to describe continuous variables for symmetric and asymmetric distributions, respectively. We used frequencies (%) for categorical variables. The Mean-T and Mann-Whitney U tests were used to compare the mean or median between two groups of interest as RDS yes or no, according to the variables' parametric or non-parametric frequency distribution. For comparisons between frequencies, the Chi-square Test evaluated the independence hypothesis between categorical variables as preterm vs. RDS yes or no, and the Likelihood ratio chi-square statistic was the alternative when more than 20% of expected values were above five. ANOVA or Kruskall Wallis tests compared three groups analysis as RDS, TTN, and none according to the variables' parametric or non-parametric frequency distribution.

The set of machine learning models provided outcomes for binary RDS (yes or no) and three classes (RDS, TTN, none). The choice of the best models occurred by means of reliability analysis. The accuracy of the prediction of best models was evaluated using sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. *P*-values of <0.05 were considered suggestive of statistical significance. SPSS software (version 19.0; IBM Corp) was used for statistical data analysis.

Results

Description of newborns

Newborns from two clinical trials summed up 1,085 tests with the medical device. From the baseline scenario dataset where we set the RDS predictive models, we analyzed data from 702 Brazilian pregnant women who gave birth to 781 newborns with gestational ages older than 24 weeks (scenario 1). One exclusion occurred due to uncertainty in either an TTN or RDS diagnosis. Among 780 included newborns, 325 (41.7%) were low-birth-weight (LBW), and 27.6% ($n = 215$) had RDS. In the validation scenario, we analyzed data from 263 pregnant women who gave birth to 308 newborns with birth weights under 2.5 kg (scenario 2). Three exclusions occurred due to incorrect enrollment. Among the 305 included newborns, 37.7% ($n = 112$) had RDS. An overview of participants, according to development and model validation steps with respective birth scenarios and test outcomes, for the best models of prediction, is shown in **Figure 3**.

The participants' baseline demographic and clinical characteristics are shown in **Table 1**, considering subgroups of newborns with and without RDS in the birth scenarios of the study. Regarding prenatal data, newborns with RDS had a higher frequency of mothers with diabetes ($p < 0.001$) and hypertensive disease ($p < 0.001$) in birth scenario 1, but not in scenario 2 ($p = 0.086$ and $p = 0.453$, respectively). An important baseline characteristic to highlight is the no-RDS subgroup profile with high maternal disease frequency, ventilatory support, and NICU admission. For instance, the no-RDS subgroup of LBW newborns in the validation scenario comprised 102 (53.1%) newborns with mothers affected by hypertensive diseases and 115 (59.6%) newborns admitted to NICU. In both scenarios, children with RDS had higher ACTMF exposition ($p < 0.001$), lower gestational age ($p < 0.001$), lower birth weight ($p < 0.001$), and lower first-minute Apgar score ($p < 0.001$) than those without RDS.

Comparing birth scenarios, the newborns had similar characteristics concerning rupture of membranes more than 18 h ($p = 0.421$), positive-pressure ventilation ($p = 0.844$), intubation at birth ($p = 0.131$) surfactant resuscitation steps, ($p = 0.697$), and mechanical ventilation (0.864) until 72 h of life. However, the LBW newborns in the birth scenario 2 had higher morbidity and mortality rates ($p < 0.001$) than newborns in the birth scenario 1.

Despite the primary outcome being RDS prediction, we still provided a more detailed analysis in the **Supplementary Material**, comparing three subgroups: RDS newborns, TTN newborns, and newborns without RDS or TTN.

Primary outcome

The machine learning modeling incorporated combinations of maternal and newborn characteristics associated with RDS to develop predictive algorithms that are useful at birth. Analyzing the importance feature given by XGBoost (**Figure 4**), and metrics

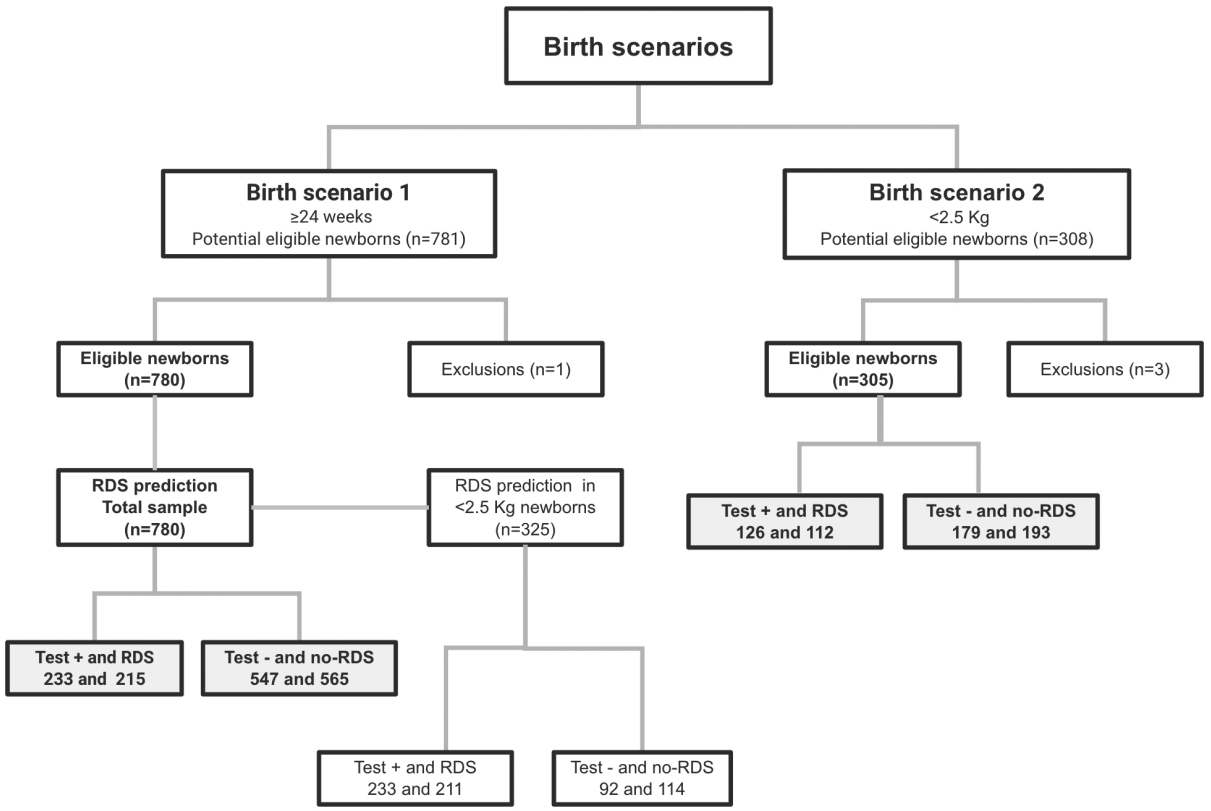

FIGURE 3
Flowchart of participants using STARD diagram, according to development and model validation birth scenarios.

of accuracy, precision, and recall (Supplementary Material), we consider the gain insufficient when maternal disease variables were inserted into the model. Models including hypertensive disease and diabetes data for the binary outcome for RDS had similar accuracy and F1 scores to models with the three baseline variables: skin reflection, birth weight, and ACTMF. The ACTMF was the variable with the highest importance in predicting RDS, followed by birth weight and skin reflection acquired by the optical component of the medical device in model 1 and model 2 (Figure 4).

In relation to discriminating among RDS, TTN, and neither of them using three classes of outcome modeling (models 3 and 4, Supplementary Material), the performance was worse than binary RDS yes/no prediction (models 1 and 2, Supplementary Material). When applying the models in the scenario of LBW newborns for external validation, metrics of prediction performance confirmed the advantages of the three-variable model with a binary RDS yes or no outcome, with an accuracy of 89.4% (95% CI: 88.6 to 90.3) and 82.3% in the cross-validation and external validation, respectively (model 1, Supplementary Material). As detailed in Supplementary Material, we chose the most parsimonious models for complete accuracy analysis.

There were no adverse events when performing the index test. The prediction accuracy of the test using the medical device at birth for RDS occurrence until 72 h of life is detailed in Table 2. Using cross-validation in the birth scenario used for modeling, algorithms with three or five independent variables delivered similar predictions regarding RDS discrimination, 89.7% (95% CI: 87.4 to 91.8) and 89.4% (95% CI: 87.0 to 91.4), respectively. Such accuracy occurred with high sensitivity and specificity, and the likelihood ratio for RDS was increased by approximately 10 times when the index test was positive. According to LBW and very-LBW newborns subgroup analysis, RDS prediction occurred with a high accuracy of 91.9% (95% CI: 86.0 to 95.9) despite a low specificity of 9.1% (95% CI: 0.23 to 41.3) when using model 1. Model 2, obtained with five variables, had no utility for RDS prediction in very-LBW newborns.

Using the models for external validation in LBW newborns, algorithms with or without maternal diseases included had similar performance in predicting RDS as RDS occurrence was correctly predicted in 82% of newborns (95% CI: 77.5 to 86.4). The likelihood ratio for RDS increased approximately five times when the index test was positive (Table 2). Regarding the subgroup analysis of very-LBW newborns, global accuracy was similar to the overall group: 84.9% (95% CI: 74.6 to 92.2) for the model with or without maternal diseases as predictors.

Analyzing the confusion matrix for RDS prediction according to gestational age at birth (Figure 5), we found false positives and false negatives more frequently around 33 and 34 weeks of gestation in both birth scenarios. However, it is relevant to notice

TABLE 1 Baseline demographic and clinical characteristics of the pregnancy and newborns of the baseline and validation cohorts.

	Birth scenario 1 (modeling) Brazil ($n = 780$, 100%)				Birth scenario 2, LBW[b] (validation) Brazil ($n = 128$, 42.0%); Mozambique ($n = 177$, 58.0%)				Comparison between scenarios
Characteristics	Total ($n = 780$)	RDS ($n = 215$)	No-RDS ($n = 565$)	*p*-value	Total ($n = 305$)	RDS ($n = 112$)	No-RDS ($n = 193$)	*p*-value	*p*-value
Prenatal conditions									
ACTFM, *n*/*N* (%)	273 (35.1)	184 (86.0)	89 (15.8)	<0.001#	141 (46,4)	86 (77.5)	55 (28.5)	<0.001#	<0.001#
Mother with diabetes, *n*/*N* (%)	125 (16.0)	54 (25.1)	71 (12.6)	<0.001#	20 (6.6)	11 (9.8)	9 (4.7)	0.086#	<0.001#
Mother with hypertensive disease, *n*/*N* (%)	169 (21.7)	80 (37.2)	89 (15.8)	<0.001#	156 (51.5)	54 (48.6)	102 (53.1)	0.453#	<0.001#
Rupture of membranes more than 18 h, *n*/*N* (%)	91 (11.7)	39 (18.1)	52 (9.3)	0.001#	41 (13.5)	22 (19.8)	19 (9.9)	0.015#	0.421#
Childbirth									
Reference gestational age at birth (weeks), median (IQR)	37.3 (6.3)	31.1 (4.4)	39.0 (3.4)	<0.001**	34.3 (3.5)	31.7 (3.5)	35.9 (3.3)	<0.001*	<0.001*
Preterm[a], *n*/*N* (%)	366 (46.9)	214 (99.5)	152 (26.9)	<0.001#	234 (76.7)	109 (97.3)	125 (64.8)	<0.001#	<0.001#
Birth weight (g), median (IQR)	2,740 (1496)	1,360 (870)	3,085 (823)	<0.001**	1,930 (687)	1,385 (771)	2,075 (430)	<0.001*	<0.001*
Low-birth-weight[b], *n*/*N* (%)	325 (41.7)	211 (98.1)	114 (20.2)	<0.001#	305 (100)	112 (100)	193 (100)	–	–
Very-low-birth-weight[c], *n*/*N* (%)	136 (17.4)	125 (58.1)	11 (1.9)	<0.001#	73 (23.9)	65 (58.0)	8 (4.1)	<0.001#	0.015#
Sex, male, *n*/*N* (%)	389 (50.1)	113 (52.6)	276 (48.8)	0.355#	131 (43.0)	54 (51.8)	116 (60.1)	0,157#	0.033#
Anthropometric reference[d]				<0.001#				0.001#	<0.001#
• Small for gestational age, *n*/*N* (%)	114 (14.6)	55 (25.6)	59 (10.4)		139 (45.6)	73 (65.2)	82 (42.5)		
• Appropriate for gestational age, *n*/*N* (%)	607 (77.8)	154 (71.6)	453 (80.2)		155 (50.8)	35 (31.3)	104 (53.9)		
• Large for gestational age, *n*/*N* (%)	59 (7.6)	6 (2.8)	53 (9.4)		11 (3.6)	4 (3.6)	7 (3.6)		
1-min Apgar score, median (IQR)	8 (1)	7 (3)*	9 (1)	<0.001**	7 (2)	7 (2)	7 (1)	0.037**	<0.001*
5-min Apgar score, median (IQR)	9 (1)	9 (1)	9 (1)	<0.983**	9 (1)	9 (2)	9 (1)	0.653**	<0.001*
Resuscitation steps: initial, *n*/*N* (%)	384 (49.4)	202 (94.0)	182 (32.4)	<0.001#	152 (50.8)	87 (77.7)	65 (34.8)	<0.001#	<0.001#
Resuscitation steps: PPV, *n*/*N* (%)	155 (19.9)	105 (48.8)	50 (8.8)	<0.001#	59 (19.5)	44 (39.6)	15 (7.9)	<0.001#	0.844#
Resuscitation steps: Intubation at birth, *n*/*N* (%)	49 (6.3)	42 (19.5)	7 (1.2)	<0.001#	12 (4.0)	11 (9.8)	1 (0.5)	<0.001#	0.131#
Resuscitation steps: drugs, *n*/*N* (%)	2 (0.3)	1	0	–	3 (1.0)	3 (2.7)	0	–	–
72 h of life follow-up									
NICU admission, *n*/*N* (%)	239 (30.6)	210 (97.7)	70 (12.4)	<0.001#	225 (73.8)	110 (98.2)	115 (59.6)	<0.001#	<0.001#
Surfactant, *n*/*N* (%)	112 (14.4)	112 (52.1)	0	<0.001#	41 (13.4)	41 (36.6)	0	<0.001#	0.697#
Ventilatory support: CPAP, *n*/*N* (%)	250 (32.1)	181 (84.2)	69 (12.2)	<0.001#	128 (42.0)	97 (86.6)	31 (16.1)	<0.001#	0.002#
Ventilatory support: other noninvasive ventilation, *n*/*N* (%)[e]	56 (7.2)	55 (25.6)	1 (0.2)	<0.001#	37 (12.1)	32 (28.6)	5 (2.6)	<0.001#	0.009#
Ventilatory support: mechanical ventilation, *n*/*N* (%)	95 (12.2)	87 (40.5)	8 (1.4)	<0.001#	36 (11.8)	33 (29.7)	3 (1.6)	<0.001#	0.864#
Newborn mortality, *n*/*N* (%)	15 (1.0)	15 (7.0)	0	<0.001##	20 (6.6)	18 (16.1)	2 (1.0)	<0.001##	<0.001##

ACMF, antenatal corticosteroid therapy for fetal maturation; CPAP, continuous positive airway pressure; IQR, interquartile range; LBW, low birth weight; NICU, neonatal intensive care unit; NTT, transient tachypnea of the newborn; PPV, positive-pressure ventilation; RDS, respiratory distress syndrome.

[a]Less than 37 weeks.

[b]birth weight <2.5 kg.

[c]birth weight <1.5 kg.

[d]According to Intergrowth 21st.

[e]Hood, nasal cannula, face mask and Biphasic Positive Airway Pressure.

*Mann Whitney *U* Test.

#Chi-square.

##Likelihood ratio chi-square statistic.

that, in external validation, the three-variable model (model 1) discriminated most of the LBW newborns with (true positive) and without (true negative) RDS in the range of 29 to 37 weeks of gestation.

In order to inspect similarities and differences between newborns with or without correct RDS prediction, we compared the clinical characteristics in the validation scenario (**Supplementary Material**). Gestational age, birth weight, maternal diseases, and TTN occurrence were statistically similar between subgroups. Only NICU admission within the first 72 h occurred more frequently in newborns with an incorrect prediction (90.7% vs. 70.9%, $p = 0.002$).

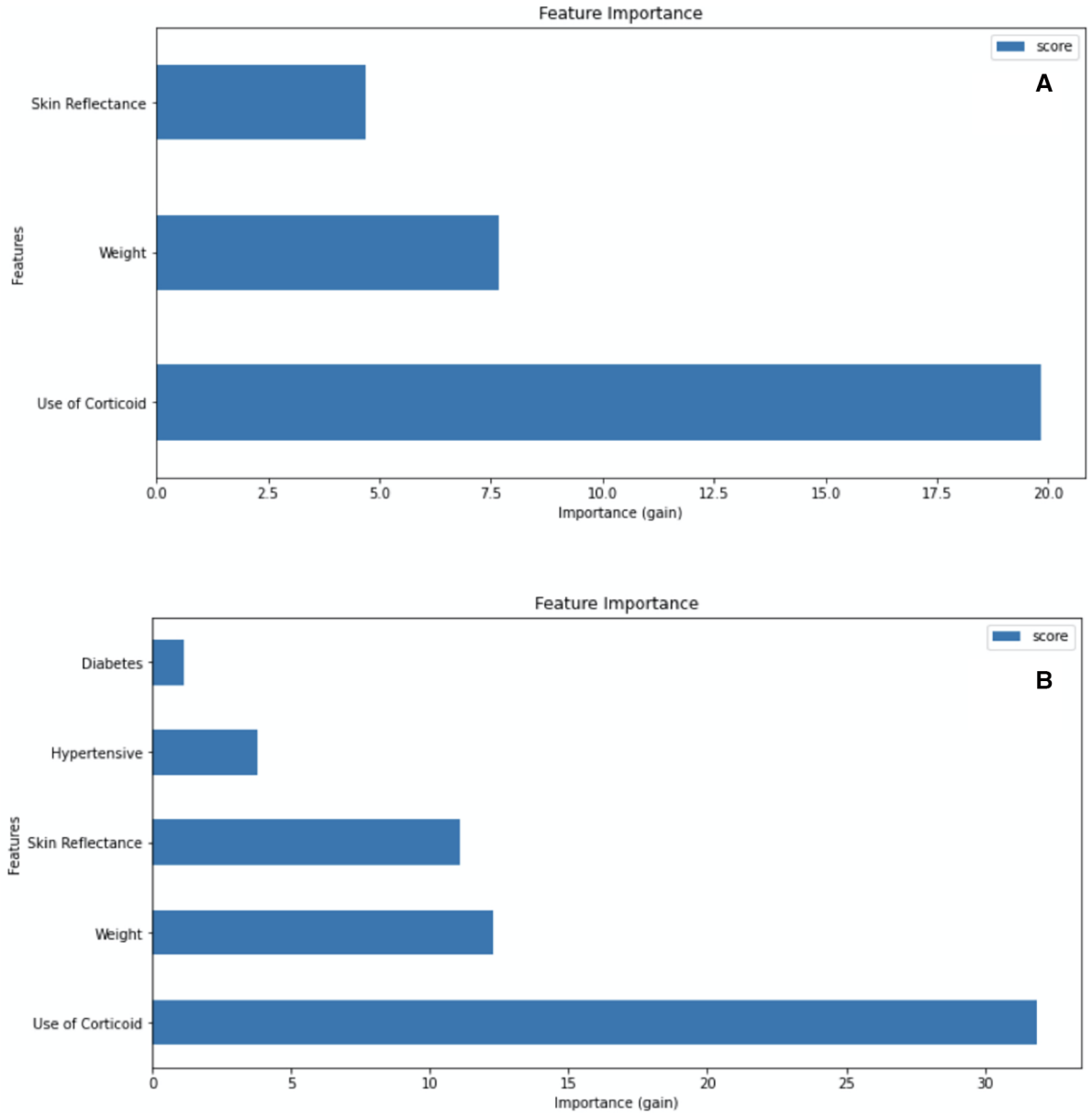

FIGURE 4
Attribute importance given by XGBoost when considering information gain that a variable brings when inserted into the model. (A) Model 1: trained with skin reflection + birth weight + Antenatal corticosteroid therapy for lung maturation, for the binary outcome RDS vs. non-RDS. (B) Model 2: trained with Skin reflection + birth weight + Antenatal corticosteroid therapy for lung maturation + diabetes + hypertensive diseases for the binary outcome RDS vs. non-RDS.

Discussion

Main findings

Improving healthcare equity is a primary goal of the United Nations — this aim makes the reduction of infant mortality a priority (27). Digital health, including affordable and valuable medical devices and artificial intelligence, has brought hope to improve health for everyone (28, 29). The main outcome of the present study was providing a promissory predictive model using a medical device with an AI algorithm inside. Of every 100 newborns assessed, 90 were correctly classified as a higher risk or not for RDS until 72 h of life, considering the dataset that provides predictive models. The prediction accuracy remained high in the LBW newborns that composed the validation scenario, 82 in every 100, where the RDS and other neonatal morbidities and mortality were more frequent than in the model development scenario.

The same sort of study has been presented, integrating computational technology to identify predictors of neonatal mortality, such as the lecithin and sphingomyelin ratio by machine learning applied to mild-infrared spectra (30) or acoustic features of the crying of newborns (31). Reviews have highlighted the importance of birth weight, Apgar score, and

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TABLE 2 Accuracy for respiratory distress syndrome during the first 72 h of life, according to the predictive algorithms with binary outcomes.

	Birth scenario 1—cross-validation ($n = 780$)		Birth scenario 2, LBW—external validation ($n = 305$)	
	Model 1 (skin reflection, BW, ACTMF)	Model 2 (skin reflection, BW, ACTMF, DB, HD)	Model 1 (skin reflection, BW, ACTMF)	Model 2 (skin reflection, BW, ACTMF, DB, HD)
Occurrence in overall group	RDS 215/780 (27.6%)	RDS 215/780 (27.6%)	RDS 112/305 (36.7%)	RDS 112/305 (36.7%)
All sample	Value (95% CI)	Value (95% CI)	Value (95% CI)	Value (95% CI)
ACU (%)	89.7 (87.4 to 91.8)	89.4 (87.0 to 91.4)	–	–
SEN (%)	85.6 (80.2 to 90.0)	84.7 (79.1 to 89.2)	–	–
SPE (%)	91.3 (88.7 to 93.5)	91.2 (88.5 to 93.4)	–	–
VPP (%)	79.0 (74.1 to 83.2)	78.5 (73.5 to 82.7)	–	–
VPN (%)	94.3 (92.3 to 95.8)	94.0 (91.9 to 95.5)	–	–
LR+	9.87 (7.51 to 12.97)	9.57 (7.30 to 12.54)	–	–
LR-	0.16 (0.11 to 0.22)	0.17 (0.12 to 0.23)	–	–
Occurrence in LBW	RDS 211/325 (64.9%)	RDS 211/325 (64.9%)	RDS 112/305 (36.7%)	RDS 112/305 (36.7%)
	Value (95% CI)	Value (95% CI)	Value (95% CI)	Value (95% CI)
ACU (%)	76.6 (71.6 to 81.1)	75.7 (70.7 to 80.3)	82.3 (77.5 to 86.4)	82.3 (77.5 to 86.4)
SEN (%)	87.2 (81.9 to 91.4)	86.3 (80.9 to 90.6)	82.1 (73.8 to 88.7)	79.5 (70.8 to 86.5)
SPE (%)	57.0 (47.4 to 66.3)	56.1 (46.5 to 65.4)	82.4 (76.3 to 87.5)	83.9 (78.0 to 88.8)
VPP (%)	79.0 (75.1 to 82.4)	78.5 (74.6 to 81.9)	73.0 (66.3 to 78.8)	74.2 (67.2 to 80.1)
VPN (%)	70.7 (62.1 to 78.0)	68.8 (60.3 to 76.3)	88.8 (84.2 to 92.2)	87.6 (83.0 to 91.1)
LR+	2.03 (1.63 to 2.52)	1.97 (1.59 to 2.44)	4.66 (3.40 to 6.40)	4.95 (3.54 to 6.92)
LR-	0.22 (0.15 to 0.33)	0.24 (0.17 to 0.36)	0.22 (0.14 to 0.32)	0.24 (0.17 to 0.35)
Occurrence in VLBW	RDS 125/136 (91.9%)	RDS 125/136 (91.9%)	RDS: 65/73 (89.0%)	RDS: 65/73 (89.0%)
	Value (95% CI)	Value (95% CI)	Value (95% CI)	Value (95% CI)
ACU (%)	91.9 (86.0 to 95.9)	91.2 (85.1 to 95.4)	84.9 (74.6 to 92.2)	84.9 (74.6 to 92.2)
SEN (%)	99.2 (95.6 to 100)	99.2 (95.6 to 100)	93.9 (85.0 to 98.3)	93.9 (85.0 to 98.3)
SPE (%)	9.1 (0.23 to 41.3)	0 (0.0 to 28.5)	12.5 (0.32 to 52.7)	12.5 (0.32 to 52.7)
VPP (%)	92.5 (91.1 to 93.7)	91.9 (91.7 to 92.0)	89.7 (86.9 to 91.9)	89.7 (86.9 to 91.9)
VPN (%)	50 (6.3 to 93.7)	0	22.0 (3.1 to 66.3)	22.0 (3.1 to 66.3)
LR+	1.09 (0.90 to 1.32)	0.99 (0.98 to 1.01)	1.07 (0.82 to 1.40)	1.07 (0.82 to 1.40)
LR–	0.09 (0.01 to 1.31)	–	0.49 (0.06 to 3.88)	0.49 (0.06 to 3.88)

ACU, accuracy; ACTFM, antenatal corticosteroid therapy for fetal maturation; BW, birth weight; DB, diabetes; CI, confidence interval; HD, hypertensive disease; LBW, low-birth-weight; LR+, likelihood ratio positive; likelihood ratio negative; LR-. SEN, sensibility; SPE, Specificity; NPV, negative predictive value; PPV, positive predictive value; VLBW, very-low-birth-weight.

antenatal steroids (28). Our approach has the advantage of using only three predictive variables obtained from a prospective temporality clinical trial approach to provide prediction before the disease occurrence. Models with five predictive variables, including maternal diseases (i.e., diabetes and hypertensive diseases) did not show advantages over models based on skin maturity optical assessment, birth weight, and steroids. This finding will certainly facilitate the use of the device by caregivers who deliver care at birth in LMICs.

Comparisons and subgroups of analysis

Considering the very-LBW subgroup of analysis, our results with a three-variables predictive model achieved an accuracy of 84.9% (95% CI, 74.6 to 92.2). In comparison, using an extensive historical 14-year inpatient dataset and many predictive variables, Jaskari et al. classified bronchopulmonary dysplasia in a retrospective dataset of very-LBW, with an accuracy of around 0.899 AUROC (32). Furthermore, analyzing a prospective dataset of newborns older than 24 weeks of gestation, our modeling achieves an accuracy of 89.7% (95% CI, 87.4 to 91.8), while Betts et al. reported RDS prediction with an accuracy of 0.923 (0.917, 0.928) among inpatients younger than 39 weeks of gestation (33), using the same dataset as Jaskari et al. (32). So far, our study is the first that has used a physical measurement of skin maturity, previously described (16, 19, 20), using a prospective dataset from clinical trials with nearly similar accuracy to other more complex models.

Early detection of severe neonatal morbidities such as RDS is critical to halt disease progression and prevent further complications or death. Risk identification of the occurrence might provide means for opportune diagnosis and due care with surfactant access, enhancing chances of survival with minimal sequelae, even with the referral of newborns (5). In LMICs, the availability of a NICU in a center of excellence is often far from the place of birth of this preterm infant (4). The limited number of intensive care beds that can receive real RDS-risk newborns justifies a reliable and helpful predictive test to support low-risk newborns' retention decisions, optimizing resources. By analyzing

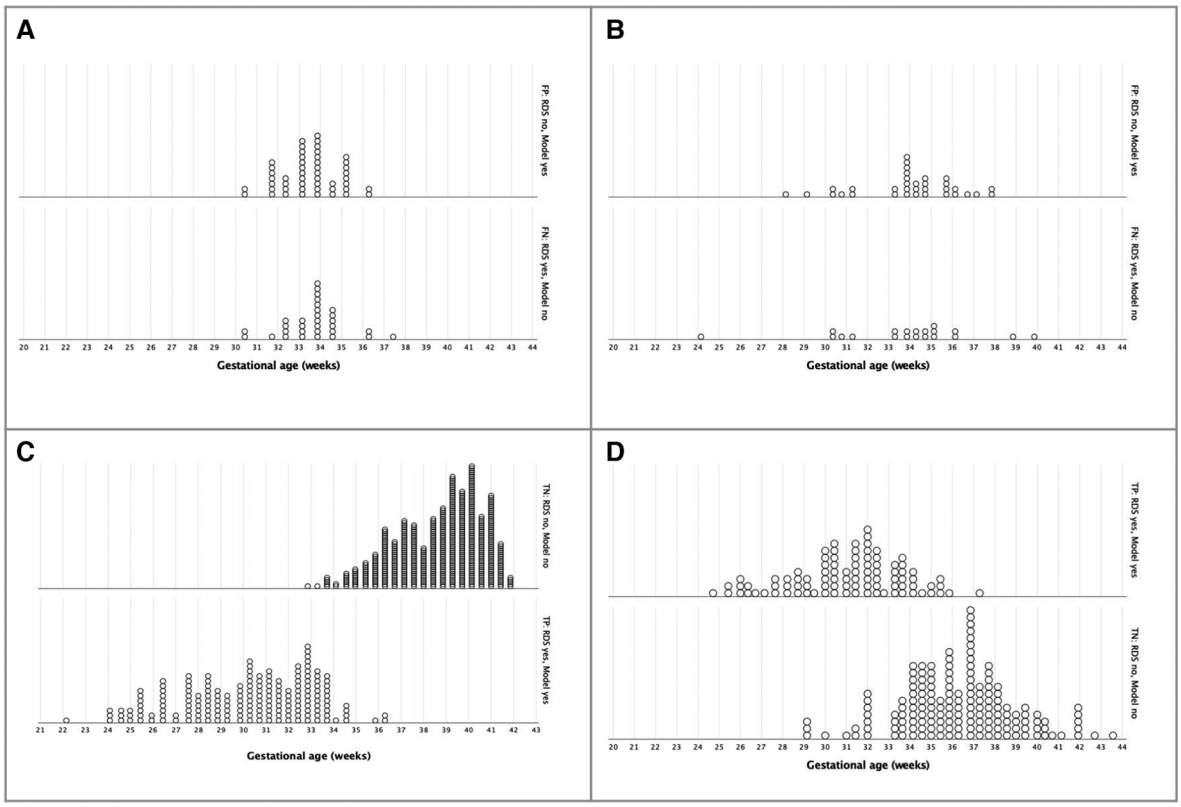

FIGURE 5
Confusion matrix for Respiratory Distress Syndrome prediction until 72 hours of life, according to gestational age at birth, using a three-variable-mode. (**A**) Incorrect prediction in birth scenario 1 - Cross-validation (*n* = 780). (**B**) Incorrect prediction in birth scenario 2, LBW - External validation (*n* = 305). (**C**) Correct prediction in birth scenario 1 - Cross-validation (*n* = 780). (**D**) Correct prediction in birth scenario 2, LBW - External validation (*n* = 305).

the confusion matrix, the outcome of the present study showed early and promising discrimination of RDS even in late preterm newborns in the development and LBW validation scenarios.

Worldwide, hard decisions in scenarios with scarce resources are taken daily based on birth weight, with particular attention to late preterm births that account for most preterm births (34). Birth weight is the most accessible and significant determinant of the likelihood of survival at birth, but it alone is not enough to predict neonatal outcomes. Placental dysfunction, maternal-fetal conditions affecting lung maturation such as smoking, cardiovascular diseases, and prenatal exposure to drugs such as steroids are also determinants (35). Known antenatal predictors of RDS, such as prenatal Doppler velocimetry and the lamellar body count test on gastric aspirates have limitations in LMICs due to high costs and a lack of professionals with the necessary skills (8, 36).

Implications for practice and the role of the index test

The role of the index test used to predict RDS might be a prompt risk indication immediately at birth, anticipating best practices of management in scenarios with limited resources or optimizing access to existing facilities. This study is a premarket approach using data from two clinical trials to validate the algorithm for real-time RDS prediction at birth. The skin reflection can be acquired from the device, and the user quickly introduces some clinical variables, as presented in **Figure 1**. Facilities without neonatologists, mobile emergency services, and caregivers in primary units where a preterm birth can occur are the potential targets of this device. The approach is intended to quickly offer a prediction based on variables easily accessible at birth scenarios added to the skin maturity assessment, even outside hospitals. In the same way, a professional in maternity and NICU settings could be interested in this prediction to manage clinical follow-up of newborns and bed occupancy.

Despite recent advances in the perinatal management of RDS, controversies still exist. Lower emphasis on radiographic diagnosis and classification of RDS, such as ground glass with air bronchograms, directs management toward a preventive surfactant treatment approach. Definitions based on blood gas analyses are also redundant, as management has moved towards a preventive surfactant treatment approach based on clinical assessment of the work of breathing and oxygen requirement to avoid worsening the syndrome. Current RDS management aims to maximize survival by minimizing complications such as air leaks and bronchopulmonary dysplasia (5).

Sources of potential bias and generalizability

Despite the development of a new technology that allows skin maturity associated with birth data to be used as a marker of lung maturity, sources of potential bias can limit the generalizability of the outcomes. The development and validation scenarios had relevant differences regarding RDS frequency in newborns, morbidity, and mortality. Moreover, the accuracy of the machine learning models was sustained by a high specificity of 91.3% (95% CI, 88.7 to 93.5). In false-positive RDS prediction in LBW newborns, unnecessary interventions such as transferring to a referral center can occur in approximately 18% of newborns. Nonetheless, assuming the implementation of a screening test, a point-of-care prediction in conjunction with clinical protocols, this approach has the potential to enhance neonatal care. Future studies are necessary to measure the influence of disease incidence on generalizing the models, as in the primary care birth scenario or low complexity hospitals where the incidence of preterm birth and RDS is lower than ours. The performance of the prediction in the subgroups analysis considering ranges of gestational age and birth weight might still require further large samples.

Regarding skin maturity importance in the model, the rationale which relies on a direct relationship between epidermal barrier competence and neonatal survival faces limitations after 35 weeks of gestation, when the epidermis is complete (37). Therefore, the test may perform better in preterm newborns than in term newborns; similar to previous studies, we used the device to predict gestational age (38). Finally, there is a potential bias associated with suboptimal pregnancy dating in the validation scenario since the inclusion criteria admitted obstetric ultrasound examinations before 24 weeks or just using a reliable last menstrual period, which has already been reported (38). At the same time, data from the clinical trials in Brazil and Mozambique provided a picture of using the test under natural conditions with barriers to high-cost technologies.

Conclusions

The objective measurement of skin maturity alongside machine learning models opens new opportunities to recognize complex patterns among variables in RDS outcome prediction. The models adjusted for skin reflection, birth weight, and ACTMF at birth as RDS predictors for 72 h of life achieved high accuracy in developing and validating modeling using clinical trial datasets. This study demonstrates a new way to assess neonatal lung immaturity, providing potential opportunities for more effective and early caring with an automated medical device tester.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data is available upon reasonable request and after anonymization to ensure ethical and legal data sharing, thus preserving the confidentiality of the persons who participated in this study. Requests to access these datasets should be directed to zilma@ufmg.br.

Ethics statement

The studies involving humans were approved by The Brazilian National Research Council approved the clinical trials under numbers 81347817.6.1001.5149 and 91134218.4.0000.5149. In Mozambique, ethical approval was under the number IRB00002657, according to the National Bioethics Council. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ZR: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. GP: Writing – original draft, Formal Analysis, Methodology, Software, Validation, Writing – review & editing. PN: Writing – review & editing, Conceptualization, Data curation, Investigation, Supervision, Validation, Writing – original draft. MM: Writing – review & editing, Conceptualization, Data curation, Investigation, Supervision, Writing – original draft. GS: Validation, Data curation, Investigation, Writing – original draft, Writing – review & editing. GV: Writing – original draft, Data curation, Investigation, Validation, Writing – review & editing. NM: Data curation, Investigation, Methodology, Writing – review & editing, Writing – original draft. IN: Data curation, Investigation, Supervision, Validation, Writing – review & editing, Writing – original draft. RR: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare a patent deposit on behalf of the Universidade Federal de Minas Gerais and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil (http://www.fapemig.br/en/). BR1020170235688 (CTIT-PN862).

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1264527/full#supplementary-material

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Randomised controlled trial to compare the effect of PIOMI (structured) and routine oromotor (unstructured) stimulation in improving readiness for oral feeding in preterm neonates

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Background: Oral motor stimulation interventions improve oral feeding readiness and earlier full oral feeding in preterm neonates. However, using a structured method may improve the transition time to full oral feeds and feeding efficiency with respect to weight gain and exclusive breastfeeding when compared to an unstructured intervention.
Objective: To compare the effect of Premature Infant Oral Motor Intervention (PIOMI) and routine oromotor stimulation (OMS) on oral feeding readiness.
Methods: Randomised controlled trial conducted in a neonatal intensive care unit between June-December 2022. Preterm neonates, 29^{+0}–33^{+6} weeks corrected gestational age, were studied. The intervention group received PIOMI and the control group received OMS. Primary outcome: time to oral feeding readiness by Premature Oral Feeding Readiness Assessment Scale (POFRAS) score ≥30. Secondary outcomes: time to full oral feeds, duration of hospitalisation, weight gain, and exclusive breastfeeding rates.
Results: A total of 84 neonates were included and were randomised 42 each in PIOMI and OMS groups. The mean chronological age and time to oral feeding readiness were lower by 4.6 and 2.7 days, respectively, for PIOMI. The transition time to full oral feeds was 2 days lower for PIOMI and the duration of hospitalisation was 8 days lower. The average weight gain was 4.9 g/kg/day more and the exclusive breastfeeding rates at 1 month and 3 months post-discharge were higher by 24.5% and 27%, respectively, for the PIOMI group. The subgroup analysis of study outcomes based on sex and weight for gestational age showed significant weight gain on oral feeds in neonates receiving PIOMI. Similarly, the subgroup analysis based on gestational age favoured the PIOMI group with significantly earlier transition time and weight gain on oral feeds for the neonates >28 weeks of gestational age. The odds of achieving oral feeding readiness by 30 days [OR 1.558 (0.548–4.426)], full oral feeds by 45 days [OR 1.275 (0.449–3.620)], and exclusive breastfeeding at 1 month [OR 6.364 (1.262–32.079)] and 3 months [3.889 (1.186–12.749)] after discharge were higher with PIOMI.

Abbreviations
PIOMI, premature infant oral motor intervention; OMS, oromotor stimulation; POFRAS, premature oral feeding readiness assessment scale; CGA, corrected gestational age; DOL, days of life.

Conclusion: PIOMI is a more effective oromotor stimulation method for earlier and improved oral feeding in preterm neonates.

Clinical trial registration: https://ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=70054&EncHid=34792.72281&modid=1&compid=19','70054det', identifier, CTRI/2022/06/043048.

KEYWORDS

neonate, oral motor stimulation, prematurity, oral feeding readiness, exclusive breastfeeding

Introduction

Annually, approximately 15 million neonates are born prematurely (1) with a high risk for oral feeding difficulties due to uncoordinated suck swallow reflexes and poor oral muscle tone (2, 3). Therapies for early attainment of oral feeding are oromotor stimulation (OMS) techniques such as intraoral, perioral stroking and non-nutritive sucking (NNS), Beckman's Oral Motor Intervention (BOMI), and Premature Infant Oral Motor Intervention (PIOMI). PIOMI is a 5-minute 8-step therapy focusing on the lip, jaw, and tongue movements. It simulates the in-utero oral motor experience and has been reported to result in a faster transition to full oral feeds, improved suck strength, and increased breastfeeding rates (4). A study by Arora et al. suggested that PIOMI improves the oromotor skills documented as improved mean Neonatal Oromotor Assessment Scale (NOMAS) scores in preterm neonates (5). As a part of feeding rehabilitation, Ghomi et al. reported the earlier introduction of first oral feeds and shorter hospitalisation with PIOMI (6). A few studies have reported the beneficial effect of PIOMI on feeding efficiency and breastfeeding rates but a statistically significant inference could not be drawn from these (7–9). Hence, conflicting evidence exists for the said outcomes and there is a paucity of data for comparison between structured and unstructured methods of oral motor stimulation. This study was, therefore, designed to test the effectiveness of PIOMI over routine OMS on oral feeding readiness.

Methodology

A single-centre randomised controlled trial was conducted in a tertiary-level neonatal intensive care unit enrolling neonates between June to December 2022. All preterm neonates with birth gestation of <34 weeks and corrected gestational age (CGA) 29^{+0}–33^{+6} weeks who were free of invasive ventilation and inotropic support were assessed for eligibility. Neonates with a neuromuscular disorder, chromosomal anomaly, or craniofacial malformation were excluded. Any neonate with maternal retroviral disease was excluded from the outcome analysis for exclusive breastfeeding. Written informed consent was taken from parents prior to enrolment. Maternal and neonatal baseline characteristics (mode of delivery, indication of delivery, gestational age, sex, birth weight, and resuscitation details) were recorded. Included neonates were randomised into two groups, namely, PIOMI and routine OMS in a 1:1 ratio by simple randomisation using a computer-generated random number table, and intervention was started after 29^{+0} weeks CGA.

The baseline Premature Oral Feeding Readiness Assessment Scale (POFRAS) assessment was done before the initiation of intervention by one of the two independent blinded scorers (**Supplementary file**). The blinding of the study participants and intervention providers could not be done, however, the intervention providers and POFRAS scorers were blinded to each other. Neonates who were randomised to the PIOMI group were administered intervention 15 min before the gavage feed once daily using all aseptic precautions and with gloved fingers if CGA was 29^{+0}–30^{+6} weeks. This process was continued for 7 days until the next POFRAS assessment. After CGA 31 weeks, PIOMI was similarly performed twice daily. PIOMI was done by the principal investigator who underwent training under the founder of PIOMI prior to the commencement of the study. The other group received OMS from trained nursing staff.

For PIOMI, the neonate was positioned in the midline position with the neck slightly flexed and the chin tucked in. Following this, the neonate underwent one cycle each of cheek C-stretch, lip roll, lip curl/stretch, and gum massage for 30 s each. This was followed by stretching of lateral borders of the tongue/cheek for 15 s and mid-blade of the tongue/palate for 30 s. After this, elicitation of suck was performed for 15 s followed by non-nutritive sucking on the mother's breast (or gloved finger/pacifier if the mother was not available) for 2 min. The entire process lasted 5 min.

The second group received OMS as part of routine care. This was a 15-min, 3-step technique comprising of two finger circular movements in a U-shaped fashion from both ears, followed by O-shaped perioral stimulation and ending with pouting stimulation of the cheeks. This method was done 15 min prior to each gavage feed by a trained nurse.

In both groups, the intervention was suspended if there was sudden heart rate acceleration/deceleration, desaturation, apnoea, hiccupping, yawning, sneezing, frowning, looking away, squirming, frantic/disorganised activity, pushing away of arms and legs or if the neonate became sick in the intervening period and required invasive ventilator support/inotropes. The intervention was resumed after 24 h of resolution of the issue and continued for the subsequent 7 days.

Each POFRAS assessment was done after 7 days of intervention. If the score was <25 in either group, the respective intervention was repeated for another 7 days and POFRAS was reassessed. If the score was 25–29 in either group, the respective intervention was repeated for another 3 days and POFRAS was reassessed. Oral feeds were started after POFRAS ≥30. Upon

tolerance, feeds were increased gradually to full oral feeds. Exclusive breastfeeding was assessed at 1 month and 3 months post-discharge in both groups. Exclusive breastfeeding was defined as feeding the infant only breastmilk from his or her mother until the time of assessment and no other solids or liquids except for drops or syrups containing vitamins, minerals, supplements, or medicines.

The primary outcome measure was time to oral feed readiness and secondary outcome measures were transition time to full oral feeds, duration of hospital stay, weight gain, and exclusive breastfeeding rate post-discharge.

The study conformed to the reporting checklist criteria for randomised trial based on the CONSORT guidelines.

Statistical analysis

Data was entered in a Microsoft Excel spreadsheet (Microsoft Corp, Redmond, WA, USA) and analysed using IBM SPSS statistical software version 25. Continuous variables were expressed as mean (standard deviation) or median (inter-quartile range), depending on the distribution of the data. Categorical variables were expressed using frequencies and percentages. For qualitative data variables, the Chi-square test was used and for quantitative data variables, two independent sample t and median tests were used. P-value < 0.05 was considered significant. Kaplan–Meier probability analysis curves were used for the establishment of oral feeds. An odds ratio analysis was performed for outcomes related to oral feeding and exclusive breastfeeding. Intention to treat and per protocol analysis was done for exclusive breastfeeding rates. For the outcomes related to the progression of feeds and weight, a subgroup analysis was conducted for sex, gestational age, and weight for gestational age. The inter-observer variability was calculated to be 0.933 (Cronbach's alpha) between the two independent blinded scorers on 20 subjects prior to the commencement of the study. The sample size calculated for statistical significance as per the feeding outcome of a previous study (5) was 42 with 21 in each group.

Results

The study included 84 neonates divided into two groups of 42 each to receive either PIOMI or routine OMS. The study flowchart is described in **Figure 1**. At birth, the mean gestational age (GA) of the neonates in the PIOMI and OMS groups was 30.6 and 30.3 weeks, respectively, and the mean birthweight was 1,304 and 1,372 g, respectively. The maternal and neonatal characteristics were comparable for both groups (**Table 1**).

The mean CGA in both groups at the start of intervention was 31.4 weeks (P- 0.851) and the mean birthweight was 1,245 and 1,323 g (P- 0.256), respectively, for PIOMI and OMS.

Although the CGA at POFRAS score ≥30 was similar for both groups, the chronological age was lower by 4.6 days for the PIOMI group (P- > 0.05) and these neonates achieved oral feeding readiness 2.7 days earlier (P- > 0.05) (**Table 2**). This primary outcome was assessed for 73 neonates who completed treatment until oral feeding readiness was achieved.

As per Kaplan–Meier analysis, the probability of not achieving oral feeding readiness by 30 days of life (DOL) was lower for the PIOMI group (**Figure 2A**).

Out of 66 neonates followed until discharge, the CGA at full oral feeds was 35.9 and 36.4 weeks, respectively, for PIOMI and OMS (P- > 0.05). The age for full oral feeds was 6.1 DOL lower, the transition time from initiation to full oral feeds was 2 days less, and the duration of hospitalisation was 8 days less for the PIOMI group (P- > 0.05). The average weight gain was higher by 4.9 g/kg/day with PIOMI (P- < 0.05) (**Table 2**).

As per Kaplan–Meier analysis, the probability of not achieving full oral feeds by 45 DOL was lower for the PIOMI group (**Figure 2B**).

A subgroup analysis for the progression of feeding characteristics of the study sample from birth till the achievement of full oral feeds was done for sex and weight for gestational age (**Table 3**). A statistically significant result could only be achieved for average weight gain from initiation to achievement of full oral feeds.

The subgroup analysis for the feeding characteristics based on gestational age (**Table 4**) favoured the PIOMI group, however, a statistically significant inference could only be drawn for transition to full oral feeds for neonates 28^{+0}–31^{+6} weeks gestation and average weight gain on oral feeds for neonates >28 weeks gestational age.

A total of 62 neonates were assessed for breastfeeding till 3 months post-discharge. The exclusive breastfeeding rate was higher by 24.5% (P- 0.015) at 1-month post-discharge in the PIOMI group (per protocol analysis) and by 14.37% (P- 0.185) (per intention to treat analysis). At 3 months post-discharge, 27% (P- 0.022) more neonates in the PIOMI group were on exclusive breastfeeding (per protocol analysis) and 16.6% (P- 0.128) (per intention to treat analysis).

Although not statistically significant, the odds of achieving oral feeding readiness and establishment of full oral feeds were higher in the PIOMI group. The odds of exclusive breastfeeding at 1 and 3 months post-discharge were significantly higher in the PIOMI group as compared to OMS (**Figure 3**).

Discussion

In this study comparing the effect of two methods of oromotor stimulation on readiness for oral feeding in preterm neonates, we did not find a significant difference. We, however, noted the significantly earlier transition from initiation to full oral feeds, better weight gain, and post-discharge breastfeeding rates in the structured method of oromotor stimulation (PIOMI).

Our study had comparable baseline characteristics with the previous studies (5, 8, 10). Most of the neonates in both groups were of GA 28^{+0}–31^{+6} weeks with a birthweight ranging from 1,000 to 1,499 g, which was appropriate for GA. However, as

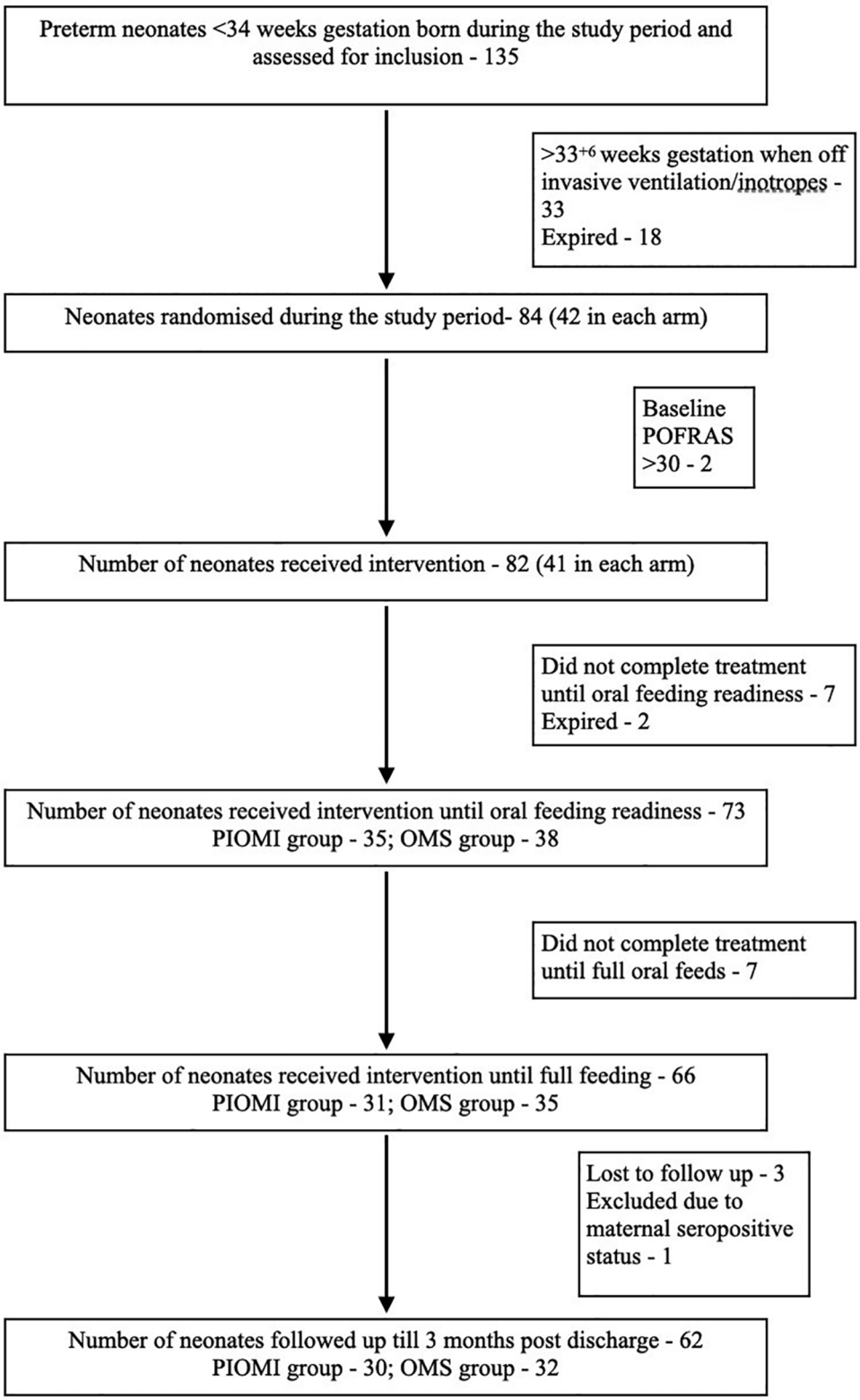

FIGURE 1
Flowchart of the study.

opposed to the previous studies (5, 8, 10), in which, intervention was started after attaining a pre-specified gavage feeding volume, in our study, the neonates were included as soon as they were clinically and hemodynamically stable and a minimum feeding volume was not considered necessary for beginning the intervention. Furthermore, most of the previous studies

TABLE 1 Birth characteristics of the study sample.

	PIOMI [*n* = 42] (%)	Routine OMS [*n* = 42] (%)	*P*-value
Mode of delivery			
LSCS	32 (76.2)	30 (71.4)	0.621
Vaginal	10 (23.8)	12 (28.6)	
Indication of delivery			
Premature labor/rupture of membranes	21 (50)	26 (61.9)	0.505
Severe pre-eclampsia/eclampsia	10 (23.8)	6 (14.3)	
Antenatal ultrasound Doppler changes	5 (11.9)	5 (11.9)	
Placenta previa/Abruptio placentae	5 (11.9)	4 (9.5)	
Severe oligohydramnios	1 (2.4)	1 (2.4)	
Parity			
Primiparous	28 (67)	32 (76.2)	0.352
Multiparous	14 (33)	10 (23.8)	
Gestational age			
<28 weeks	3 (7.1)	4 (9.5)	0.570
28–31 + 6 weeks	26 (61.9)	27 (64.3)	
32–33 + 6 weeks	13 (31)	11 (26.2)	
Mean gestational age in weeks	30.6 ± 1.66	30.3 ± 1.85	
Sex			
Male	21 (50)	25 (59.5)	0.383
Female	21 (50)	17 (40.5)	
Birth weight			
<1,000 g	9 (21.4)	7 (16.6)	0.525
1,000–1,499 g	22 (52.4)	22 (52.4)	
>1,500 g	11 (26.2)	13 (31)	
Mean weight in grams	1,304 ± 350	1,372 ± 333	0.365
Weight for gestational age			
SGA	8 (19)	5 (11.9)	0.368
AGA	34 (81)	37 (88.1)	
Mean 5-min APGAR	8.2 ± 1.2	7.97 ± 1.1	0.363

PIOMI, premature infant oral motor intervention; OMS, oro-motor stimulation; LSCS, lower segment caesarean section; SGA, small for gestational age; AGA, appropriate for gestational age.

compared PIOMI to routine care where the control groups had not received any form of oral motor stimulation.

Both the intervention groups achieved oral feeding readiness at a similar CGA and a trend for lower chronological age for oral feeding readiness was noted with PIOMI but this was not

TABLE 2 Characteristics of the study sample at the time of feeding readiness and full oral feeds.

	PIOMI (*n* = 35)	Routine OMS (*n* = 38)	*P*-value
Mean gestational age in weeks at score ≥30	34.1 ± 1	34.3 ± 1.5	0.542
Mean age at score ≥30, days of life	24.7 ± 13.6	29.3 ± 18.3	0.233
Median [IQR] age at score ≥30, days of life	21 [14, 31]	22 [15, 40]	0.911
Mean number of days from the start of the intervention to score ≥30	18.6 ± 11.6	21.3 ± 13.6	0.374
Median [IQR] number of days for score ≥30	16 [10, 28]	16 [11, 34]	0.911
	PIOMI (*n* = 31)	Routine OMS (*n* = 35)	*P*-value
Mean gestational age in weeks at full oral feeds	35.9 ± 1.22	36.4 ± 1.9	0.248
Mean age at full oral feeds, days of life	38.3 ± 15.1	44.4 ± 23.4	0.210
Median [IQR] age at full oral feeds, days of life	37 [26, 48]	35 [27, 69]	0.468
Mean number of days from the start of oral feeds to full oral feeding	9.1 ± 2.2	11.1 ± 3.3	0.007
Mean weight in grams at full oral feeds	1,862 ± 185	1,874 ± 201	0.8
Average duration of hospital stay in days	37.06 ± 16.2	45.1 ± 23.1	0.104
Median [IQR] duration of hospital stay in days	38 [27, 48]	36 [27, 69]	1
Average weight gain [g/kg/day]	14.6 ± 3.7	9.7 ± 2.9	0.0001

PIOMI, premature infant oral motor intervention; OMS, oro-motor stimulation; PMA, post menstrual age; IQR, inter-quartile range.

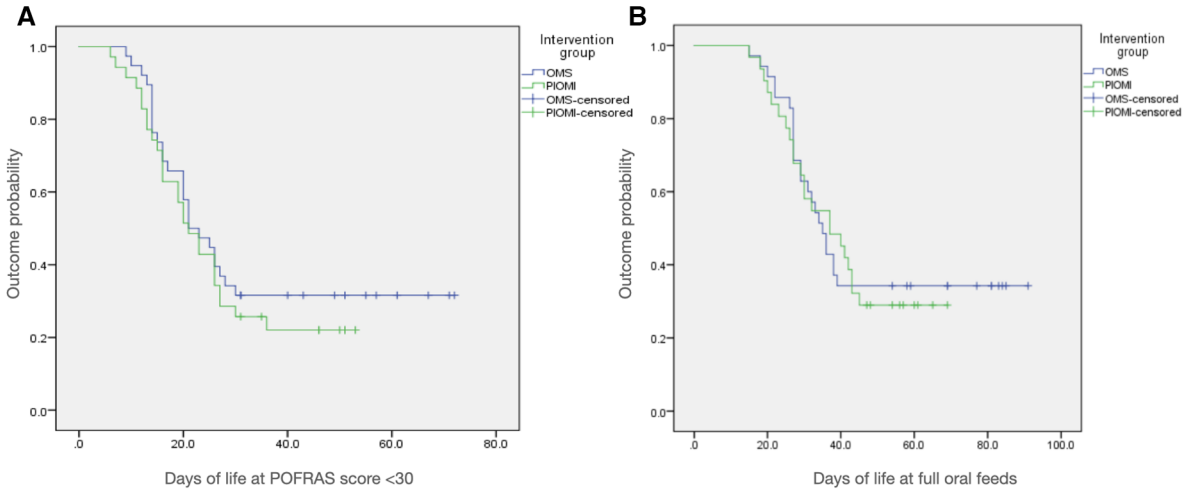

FIGURE 2
Kaplan-Meier analysis curves for the probability of (A) not achieving oral feeding readiness by 30 days of life and (B) not achieving full oral feeds by 45 days of life.

TABLE 3 Progression of feeding characteristics of the study sample from birth till achievement of full feeds based on sex and weight for gestational age.

	PIOMI ($n = 42$)		Routine OMS ($n = 42$)		*P*-value
Mean gestational age in weeks at birth	30.6 ± 1.66		30.3 ± 1.85		0.436
Male AGA	$n = 19$	30.8 ± 1.4	$n = 21$	30.4 ± 2.1	0.487
Male SGA	$n = 2$	29.3	$n = 4$	30.9 ± 1.8	0.333
Female AGA	$n = 15$	30.5 ± 2.2	$n = 16$	30.2 ± 1.6	0.666
Female SGA	$n = 6$	30.8 ± 1	$n = 1$	28.6	–
Mean weight in grams at birth	1,304 ± 350		1,372 ± 333		0.365
Male AGA	$n = 19$	1,401 ± 295	$n = 21$	1,424 ± 345	0.823
Male SGA	$n = 2$	800 ± 141	$n = 4$	1,140 ± 209	0.113
Female AGA	$n = 15$	1,371 ± 377	$n = 16$	1,401 ± 301	0.784
Female SGA	$n = 6$	996 ± 165	$n = 1$	745	–
	PIOMI ($n = 35$)		Routine OMS ($n = 38$)		*P*-value
Mean gestational age in weeks at score ≥30	34.1 ± 1		34.3 ± 1.5		0.542
Male AGA	$n = 17$	33.8 ± 1.05	$n = 19$	34.3 ± 1.1	0.173
Male SGA	$n = 1$	34.5	$n = 4$	35.8 ± 1.8	–
Female AGA	$n = 12$	34.1 ± 0.8	$n = 14$	33.5 ± 0.9	0.087
Female SGA	$n = 5$	34.9 ± 1	$n = 1$	39	–
Mean number of days from the start of the intervention to score ≥30	18.6 ± 11.6		21.3 ± 13.6		0.374
Male AGA	$n = 17$	17.2 ± 11.1	$n = 19$	21.4 ± 13.9	0.327
Male SGA	$n = 1$	33	$n = 4$	21.5 ± 10.4	–
Female AGA	$n = 12$	19 ± 13.6	$n = 14$	18.4 ± 10.9	0.901
Female SGA	$n = 5$	19.2 ± 11.6	$n = 1$	58	–
	PIOMI ($n = 31$)		Routine OMS ($n = 35$)		*P*-value
Mean gestational age in weeks at full oral feeds	35.9 ± 1.22		36.4 ± 1.9		0.248
Male AGA	$n = 15$	35.8 ± 1.3	$n = 18$	36.3 ± 1.9	0.394
Male SGA	$n = 1$	36.2	$n = 4$	37.6 ± 1.9	–
Female AGA	$n = 11$	35.6 ± 0.8	$n = 12$	35.9 ± 1.5	0.561
Female SGA	$n = 4$	37.2 ± 1.3	$n = 1$	40.5	–
Mean number of days from the start of oral feeds to full oral feeding	9.1 ± 2.2		11.1 ± 3.3		0.007
Male AGA	$n = 15$	8.7 ± 2.5	$n = 18$	9.9 ± 2.4	0.170
Male SGA	$n = 1$	10	$n = 4$	11.8 ± 1.5	–
Female AGA	$n = 11$	9.8 ± 2	$n = 12$	12.5 ± 4.4	0.076
Female SGA	$n = 4$	8.8 ± 1.3	$n = 1$	13	–
Mean weight in grams at full oral feeds	1,862 ± 185		1,874 ± 201		0.8
Male AGA	$n = 15$	1,888 ± 187	$n = 18$	1,931 ± 220	0.554
Male SGA	$n = 1$	1,875	$n = 4$	1,731 ± 108	–
Female AGA	$n = 11$	1,902 ± 173	$n = 12$	1,845 ± 177	0.444
Female SGA	$n = 4$	1,650 ± 103	$n = 1$	1,750	–
Average weight gain [g/kg/day]	14.6 ± 3.7		9.7 ± 2.9		0.0001
Male AGA	$n = 15$	13.6 ± 3.7	$n = 18$	8.6 ± 2.6	0.0001
Male SGA	$n = 1$	13.1	$n = 4$	10.5 ± 4.1	–
Female AGA	$n = 11$	15.8 ± 3.7	$n = 12$	11.2 ± 2.4	0.0018
Female SGA	$n = 4$	15.5 ± 3.5	$n = 1$	7.7	–

PIOMI, premature infant oral motor intervention; OMS, oro-motor stimulation; AGA, appropriate for gestational age; SGA, small for gestational age.

statistically significant. The probability of achieving oral feeding readiness by 30 DOL was higher with PIOMI.

Similar to our observation, Sumarni et al. (11) evaluated oral feeding readiness by POFRAS score before and after administration of 7 days of oral motor stimulation and observed that the neonates receiving PIOMI had a higher increment in post-POFRAS scores but the result was not statistically significant. Variability in statistical significance has also been observed for this outcome in other studies, most of which did not utilise any feeding readiness assessment tool (8, 10, 12).

The lower CGA and chronological age for achieving full oral feeds for the PIOMI group was not statistically significant, however, a significantly faster transition to full oral feeding was observed with PIOMI. The probability of achieving full oral feeds by 45 DOL was also higher with PIOMI. Some of the previous studies have also suggested a shorter transition time to full oral feeds using PIOMI (5, 6, 10, 13, 14). The difference in the days to independent oral feeding as compared to the present study could be attributed to variable methodology.

Neonates in the PIOMI group in our study could be discharged 8 days earlier. Similarly, Arora et al. (5) reported that neonates receiving PIOMI could be discharged earlier as compared to sham intervention ($P > 0.05$). Some of the other studies have observed a statistically significant reduction in the duration of stay with PIOMI, however, the control groups in these studies had not received any form of oral motor stimulation (4, 6, 8, 12, 14–16).

TABLE 4 Progression of feeding characteristics of the study sample from birth till achievement of full feeds based on gestational age.

	PIOMI ($n = 35$)		Routine OMS ($n = 38$)		*P*-value
Mean gestational age in weeks at score ≥30	34.1 ± 1		34.3 ± 1.5		0.542
<28 weeks	$n = 2$	34.6 ± 0.8	$n = 4$	35.2 ± 0.5	0.305
28–31 + 6 weeks	$n = 24$	34.1 ± 1.1	$n = 25$	34.2 ± 1.8	0.816
32–33 + 6 weeks	$n = 9$	33.9 ± 0.6	$n = 9$	34.2 ± 0.2	0.174
Mean number of days from the start of the intervention to score ≥30	18.6 ± 11.6		21.3 ± 13.6		0.374
<28 weeks	$n = 2$	39.5 ± 0.7	$n = 4$	41.8 ± 4.6	0.543
28–31 + 6 weeks	$n = 24$	20.9 ± 10.3	$n = 25$	22 ± 12.6	0.740
32–33 + 6 weeks	$n = 9$	7.7 ± 3.6	$n = 9$	9.8 ± 3.1	0.203
	PIOMI ($n = 31$)		Routine OMS ($n = 35$)		*P*-value
Mean gestational age in weeks at full oral feeds	35.9 ± 1.22		36.4 ± 1.9		0.248
<28 weeks	$n = 2$	36.1 ± 1.2	$n = 4$	38.4 ± 1.1	0.077
28–31 + 6 weeks	$n = 22$	36.1 ± 1.3	$n = 22$	36.4 ± 2.1	0.572
32–33 + 6 weeks	$n = 7$	35.4 ± 0.7	$n = 9$	35.7 ± 0.7	0.417
Mean number of days from the start of oral feeds to full oral feeding	9.1 ± 2.2		11.1 ± 3.3		0.007
<28 weeks	$n = 2$	11 ± 1.4	$n = 4$	13.5 ± 3.1	0.357
28–31 + 6 weeks	$n = 22$	8.9 ± 2	$n = 22$	10.7 ± 2.7	0.016
32–33 + 6 weeks	$n = 7$	9.2 ± 2.8	$n = 9$	11.1 ± 4.4	0.338
Mean weight in grams at full oral feeds	1,862 ± 185		1,874 ± 201		0.8
<28 weeks	$n = 2$	1,925 ± 134	$n = 4$	2,107 ± 358	0.544
28–31 + 6 weeks	$n = 22$	1,845 ± 199	$n = 22$	1,842 ± 174	0.958
32–33 + 6 weeks	$n = 7$	1,897 ± 164	$n = 9$	1,847 ± 114	0.483
Average weight gain [g/kg/day]	14.6 ± 3.7		9.7 ± 2.9		0.0001
<28 weeks	$n = 2$	12.3 ± 1.1	$n = 4$	9.8 ± 2.2	0.219
28–31 + 6 weeks	$n = 22$	14.5 ± 3.7	$n = 22$	9.9 ± 3.1	0.0001
32–33 + 6 weeks	$n = 7$	15.6 ± 4.2	$n = 9$	9 ± 2.8	0.002

PIOMI, premature infant oral motor intervention; OMS, oro-motor stimulation.

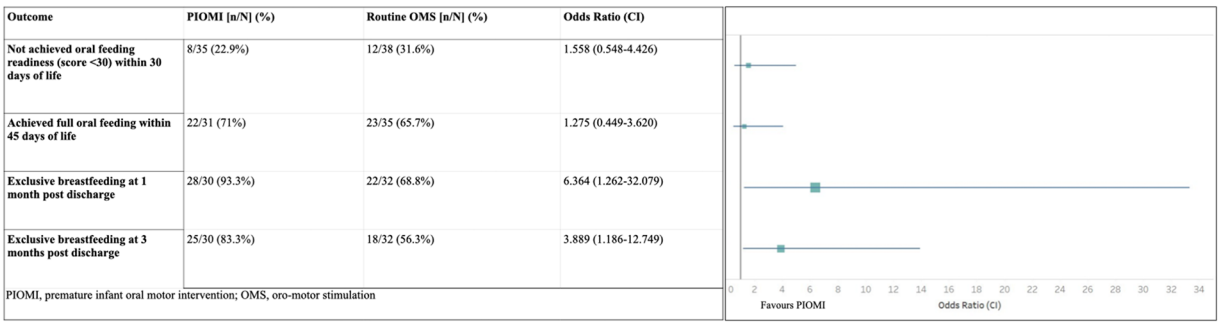

FIGURE 3
Outcome analysis based on the odds ratio.

Although the difference between the groups for oral feeding readiness, full oral feeding, and duration of hospitalisation was not statistically significant, each day saved in terms of clinical management has a significant implication on the expenditure for the affected family and the healthcare system. Earlier initiation and achievement of oral feeds will help to establish the emotional bond between the mother-infant dyad and enhance the mother's confidence in feeding and taking care of the neonate. Decreased duration of hospitalisation would reduce the financial burden on the family, especially in a low-middle income setting. Additionally, this will have a profound effect on the available health resources and the economics of the health structure.

The neonates receiving PIOMI had significantly higher weight gain on oral feeds in our study. A similar observation was noted in the study by Thakkar et al. (10). This may indirectly be indicative of better oral feeding efficiency and milk volume transferred in each feed, as has been suggested by some previous studies (7, 10, 17) in favour of PIOMI. However, overall the results have been variable (6, 8). This could be attributed to not following a feeding readiness assessment scale across the previous studies, which may have subjectively altered the judgement of feeding efficiency.

While the subgroup analysis as per sex, weight for gestational age, and gestational age did not reveal statistically significant differences for all study outcomes, it favoured the PIOMI group, particularly the neonates >28 weeks gestation. The results of

individual analyses, however, need interpretation, taking into account the small sample size.

The exclusive breastfeeding rates in the present study were significantly higher after discharge in the neonates who had received PIOMI per protocol ($p < 0.05$). The OR analysis of the same also favored PIOMI, with statistical significance. This finding supports that PIOMI improves the feeding efficiency in preterm neonates (7, 10, 17). Sasmal et al. (8) observed higher breastfeeding rates with PIOMI at 1 month after discharge. Skaaning et al. (9) evaluated the effect of a parent-administered PIOMI-based oral motor stimulation method. Both studies, however, could not establish a significant impact on exclusive breastfeeding with PIOMI. This could be speculated to lower sample size (8), variable methodology, and caregiver-dependent method of PIOMI.

The abovementioned observations suggest that although a structured form of oral motor stimulation may not have resulted in statistically significant differences in initiation and attainment of oral feeds, its effects on improving oral feeding efficiency and exclusive breastfeeding rates are evident.

Our study has several strengths. More than the required number of participants were recruited to achieve statistical power. Both structured and unstructured methods of oral motor stimulation were compared in the present study, thereby, assessing the overall effect of various methods of oral motor stimulation utilised in clinical settings. Additionally, the intervention was started as soon as the neonate was hemodynamically stable, as has been suggested by Lessen et al. (4). The oral feeding was established as per validated scoring systems and not based on subjective assessment. However, the study is not devoid of limitations. It is a single-centre study and, therefore, the findings may not be generalizable. Although the intervention providers were blinded to the weekly POFRAS assessment and scores, the blinding of study participants at the time of providing intervention could not be achieved. The allocation concealment for randomisation was also not performed. Data on maternal education and socio-economic status was not collected, which may have been significant attributing factors for exclusive breastfeeding.

Conclusion

The neonates receiving PIOMI showed higher weight gain and exclusive breastfeeding rate post-discharge. This suggests improvement in feeding efficiency with a structured intervention. Although a statistically significant difference could not be derived for all outcomes, it may still offer clinical benefit for the patient and the treating facility. We, thus, recommend PIOMI to be more effective for improved oral feeding in preterm neonates 29^{+0}–33^{+6} weeks GA. However, multicentric trials with larger sample sizes would be necessary to further strengthen the recommendation.

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 humans were approved by Institutional Ethics Committee, Bharati Vidyapeeth (Deemed to be) University Medical College. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

PS: Data curation, Formal Analysis, Writing – original draft. NM: Conceptualization, Formal Analysis, Supervision, Writing – review & editing. AK: Data curation, Writing – review & editing. RG: Data curation, Writing – review & editing. AV: Data curation, Writing – review & editing. NN: Supervision, Writing – review & editing. RM: Supervision, Writing – review & editing. PS: Conceptualization, Project administration, Supervision, Visualization, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1296863/full#supplementary-material

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Diagnostic utility of lung ultrasound in predicting the need for surfactant therapy in preterm neonates with respiratory distress

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Background: Lung ultrasound is an accurate and early predictor for surfactant replacement therapy in respiratory distress syndrome (RDS) as compared to clinical parameters and chest x-ray. However, lung pathologies for respiratory distress at birth have overlapping symptomatology and low middle-income countries have a higher incidence of congenital pneumonia, in addition to RDS, making the immediate diagnosis difficult. Thus, there is a need for assessing a cutoff for lung ultrasound scores in the given setting.
Objectives: The primary objective was to determine the diagnostic accuracy of the lung ultrasound score (LUS) in predicting the need for surfactant therapy in preterm neonates with respiratory distress. Secondary objectives were to correlate LUS with corresponding oxygen saturation to the fraction of inspired oxygen ratio (SpO2/FiO2), arterial/Alveolar oxygen pressure ratio (a/A), and chest x-ray (CXR) findings.
Methodology: A prospective observational study was carried out at a tertiary-level neonatal intensive care unit in India in 2022 enrolling 100 neonates <34 weeks gestational age with respiratory distress at birth. After initial stabilization of the neonate, LUS was performed and baseline parameters were noted. Surfactant was administered as per the 2019 European Consensus guidelines and LUS was repeated after 6 h of therapy.
Results: The mean gestation of enrolled neonates was 31.06 ± 2.12 weeks and the mean birthweight was 1,412 ± 391 g. Approximately 58% were diagnosed with RDS and 30% had congenital pneumonia. Surfactant was administered to 40% of neonates. The cutoff LUS for surfactant therapy was 7 [area under the curve (AUC) 0.977; 95% CI, 0.947–1; $P < 0.001$; with sensitivity 92.5%, specificity 96.67%, PPV 94.87%, and NPV 95.08%] and the cutoff LUS for the second dose of surfactant was 10 (AUC 0.964; 95% CI, 0.913–1; $P < 0.001$). The score decreased by 3.24 (2.44–4.05) after 6 h of the first dose and correlated significantly with SpO2/FiO2 ratio (–0.750), a/A ratio (–0.650), and CXR findings (0.801).
Conclusion: The study predicted an optimal LUS cutoff of 7 and 10 for the need for the first dose of surfactant and re-treatment, respectively, in neonates <34 weeks gestational age with respiratory distress.

KEYWORDS

lung ultrasound score, prematurity, neonate, respiratory distress, surfactant therapy

Abbreviations
RDS, respiratory distress syndrome; LUS, lung ultrasound score; SpO2/FiO2, oxygen saturation to the fraction of inspired oxygen ratio; a/A, arterial/Alveolar oxygen pressure ratio; CXR, chest x-ray; CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; NICU, neonatal intensive care unit; PEEP, peak end-expiratory pressure; NIPPV, nasal intermittent positive pressure ventilation; TTNB, transient tachypnea of the newborn.

Introduction

One of the most important causes of morbidity and mortality in preterm neonates, respiratory distress occurs in almost 5.8% of all live births (1) and accounts for 30%–40% of admissions to neonatal units (2). The management is based on earlier and timely administration of surfactant along with continuous positive airway pressure (CPAP) support. However, identifying the narrow window for administering surfactant remains challenging, given the advantages of early rescue surfactant therapy in reducing the risk of acute pulmonary injury, neonatal mortality, and chronic lung disease (3).

In recent times, lung ultrasound has gained a crucial role in the early diagnosis and evaluation of respiratory distress in neonates (4). It is a quick and safe bedside technique and can be repeated several times a day (5).

Over the years, studies have developed a lung ultrasound score (LUS) for the evaluation of lung aeration and prediction of surfactant administration (6, 7). The same was validated in 2015, demonstrating its utility in the management of respiratory distress syndrome (RDS) (8).

The indication of surfactant administration is variable among different neonatal intensive care units (NICU) and is guided by parameters such as chest x-ray (CXR), arterial/Alveolar oxygen pressure ratio (a/A), and FiO2. Presently, the guidelines for surfactant therapy are based on the fraction of inspired oxygen (FiO2) values (9), which may be arbitrary and non-specific (10).

In previous studies, lung ultrasound aided in guiding early rescue therapy within 2 h of delivery, thereby reducing the need for a repeat dose of surfactant, the need for invasive ventilation, and the number of days on a ventilator (11–14). When compared with chest x-ray, it was found to have higher specificity and sensitivity in predicting the need for surfactant in RDS (12).

Although the utility of LUS in predicting the disease severity and need for surfactant has been reported (15), data related to lung ultrasound scoring and its accuracy in predicting the need for surfactant in preterms with respiratory distress is lacking for the Indian population. It has the potential to be an accurate and early predictor of the need for surfactant therapy in this population cohort, thus, allowing timely treatment and reduced radiation exposure.

Therefore, this study was conducted to determine the diagnostic accuracy of LUS in predicting the need for surfactant in preterm neonates with respiratory distress and correlate it with corresponding oxygen saturation to the fraction of inspired oxygen ratio (SpO2/FiO2), a/A ratio, and findings on CXRs.

Methodology

A single-centre prospective observational study was conducted in a tertiary care NICU attached to a medical college with approximately 1,500 annual admissions and 130–150 admissions per month. The study was approved by the institutional ethics committee and registered in the clinical trials registry. All inborn as well as outborn neonates <34 weeks gestational age admitted to the NICU within 24 h of life with respiratory distress were included. Informed consent was obtained from the patient's parents. Neonates with complex cyanotic congenital heart disease, congenital malformation, chromosomal abnormality, inborn error of metabolism, and congenital lung disorder were excluded. The included neonates were started on non-invasive respiratory support from the time of admission to the NICU with an appropriately sized nasal interface. Peak end-expiratory pressure (PEEP) was set at 6 cm H2O and FiO2 levels were adjusted to maintain target oxygen saturations within the 90% to 95% target range. In case of failure of CPAP support (not maintaining target oxygen saturation on PEEP 6 cm H2O and FiO2 up to 0.3 or persistent/worsening respiratory distress), mode of respiratory support was stepped up to nasal intermittent positive pressure ventilation (NIPPV) support. The NIPPV support was started on peak inspiratory pressure (PIP) of 14 cm H2O and escalated as required up to 20 cm H2O and 0.4 FiO2 to alleviate respiratory distress and maintain the target oxygen saturation. A trial of NIPPV support was opted before invasive ventilation, considering it to be a superior modality of respiratory support to CPAP for preterm neonates with respiratory distress (16). The following criteria were used for considering mechanical ventilation: (a) repeated episodes of apnea defined as more than four episodes of apnea per hour or more than two episodes requiring bag and mask ventilation, (b) hypoxia defined as FiO2 >0.40 to maintain SpO2, and (c) respiratory acidosis with PaCO2 >60 mmHg and pH <7.20. The same criteria were utilised for the requirement of respiratory support post-surfactant therapy.

On admission, as per the unit protocol, a baseline arterial blood gas and CXR were performed. Baseline lung ultrasound scoring was done and was denoted as "pre-surf LUS". The surfactant was administered as per the European consensus guidelines (early rescue surfactant therapy if FiO2 >0.3 on CPAP pressure of at least 6 cm H2O) (9). The neonates requiring NIPPV or invasive ventilation were also given rescue surfactant therapy in case of FiO2 >0.3 and PEEP >6 cm H2O. All the neonates were administered surfactant via the intratracheal route and the INSURE (intubate-surfactant-extubate) technique was utilised for the neonates on non-invasive ventilation. The type of surfactant administered was as per the available and affordable option and hence, both beractant and poractant alfa were administered at a dose of 100 mg/kg of phospholipid. Following this, a repeat LUS was done after 6 h of the first dose of surfactant and was denoted as "post-surf LUS". A second dose of surfactant at 100 mg/kg of phospholipid was administered if the FiO2 value remained above the cutoff (9). Apart from this, SpO2/FiO2 ratio and a/A ratio were calculated for all the neonates prior to surfactant therapy, and CXR grading was done based on the radiological characteristics, namely, reticulogranular pattern, radiolucency, cardiac silhouette, and air-bronchograms—Stage 1: fine granular pattern with few air-bronchograms; Stage 2: distinct granularity and excessive air-bronchograms; Stage 3: increased opacity with reduced air-bronchograms; and Stage 4: diffuse bilateral opacified lung (white-out) with lack of cardiac borders and loss of all air-bronchograms (17).

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Lung ultrasound scoring

Lung ultrasound was done on the Philips Affinity 50G (Koninklijke Philips, Nevada, USA) machine with the "hockey stick" L15–17 MHz transducer. Each lung was divided into three areas (upper anterior, lower anterior, and lateral) and scored.

Each area of the lung was given a score between 0 and 3, with the total score ranging from 0 to 18, where 0 indicated A-pattern [defined by the presence of A-lines only (horizontal, parallel echogenic lines under the pleural line)]; 1 indicated B-Pattern [defined as the presence of ≥3 well-spaced B lines (well defined vertical lines that originated on the pleural line, ran perpendicular to and obscured the A-lines)]; 2 indicated severe B pattern (defined as the presence of crowded and coalescent B lines with or without consolidation limited to subpleural space and/or white out of lung); and 3 indicated extended consolidation (**Figure 1**) (8).

Lung ultrasound was performed by a clinician who had received formal training under senior faculty and who had at least 6 months of experience in the NICU. The pre-recorded ultrasound videos were scored by a single trained blinded observer with an acceptable level of expertise.

Maternal characteristics (antenatal corticosteroid cover, mode of delivery, and risk factors) and neonatal characteristics [sex, gestational age, birth weight, weight for gestational age, the requirement of resuscitation at birth, age at enrolment, doses of surfactant, SpO2/FiO2 and a/A ratios just prior to surfactant administration and before each dose, CXR grading before each dose of surfactant, days on mechanical ventilation, days on non-invasive ventilation, duration of oxygen support (days), length of NICU stay (days), bronchopulmonary dysplasia (%)] were recorded. The neonates were subdivided as per respiratory pathology into RDS, transient tachypnea of the newborn (TTNB), and congenital pneumonia. The criteria for diagnosing congenital pneumonia was respiratory distress along with at least two laboratory parameters positive for sepsis (c-reactive protein ≥6 mg/L, thrombocytopenia with platelet count <100,000/mm^3, immature:total neutrophil ratio >0.2:1, neutropenia as per newborn cutoffs) (18). RDS was diagnosed based on clinical respiratory distress, chest x-ray showing features consistent with the disease, and no laboratory features of sepsis (19). The presence of respiratory distress (transient and self-limiting) with a radiographic picture of inter-fissural fluid or interstitial fluid was diagnosed as TTNB (20).

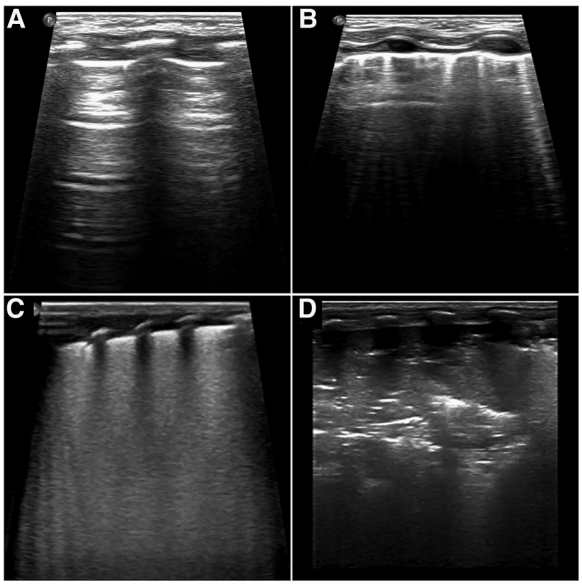

FIGURE 1
Score values correspond to different patterns as shown. Scores were given as follows: (A) 0, presence of only A-lines; (B) 1, presence of ≥3 well-spaced B lines; (C) 2, presence of crowded and coalescent B lines with or without consolidations limited to sub-pleural space; (D) 3, presence of extended consolidation.

Statistics

Categorical variables were expressed as frequency (percentage) and compared using the chi-squared test or Fisher's exact test, as needed. Quantitative data was expressed as mean ± SD and median (IQR). A value of $p < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) analysis was used to evaluate the reliability of the LUS to predict the need for surfactant treatment and re-treatment; area under the curve (AUC) and reliability data were reported with confidence intervals (CIs). Paired analysis was done for comparison of LUS at 0 and 6 h post surfactant. Correlational analysis using Pearson's coefficient was done to determine the correlation of LUS with the SpO2/FiO2 ratio, a/A ratio, and CXR grading. To determine the correlation between LUS and CXR at <3 and >3 h of life at enrolment, correlational analysis was conducted using the Spearman coefficient.

The sample size was calculated using observational data from the previous year where surfactant was administered to approximately 50% of NICU-admitted infants who fulfilled the same inclusion criteria and followed the same surfactant administration protocol. To achieve an AUC of ≥0.7 in ROC analysis with α error of 0.05 and power of 0.95, 100 samples were needed.

Results

A total of 100 neonates were included in the study. The mean (SD) gestation of enrolled neonates was 31.06 ± 2.12 weeks and the mean birthweight was 1,412 ± 391 g. Upon diagnosis, 58% of the enrolled neonates had RDS, 30% had congenital pneumonia, and 12% had TTNB. Baseline characteristics of the study population are reported in **Table 1**. Out of the 100 enrolled patients, 40 neonates received surfactant therapy. Among these, 18 received beractant and 22 received poractant alfa surfactant preparation. The mean age at first dose of surfactant was 1.9 ± 1 h of life. The characteristics of the neonates who received surfactant therapy are given in **Table 2**. The pre-surf LUS was done at the hour of enrolment and with an AUC 0.977, 95% CI (0.947–1), and

TABLE 1 Characteristics of the study cohort, $n = 100$.

Maternal characteristics ($n = 100$)	*N* (%)
Maternal history	
Preterm labor	49 (49)
Severe pre-eclampsia/eclampsia	21 (21)
Antepartum haemorrhage	10 (10)
Antenatal Doppler changes	16 (16)
Severe oligo/anhydramnios	2 (2)
Fetal bradycardia	1 (1)
Scar tenderness	1 (1)
Antenatal steroid course	
Complete	42 (42)
Incomplete	58 (58)
Mode of delivery	
Caesarean section	77 (77)
Vaginal delivery	23 (23)
Neonatal characteristics ($n = 100$)	***N* (%)**
Male	50 (50)
Inborn	80 (80)
Gestational age (weeks)	
<28	9 (9)
28–31 + 6	48 (48)
32–33 + 6	43 (43)
Birth weight (g)	
<1,000	16 (16)
1,000–1,499	45 (45)
≥1,500	39 (39)
Small for gestational age	21 (21)
Hours of life at enrolment	
<3	86 (86)
≥3	14 (14)
Resuscitation at birth	
No resuscitation	46 (46)
Physical stimulation	5 (5)
Positive pressure ventilation	29 (29)
Delivery room intubation	18 (18)
Chest compressions	2 (2)
Medications	–
Respiratory pathology	
Respiratory distress syndrome	58 (58)
Congenital pneumonia	30 (30)
Transient tachypnea of the newborn	12 (12)
Surfactant therapy	40 (40)
Number of doses of surfactant required	
1	17 (43)
2	23 (58)
Type of surfactant used	
Beractant	22 (55)
Poractant alfa	18 (45)
LUS, median (IQR)	
1st dose of surfactant	6 (5–12)
2nd dose of surfactant	8.5 (6–10.5)
SpO2/FiO2 ratio, median (IQR)	
1st dose of surfactant	3.7 (2.3–4.5)
2nd dose of surfactant	4.5 (2.8–4.6)
a/A ratio, median (IQR)	
1st dose of surfactant	0.42 (0.28–0.55)
2nd dose of surfactant	0.345 (0.275–0.38)
Median LUS as per respiratory pathology	
Respiratory distress syndrome	10 (5–12)
Congenital pneumonia	7 (5.5–12)
Transient tachypnea of the newborn	5 (4–6)

(*Continued*)

TABLE 1 Continued

LUS, lung ultrasound score; SpO2/FiO2, oxygen saturation to fraction of inspired oxygen ratio; a/A, arterial/Alveolar oxygen pressure.

$P < 0.001$, the cutoff score as per ROC curve was 7 (sensitivity 92.5%, specificity 96.7%, positive predictive value (PPV) 94.87%, and negative predictive value (NPV) 95.08%) (**Figure 2A** and **Table 3**). The mean age of the neonates at the time of pre-Surf LUS was 1.37 ± 0.84 h. The mean LUS of neonates with RDS, congenital pneumonia, and TTNB were 8.9 ± 3.5, 8.6 ± 3.7, and 4.8 ± 1.6, respectively. The mean (SD) LUS for neonates with RDS who did not require surfactant was 5.5 ± 1.6 and the median (IQR) was 4 (4–6), and the mean LUS for neonates with RDS who required surfactant was 11.6 ± 2 and the median was 12 (11–13). This result was statistically significant with $P < 0.0001$. The pre-surf LUS cutoff determining requirement of >1 dose of surfactant was 10 (sensitivity 100%, specificity 86.36%, PPV 95.24%, and NPV 100%) as per ROC with an AUC 0.964, 95% CI (0.913–1), and $P < 0.001$ (**Figure 2B**). A total of 23 neonates required a repeat dose of surfactant, 17 of these were diagnosed with RDS and the remaining 6 had congenital pneumonia. The mean (SD) age at repeat dose of surfactant therapy was 7.5 ± 0.8 h of life. In neonates requiring one dose of surfactant therapy, the LUS decreased by a median value of 3.24 (2.44–4.05) over 6 h. The mean difference between pre- and post-surf LUS for neonates who received beractant was 3.73 ± 1.35 (*P* 0.1) and for neonates who received poractant alfa, it was 2.94 ± 1.76 (*P* 0.12). **Figure 3** shows the distribution of LUS values with the corresponding FiO2. A correlation of −0.75 ($P < 0.001$) was found between pre-surf LUS and SpO2/FiO2 ratio and a correlation of −0.235 (*P* 0.144) was found between post-surf LUS and SpO2/FiO2 ratio after 6 h of surfactant. Between pre-surf LUS and a/A, the correlation was −0.65 ($P < 0.001$), and between post-surf LUS and a/A at 6 h

TABLE 2 Characteristics of the neonates receiving surfactant therapy, $n = 40$.

Neonatal characteristics	*N* (%)
Male	23 (58)
Inborn	31 (78)
Mean gestational age (weeks)	30.1 ± 2.3
Mean birth weight (g)	1,344 ± 441
Respiratory pathology	
Respiratory distress syndrome	29 (73)
Congenital pneumonia	11 (27)
Transient tachypnea of the newborn	0 (0)
Hours of life at 1st dose of surfactant	
<3	28 (70)
≥3	12 (30)
Mean age at 1st dose of surfactant (hours)	
Inborn	1.6 ± 0.8
Outborn	2.9 ± 0.9

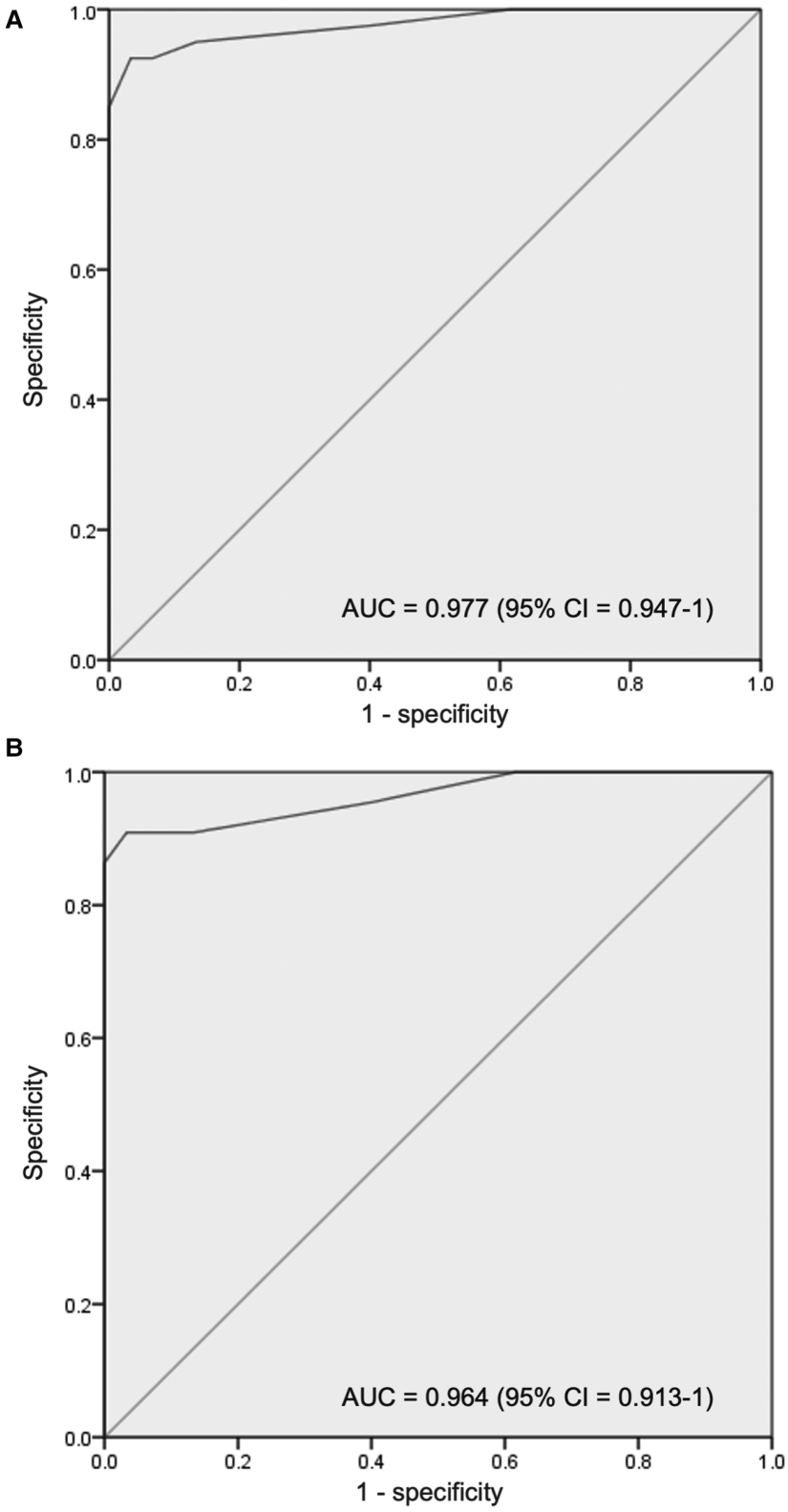

FIGURE 2
(A) Receiver operating characteristic (ROC) curve for pre-surfactant LUS cutoff for the requirement of surfactant therapy (B) receiver operating characteristic (ROC) curve for pre-surfactant LUS cutoff for the requirement of repeat surfactant therapy.

post-therapy, it was −0.075 (*P* 0.645). A significant correlation was found between pre-surf LUS and first CXR at 0.801 ($P < 0.001$) and post-surf LUS and CXR in babies requiring a repeat dose of surfactant at 0.811 ($P < 0.001$). The correlation between pre-surf LUS and CXR at <3 h of enrolment was 0.829 ($P < 0.001$) and it was 0.832 ($P < 0.001$) at ≥3 h of enrolment. A total of 80

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TABLE 3 Diagnostic utility of lung ultrasound score with surfactant therapy.

Lung ultrasound score	Surfactant therapy	
	Yes	No
≤7	3	58
>7	37	2
Sensitivity	92.5% (76.91–98.43	
Specificity	96.67% (88.47–99.59)	
Positive predictive value	94.87% (82.52–98.64)	
Negative predictive value	95.08% (86.67–98.29)	
Positive likelihood ratio	27.75 (7.08–108.71)	
Negative likelihood ratio	0.08 (0.03–0.23)	

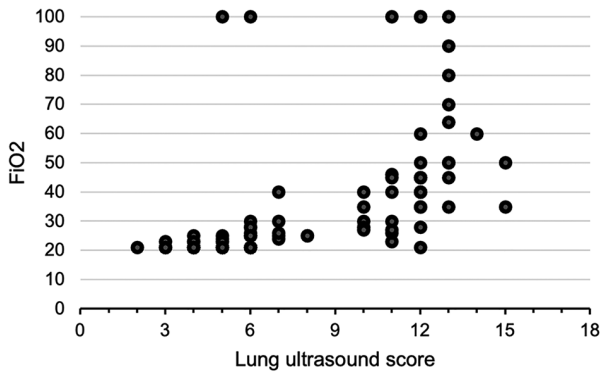

FIGURE 3
Scatter plot showing the distribution of pre-surfactant LUS with corresponding FiO2.

neonates were followed up till discharge. Six neonates among the enrolled patients died. Caregivers of 12 and 2 neonates opted to leave against medical advice due to financial constraints and poor neurodevelopmental outcomes (secondary to post-hemorrhagic hydrocephalus), respectively. A total of 80 neonates were given non-invasive respiratory support after birth, 31 of which required escalation to mechanical ventilation, and 22 of these were administered surfactant therapy as per eligibility criteria.

Discussion

In this study, a quantitative lung ultrasound score was observed to be an excellent predictor of the need for surfactant therapy in respiratory distress in preterm neonates. It was noted that this ultrasonographic marker of lung aeration has a significant correlation with other clinical markers (a/A ratio and SpO2/FiO2 ratio) and radiological markers (CXR grading).

In 2012, Raimondi et al. (21) highlighted the role of lung ultrasonography in respiratory distress in newborns and since then there have been multiple studies to evaluate the same. It is now increasingly being recognised as a primary modality of choice for the assessment of respiratory distress in newborns. However, the existing cutoffs for surfactant replacement therapy have been developed through studies from high-income countries enrolling neonates with RDS and limited data from the Indian population exist for the same, especially in the setting of congenital pneumonia.

Our study population was similar in terms of gestational age and birth weight to the studies previously reported (12, 13). The median time for the first LUS assessment in the present study was 1 h. Taking into account that the study population included newborns that were delivered in the hospital as well as those that were referred from outside hospitals for respiratory distress, this time of assessment was lower as compared to other studies. In their research, Perri et al. reported the time of first assessment as 3.3 (1.8) hours and 2.5 h (12, 13). It has been observed that LUS may vary and even worsen in the first 4 h of life owing to the liquid clearance from airways (22). Therefore, earlier evaluation within the first 1–2 h of life is expected to increase the clinical value of the score and reduce false positive results. Previously, the superiority of LUS done as early as 5–10 min of life has been reported (23).

Developing countries have a higher incidence of congenital pneumonia (24). Moreover, it is difficult to differentiate and establish this diagnosis at birth and the time frame for early rescue surfactant therapy is limited. For this reason, all neonates with respiratory distress were enrolled in our study cohort in contrast to previous studies where inclusion criteria for respiratory pathology were restricted to RDS. Notably, almost one-third of our study population was diagnosed with congenital pneumonia and the average LUS of these neonates was comparable with RDS. Therefore, through this study, the diagnostic utility of lung ultrasound for timely surfactant replacement therapy is highlighted in congenital pneumonia as well as RDS.

For an objective assessment of the requirement of surfactant in neonates with respiratory distress, Brat et al. (8) developed and established LUS through their study in 2015. However, the LUS cutoff as per their study in 65 infants <34 weeks gestation was 4 in comparison to our cutoff score of 7. The LUS cutoff for the second dose of surfactant as per our study was 10. Our findings were similar to those of De Martino et al. (14), who studied more preterm populations (≤30 weeks gestational age) but had ultrasound protocols that matched ours. In similar studies, Perri et al. reported the LUS cutoff for surfactant treatment to be 5 and for retreatment to be 7 (12, 13). A recent study by Raimondi et al. reported 9 as the LUS cutoff for surfactant therapy (11). Another recently published study (25) from India reported an optimal cutoff score ≥9 for giving surfactants. However, the sensitivity and specificity for the same was lower. Additionally, posterior chest areas were also included in their scoring system to calculate the final LUS. This may account for the differences in their findings as compared to ours.

In the present study, we found that LUS decreased after surfactant administration. This was expected owing to changes in lung mechanics after surfactant replacement, which has been reflected in some of the previous studies (11, 13).

In the present study, the LUS correlated significantly with SpO2/FiO2 ratio, a/A ratio, and CXR. Brat et al. (8) also showed a significant correlation between LUS and a/A ratio, and Perri et al. (12, 13) observed a significant correlation between LUS and SpO2/FiO2 ratio and LUS and CXR. Since the calculation of mean airway pressures was not possible in all neonates across the various modes of respiratory support used (especially CPAP), oxygenation indices considered for correlation with LUS were SpO2/FiO2 and a/A ratios. SpO2/FiO2 ratio was utilised in the study due to it being an accurate surrogate marker of oxygenation status (26). Raschetti et al., in their quality improvement project, noted FiO2 to be a later predictor of surfactant therapy as compared to LUS, and FiO2 based criteria was shown to have increased the duration of oxygen exposure due to delayed surfactant therapy (10). This affirms that LUS in conjunction with other baseline parameters is a better predictor for surfactant therapy in preterms as compared to FiO2 alone and with comparable findings on CXR.

Our study methodology was in accordance with the existing standard guidelines for surfactant use. The first LUS was done relatively earlier as compared to previous studies, therefore, the reliability is expected to be more when compared with other baseline parameters at enrolment with lower false positivity. The scoring of all lung ultrasounds by a single trained observer eliminated the risk of interobserver bias. The inclusion of all neonates with respiratory distress at birth foregrounded the wider applicability of LUS in pathologies other than RDS.

The study, however, was not devoid of limitations. It was conducted at a single centre with a relatively small sample size. The number of extremely preterm neonates was rather limited, therefore limiting the generalizability of the results for that population. Additionally, the role of LUS in late preterm neonates (gestational age >34 weeks) with respiratory distress remains to be studied. The LUS score was correlated with CXR findings for all neonates with respiratory distress, however, the grading scale used for the same was as per the radiological characteristics of RDS. The study was conducted in a low-resource setting and therefore, both preparations of surfactant (beractant and poractant alfa) were administered to the neonates according to availability and affordability. Furthermore, poractant alfa had to be administered at a dose lower than the recommended 200 mg/kg of phospholipid as it was a more expensive option. The mean airway pressure could not be recorded as part of the study due to variations in the mode of respiratory support and, therefore, the LUS could not be correlated against better oxygenation indices such as oxygenation index (OI) and oxygen saturation index (OSI).

Conclusion

The study predicted an optimal LUS cutoff of 7 and 10 for the need for the first dose of surfactant and re-treatment, respectively, in neonates <34 weeks gestational age with respiratory distress. LUS correlated significantly with SpO2/FiO2 and a/A ratios and findings on CXR. However, larger multi-centric trials in India as well as low- and middle-income settings, including neonates >34 weeks gestational age with respiratory distress, are required to validate these cutoffs for surfactant replacement therapy. Future studies aimed at more homogeneity, with respect to the type of surfactant, at the recommended dose of phospholipids, and utilising superior oxygenation indices are warranted to further elaborate upon the clinical utility of lung ultrasound scoring.

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 humans were approved by Institutional Ethics Committee, Bharati Vidyapeeth (Deemed to be) University Medical College, Pune, India. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

PS: Data curation, Formal Analysis, Investigation, Writing – original draft. SP: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – review & editing. AV: Data curation, Methodology, Writing – review & editing. RG: Data curation, Writing – review & editing. RM: Writing – review & editing. PS: Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing.

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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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Effectiveness of a novel bubble CPAP system for neonatal respiratory support at a referral hospital in the Philippines

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Aim: To examine the impact of introducing and implementing the Vayu bubble continuous positive airway pressure (bCPAP) system on neonatal survival and neonatal respiratory outcomes in a neonatal intensive care unit (NICU) in the Philippines.

Methods: We compared clinical outcomes of 1,024 neonates before to 979 neonates after introduction of Vayu bCPAP systems into a NICU. The primary outcome was survival to discharge. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated. Analyses were undertaken separately for the entire NICU population and for neonates who received any form of respiratory support.

Results: The introduction of the Vayu bCPAP system was associated with (1) significant reductions in intubation (aOR: 0.75; 95% CI: 0.58–0.96) and in the use of nasal intermittent positive-pressure ventilation (NIPPV) (aOR: 0.69; 95% CI: 0.50–0.96) among the entire NICU population and (2) a significant increase in survival to discharge (aOR: 1.53; 95% CI: 1.09–2.17) and significant reductions in intubation (aOR: 0.52; 95% CI: 0.38–0.71), surfactant administration (aOR: 0.60; 95% CI: 0.40–0.89), NIPPV use (aOR: 0.52; 95% CI: 0.36–0.76), and a composite neonatal adverse outcome (aOR: 0.60; 95% CI: 0.42–0.84) among neonates who received any form of respiratory support.

Conclusion: The use of the Vayu bCPAP system in a NICU in the Philippines resulted in significant improvement in neonatal respiratory outcomes.

KEYWORDS

CPAP therapy, neonatal mortality, low-resource settings, respiratory support, preterm birth, neonatal intensive care unit

1. Introduction

In 2021, 2.3 million infants worldwide died in their first month of life (1). Complications related to preterm birth are the leading cause of neonatal death around the world, most of which occur in low-resource settings (2–4). Respiratory distress, particularly respiratory distress syndrome (RDS), is the single most important cause of complications and death in preterm infants (5). Currently, continuous positive airway pressure (CPAP) therapy is

recommended for the treatment of preterm infants (<37 weeks of gestation) with RDS and may be considered immediately after birth for very preterm infants (<32 weeks of gestation) with or without respiratory distress (6, 7).

Treatment of neonates with CPAP improves gas exchange, decreases the work of breathing, and can reduce mortality by as much as 66% (8). CPAP therapy also decreases the need for surfactant administration and mechanical ventilation and reduces the length of hospital stay and referrals to higher levels of care (8–10). In the November 2022 World Health Organization (WHO) *Recommendations for Care of the Preterm or Low-Birth-Weight Infant*, initiation of CPAP therapy was strongly recommended for neonates with respiratory distress (6, 7). The WHO has also recommended considering the use of bubble CPAP (bCPAP), a method that provides CPAP by using a column of water to generate pressure that is carried into the pulmonary system, for preterm infants for whom CPAP is warranted (6, 7). This recommendation was based on evidence of small-to-moderate decreased risk of pneumothorax, decreased bronchopulmonary dysplasia, and decreased failed treatment in trials involving preterm infants (6, 7).

Neonatal mortality has not decreased over the past five years in the Republic of the Philippines (11). High costs of commercially available CPAP devices, lack of consumables and compressed air for medical purposes, and the need for uninterrupted electricity are barriers to the provision of CPAP worldwide and throughout the Philippines (12). The novel Vayu bCPAP system has been designed specifically to overcome barriers to global access to CPAP. This system generates continuous pressure throughout the respiratory system and delivers blended, humidified, and filtered breathing gases at precise oxygen concentrations without the use of electricity (13). In early 2021, a total of 14 Vayu bCPAP systems were introduced and implemented in the neonatal intensive care unit (NICU) of the Ilocos Training and Regional Medical Center (ITRMC) in the Philippines. Details regarding the Vayu bCPAP system have been described previously elsewhere (13).

The objective of this study was to evaluate the impact of introducing and implementing Vayu bCPAP systems on neonatal survival and on the incidence of intubation, surfactant administration, and use of nasal intermittent positive-pressure ventilation (NIPPV) in the NICU at the ITRMC in the Philippines.

2. Methods

2.1. Study design

This was a baseline (admissions from March 1, 2020 to February 28, 2021) and intervention (admissions from March 1, 2021 to February 26, 2022) comparative study that evaluated the impact of introducing Vayu bCPAP systems for neonatal respiratory support into the NICU at ITRMC. Demographic and clinical characteristics and outcomes of neonates admitted to the ITRMC NICU during the two study periods were compared. The entire NICU population and a subgroup of neonates who received any form of respiratory support (intubation, NIPPV, CPAP therapy, low-flow oxygen, or low-flow medical compressed air) were evaluated separately.

2.2. Study setting

ITRMC is a public regional referral hospital in San Fernando City, La Union, the Philippines. The pediatric department has a level III NICU with 25 beds. This NICU can provide 40 beds when needed. The equipment in the NICU includes radiant warmers, incubators, and monitoring equipment. Support for kangaroo mother care (i.e., skin-to-skin contact between the mother and infant) and breast-feeding is available 24 h daily. Surfactant therapy is readily available, and the cost is covered by the Philippines Health Insurance Corporation. The average ratio of nurses to neonates in the NICU is one to 10.

Before the implementation of the Vayu bCPAP systems, three CareFusion synchronized inspiratory positive airway pressure (SiPAP) devices, two Fisher & Paykel CPAP machines, and one Dräger CPAP device were available for use in the ITRMC NICU. Ventilator-driven CPAP therapy was also available. The reuse of consumables for the Fisher & Paykel CPAP devices began three quarters of the way through the baseline period (December 2020), and Dräger and CareFusion consumables became unavailable due to a lack of affordability. Since early in the intervention period, 14 Vayu bCPAP systems, two Fisher & Paykel CPAP devices, and mechanical ventilators in CPAP mode were available for provision of CPAP in the ITRMC NICU. Throughout both the baseline and the intervention periods, only two staff members were able to operate the CareFusion SiPAP systems, and there was no set number of available mechanical ventilators because the NICU shares the 30 mechanical ventilators in the hospital (Mindray, Puritan Bennet, and Hamilton-G5 ventilators) with all hospital departments.

Infants admitted to the ITRMC NICU vary from the critically ill to those who are premature, have very low birth weight (LBW), or both. Premature infants are discharged from the NICU only once they reach 1.2–1.5 kg. Guidelines for initiation of CPAP therapy, NIPPV use, and intubation did not change between the baseline and intervention periods. Prophylactic application of CPAP therapy was not practiced at ITRMC at any point during the study. Surfactant was administered to neonates whose condition did not improve with a fraction of inspired oxygen (FiO_2) of 30% while receiving CPAP and to those who required intubation. Apneic infants and those in whom CPAP or NIPPV therapy failed were intubated.

2.3. Intervention

2.3.1. Introduction of Vayu bCPAP systems

At the beginning of March 2021, four Vayu bCPAP systems were introduced into the ITRMC NICU. In April 2021, 10 more Vayu bCPAP systems were added for a total of 14 devices available during the intervention period.

2.3.2. Training

Initial training in the use of the Vayu bCPAP system was performed virtually on Zoom by the Vayu Global Health Foundation implementation team. The training was conducted in English, translations were not needed. The training covered device assembly, application, troubleshooting, and reprocessing. Attendees of the virtual training session assumed the roles of master trainers in charge of cascade training in the NICU. They subsequently transferred knowledge and skills to the NICU staff via one-to-one mentorship during shifts. A link to an online certification course on the Vayu bCPAP system was provided but participation was voluntary.

2.4. Data collection

2.4.1. Demographic and clinical characteristics of the neonates

Data on all neonates admitted to the ITRMC NICU during the baseline period were collected retrospectively from patient files. Data on all neonates admitted during the intervention period were collected prospectively. Sex, birth weight, gestational age at birth, delivery method (vaginal or cesarean delivery), primary diagnosis, and vital signs [heart rate, respiratory rate, temperature, and oxygen saturation as measured by pulse oximetry (SpO_2)] were obtained for every neonate admitted to the NICU. The use of CPAP and other respiratory support therapies was recorded. A patient was recorded as a primary user of CPAP if their first form of advanced respiratory support after being admitted to the NICU was CPAP therapy. The primary diagnosis was recorded and tabulated for each NICU admission.

2.4.2. Outcomes

The primary outcome was survival to discharge. Secondary outcomes included intubation, surfactant administration, NIPPV use, length of NICU stay, and a composite neonatal adverse outcome defined as the occurrence of any of the following: death, intubation, surfactant use, or NIPPV use.

2.5. Statistical analysis

Analyses were conducted in the two groups of interest: the entire NICU population and neonates who received any form of respiratory support. Between-group differences in demographic and clinical characteristics were assessed with univariate analyses. Categorical data were presented as total numbers and percentages, and continuous variables were expressed as means (±SD). Categorical data were analyzed with the use of chi-square or Fisher's exact testing, and continuous data were analyzed with the use of a *t*-test for parametric data and the Wilcoxon rank-sum test for nonparametric data. Two-sided *P* values of less than 0.05 were considered to be statistically significant. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated as the measure of association between the exposure (introduction of the Vayu bCPAP system) and the outcomes. Differences in outcomes between the two study periods were determined with the use of logistic-regression models for binary outcomes and linear regression models for continuous outcomes. In these models, assignment to the baseline and intervention periods was the independent variable and the outcome was the dependent variable.

To account for the potential effect of confounders, analyses were adjusted for demographic and clinical characteristics that were observed to have statistically significant differences between the two study periods (using a *P* threshold of <0.10 for inclusion in the adjustment). Primary diagnoses were not included in the logistic-regression models because senior providers at the trial site indicated that many of the diagnoses were interchangeable. Since neonates were kept in the NICU until they met specific weight-gain criteria, irrespective of their clinical condition, lengths of stay were recorded but were not analyzed further. Analyses were conducted with the use of R software, version 4.2.1 (R Foundation).

2.6. Ethical considerations

The study was approved by the technical and ethical review board of ITRMC (ITRMC REC-2022-04).

3. Results

3.1. Entire NICU population

Between March 2020 and February 2022, a total of 2,003 neonates were admitted to the NICU at ITRMC: 1,024 during the baseline period and 979 during the intervention period. The two groups were similar in terms of sex, gestational age at birth, birth weight, incidence of LBW, and vital signs on admission (**Table 1**). The proportion of infants who were delivered by cesarean section was statistically significantly higher in the intervention period than in the baseline period. Of the 2,003 neonates admitted to the NICU, 639 (31.9%) received some form of respiratory support—310 (30.3%) in the baseline group and 329 (33.6%) in the intervention group. CPAP therapy was the primary respiratory intervention for 24 neonates (2.3%) in the baseline group and 129 infants (13.2%) in the intervention group ($P < 0.001$), 119 (92.2%) of whom were treated with Vayu bCPAP systems.

The introduction and implementation of the Vayu bCPAP system in the entire NICU population was associated with a significant (25%) reduction in the odds of intubation (adjusted OR: 0.75; 95% CI: 0.58–0.96; $P = 0.02$) and a significant (31%) reduction in the odds of the use of NIPPV (adjusted OR: 0.69: 95% CI: 0.50–0.96; $P = 0.026$) (**Table 2**). In the overall NICU population there were no statistically significant differences between the baseline and intervention groups with respect to survival to discharge, surfactant use, length of NICU stay, and the composite neonatal adverse outcome.

TABLE 1 Demographic and clinical characteristics of infants admitted to the NICU, before and after introduction of the Vayu bCPAP system[a].

Characteristic	Baseline period ($N = 1,024$)	Intervention period ($N = 979$)	P value
Gestational age at birth—weeks	36.7 ± 2.6	36.8 ± 2.9	0.73
Birth weight—kg	2.5 ± 0.7	2.5 ± 0.7	0.70
Birth weight <2,500 g—no. (%)	583 (56.9)	534 (54.5)	0.28
Male sex—no. (%)	531 (51.9)	527 (53.8)	0.38
Delivery method—no. (%)			<0.001
Vaginal	767 (74.9)	657 (67.1)	
Cesarean	257 (25.1)	322 (32.9)	
Vital signs on admission to the NICU			
Heart rate—beats/min	157.1 ± 9.6	158.1 ± 8.1	0.02
Breathing rate—breaths/min	62.7 ± 5.1	62.7 ± 4.8	0.78
Temperature—°C	37.0 ± 0.3	37.0 ± 0.3	0.90
SpO_2—%	95.1 ± 3.0	94.6 ± 2.2	<0.001
Primary CPAP use—no. (%)[b]	24 (2.3)	129 (13.2)	<0.001
Admission diagnosis—no. (%)			
Small for gestational age	357 (34.9)	296 (30.2)	
RDS, pneumonia, or both	286 (27.9)	232 (23.7)	
Mother had Covid-19 when infant was born	0 (0)	157 (16.0)	
Sepsis	97 (9.5)	77 (7.9)	
Prematurity	51 (5.0)	38 (3.9)	
Jaundice	66 (6.4)	32 (3.3)	
Mother had diabetes when infant was born	47 (4.6)	24 (2.5)	
Large for gestational age	26 (2.5)	27 (2.8)	
Mother had hepatitis when infant was born	26 (2.5)	22 (2.2)	
Birth asphyxia	12 (1.2)	7 (0.7)	
Other	56 (5.5)	67 (6.8)	

[a]Plus-minus values are means ± SD. The abbreviation bCPAP denotes bubble continuous positive airway pressure, Covid-19 coronavirus disease 2019, CPAP continuous positive airway pressure, NICU neonatal intensive care unit, RDS respiratory distress syndrome, and SpO_2 oxygen saturation as measured by pulse oximetry.
[b]Primary CPAP use involves use of CPAP as the primary mode of respiratory support.

3.2. Neonates receiving any form of respiratory support

A total of 310 neonates received respiratory support of any kind (: intubation, NIPPV, CPAP therapy, low-flow oxygen, low-flow compressed air, or more than one of these types of therapy) in the baseline period as compared with 329 in the intervention group (**Table 3**). CPAP therapy was the primary respiratory-support intervention for 24 of these neonates (7.7%) in the baseline group and 129 of those (39.2%) in the intervention group ($P < 0.001$). Among the neonates who received respiratory support, there were no significant differences between the two groups with respect to gestational age at birth, birth weight, sex, incidence of LBW, vital signs on admission, and delivery method.

Among infants who received any form of respiratory support, the use of a Vayu bCPAP system was associated with a significant (53%) increase in the odds of survival to discharge (adjusted OR: 1.53; 95% CI: 1.09–2.17, $P = 0.01$), a significant (48%) decrease in the odds of intubation (adjusted OR: 0.52; 95% CI: 0.38–0.71, $P < 0.001$) and NIPPV use (adjusted OR: 0.52; 95% CI: 0.36–0.76, $P < 0.001$), and a significant (40%) decrease in the odds of surfactant administration (adjusted OR: 0.60; 95% CI:

TABLE 2 Impact of Introduction of the Vayu bCPAP system on the entire NICU population[a].

Outcome	Baseline period ($N = 1,024$)[b]	Intervention period ($N = 979$)	Crude OR or Mean difference (95% CI)	P value	Adjusted OR or Mean difference (95% CI)	P value
Survival to discharge—no. (%)	902 (88.1)	880 (89.9)	1.20 (0.91 to 1.59)	0.20	1.21 (0.91 to 1.56)	0.19
Surfactant treatment—no. (%)	106 (10.4)	98 (10.0)	0.96 (0.72 to 1.29)	0.80	0.92 (0.69 to 1.23)	0.56
Intubation—no. (%)	160 (15.6)	120 (12.3)	0.75 (0.59 to 0.97)	0.03	0.75 (0.58 to 0.96)	0.02
NICU stay—days	6.9 ± 7.0	6.9 ± 8.2	0.03 (−0.53 to 0.70)	0.94	−0.03 (−0.69 to 0.64)	0.94
NIPPV use—no. (%)	96 (9.4)	69 (7.0)	0.73 (0.53 to 1.01)	0.06	0.69 (0.50 to 0.96)	0.03
Composite neonatal adverse outcome—no. (%)[c]	218 (21.3)	208 (21.2)	0.97 (0.78 to 1.20)	0.76	0.94 (0.76 to 1.17)	0.57

[a]Plus-minus values are means ± SD. NIPPV denotes nasal intermittent positive-pressure ventilation, and OR odds ratio.
[b]The group evaluated in the baseline period was the reference group.
[c]The composite neonatal adverse outcome was defined as the occurrence of any of the following events: death, intubation, surfactant use, or NIPPV use.

TABLE 3 Demographic and clinical characteristics of infants receiving Any form of respiratory support in the NICU before and after Introduction of the Vayu bCPAP system[a].

Characteristic	Baseline period (*N* = 310)	Intervention period (*N* = 329)	*P* value
Gestational age at birth—weeks	35.3 ± 3.7	35.3 ± 3.3	0.90
Birth weight—kg	2.3 ± 0.8	2.2 ± 0.8	0.17
Birth weight <2,500 g—no. (%)	167 (53.9)	200 (60.8)	0.08
Male sex—no. (%)	165 (53.2)	187 (56.8)	0.36
Delivery method—no. (%)			0.06
Vaginal	219 (70.6)	208 (63.2)	
Cesarean	91 (29.4)	121 (36.8)	
Vital signs at admission to the NICU			
Heart rate—beats/min	157 ± 9.5	158 ± 7.9	0.16
Breathing rate—breaths/min	62.9 ± 5.9	63.0 ± 4.9	0.74
Temperature—°C	37.0 ± 0.3	37.0 ± 0.3	0.46
SpO_2—%	94.3 ± 4.0	94.5 ± 2.4	0.56
Primary CPAP use—no. (%)	24 (7.7)	129 (39.2)	<0.001
Admission diagnosis			
RDS	97 (31.3)	112 (34.0)	
Pneumonia	92 (29.7)	101 (30.7)	
Sepsis	78 (25.2)	61 (18.5)	
Birth asphyxia	12 (3.9)	5 (1.5)	
Other	31 (10.0)	50 (15.2)	

[a]Plus-minus values are means ± SD.

0.40–0.89, $P = 0.011$) and the composite neonatal adverse outcome (adjusted OR: 0.60; 95% CI: 0.42–0.84, $P = 0.003$) (Table 4). The mean length of NICU stay was similar in the two study groups.

4. Discussion

This two-year study compared outcomes before and after introduction and implementation of Vayu bCPAP systems in the NICU at a public regional referral hospital in the Philippines. We found that the use of this system was associated with a significant reduction in intubation and NIPPV among the entire NICU population and a significant increase in survival to discharge and a significant decrease in intubation, surfactant administration, NIPPV use, and the composite neonatal adverse outcome among the subgroup of infants who received any form of respiratory support. The use of CPAP in the NICU was 5.6 times higher after introduction of the Vayu bCPAP system than in the use in the baseline period.

The increased use of CPAP in the intervention period was associated with a simultaneous decrease in intubation and NIPPV use. Although several options for CPAP were theoretically available before the introduction of Vayu systems, as in most hospitals throughout the world, the available medical devices listed in the inventory were often not consistent with clinical availability (14). The Vayu bCPAP system was specifically engineered to overcome common barriers to CPAP use such as a lack of consumables, bioengineering support, and medical air and the need for uninterrupted electricity, among other critical features (13). In the ITRMC NICU, there were no changes to staffing or clinical guidelines between the two study periods, and there was no instruction to use CPAP with greater frequency. The introduction of Vayu bCPAP systems appeared to directly cause a major shift from the use of invasive and noninvasive positive-pressure ventilation to CPAP.

In the overall NICU population, less than one third of the neonates (31.9%) over both study periods had respiratory distress for which any form of respiratory treatment was received.

TABLE 4 Impact of Introduction of the Vayu bCPAP system on infants receiving Any form of respiratory support[a].

Outcome	Baseline period (*N* = 310)[b]	Intervention period (*N* = 329)	Crude OR or Mean difference (95% CI)	*P* value	Adjusted OR or Mean difference (95% CI)	*P* value
Survival to discharge—no. (%)	203 (65.5)	245 (74.5)	1.54 (1.09 to 2.16)	0.01	1.53 (1.09 to 2.17)	0.01
Surfactant treatment—no. (%)	106 (34.2)	98 (29.8)	0.82 (0.59 to 1.14)	0.23	0.60 (0.40 to 0.89)	0.01
Intubation—no. (%)	160 (51.6)	120 (36.5)	0.54 (0.39 to 0.74)	<0.001	0.52 (0.38 to 0.71)	<0.001
NICU stay—days	13.6 ± 8.8	13.5 ± 11.1	−0.075 (−1.63 to 1.48)	0.93	−0.18 (to 1.74 to 1.39)	0.82
NIPPV use—no. (%)	96 (31.0)	69 (21.0)	0.59 (0.41 to 0.85)	0.004	0.52 (0.36 to 0.76)	<0.001
Composite neonatal adverse outcome—no. (%)[c]	203 (65.5)	188 (57.1)	0.73 (0.51 to 0.97)	0.03	0.60 (0.42 to 0.84)	0.003

[a]Plus–minus values are means ± SD.
[b]The group evaluated in the baseline period was the reference group.
[c]The composite neonatal adverse outcome was the occurrence of any of the following events: death at discharge, intubation, surfactant use, and NIPPV use.

Although there were significant reductions in the odds of intubation and NIPPV use (25% and 31%, respectively) after the introduction of bCPAP systems, given that the majority of neonates in the overall NICU population (68.1%) had nonrespiratory clinical conditions, it is not surprising that there were no statistically significant differences in survival to discharge or surfactant use.

To better evaluate the impact of introduction of Vayu bCPAP systems in neonates who could potentially benefit from the intervention, we conducted an analysis involving the population of newborns who had received any form of respiratory support in both the baseline and intervention groups. Since there were no major differences between these two groups with respect to patient clinical characteristics or the environments ecosystems in which they received care, the 53% ($P = 0.01$) improved survival could be attributed to the sharp increase in the use of CPAP, and the simultaneous 48% decrease in the odds of both intubation and NIPPV use may have been afforded by the introduction of the bCPAP system.

An additional effect of the introduction of the Vayu system was the reduction in surfactant administration. In the population of neonates who had received any form of respiratory support, the odds of surfactant administration decreased by 40% ($P = 0.01$) because neonates no longer had hypoxia at the frequency seen previously. The finding that fewer newborns met criteria for surfactant administration after the intervention suggests that there were considerable improvements in the clinical conditions of the newborns after introduction of Vayu systems. It is notable that the unexpected extra surfactant vials were redistributed to other hospitals in the surrounding region.

CPAP therapy has been shown to increase survival and decrease types of disability such as bronchopulmonary dysplasia in highly-resourced hospitals; however, studies conducted in low-resource settings have had mixed outcomes (15–19). The introduction of a device alone cannot improve outcomes. A medical device must be appropriate for a setting; technical support and the supply chain must be responsive to the health system's needs; interval training and mentorship around the role of the device in quality care are critical; and there must be integration of the devices into the overall health care delivery system (20).

The major strengths of this study are the rigorous methodology used in its conduct, the large number of participants relative to similar studies, the similarity in baseline characteristics in the baseline and intervention groups, and the limitation of the overall study time frame to 2 years, which decreased potential confounding factors of practice variability that may have affected patient outcomes.

Our study has some potential limitations. The outcomes in this before-and-after study may have been influenced by temporal confounders that were not measured, although the clinical setting, staffing, guidelines, and clinical characteristics of the two study groups were similar. In addition, the retrospective collection of data on the baseline group came with the inherent potential for lack of standardization in data recording. The coronavirus disease 2019 (Covid-19) pandemic influenced part of the intervention time period. The three relevant issues during the pandemic were that babies of Covid-19–positive mothers went to a separate unit and their data were included in the NICU database, health care staffing was often critically short, and no new programs were instituted other than the Vayu bCPAP system. The additional data on asymptomatic babies in the NICU database were removed in accordance with the study design in the analysis of the populations that received respiratory support, and the other two Covid-19-related issues contributed to lower or no change in the quality of clinical care. None of the Covid-19-related differences would have favored the respiratory-support intervention group. Finally, introduction of medical devices such as the Vayu bCPAP system is highly dependent on the clinical environment. Therefore, the findings from this study may not be generalizable to other settings.

Future research efforts should focus on implementation of the Vayu bCPAP system into settings where neonatal outcomes may be optimized. For example, early application in labor and delivery, use in transport, integration into lower-level facilities, and use during kangaroo mother care are all potential opportunities for quality care, but each must be evaluated for its contribution to outcomes.

In summary, introduction and implementation of the Vayu bCPAP system into the NICU of a regional referral center in the Philippines was associated with significant reductions in intubation and NIPPV use in the entire NICU population, as well as improved survival and a decreased incidence of intubation, NIPPV use, and surfactant administration among neonates who required any form of respiratory support.

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 humans were approved by Ilocos Training and Regional Medical Center Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

PR: Data curation, Formal analysis, Project administration, Writing – original draft. GB: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft. GM: Formal analysis, Writing – original draft. NR: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. AC: Formal analysis, Writing – review & editing. DG: Conceptualization, Methodology,

Supervision, Validation, Writing – review & editing. TB: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

TB is the Founder of Vayu Global Health Innovations, a public benefit company that has signed with and is accountable to the Bill and Melinda Gates Foundation, UNITAID, and World Health Organization in its commitment to global good and global access in the development of high quality ultra-low-cost bubble continuous positive airflow pressure and oxygen blender systems. Vayu Global Health Innovations played no role in the manuscript's conception, writing, or the decision to submit for publication.

The remaining 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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The novel LESS (low-cost entrainment syringe system) O_2 blender for use in modified bubble CPAP circuits: a clinical study of safety

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Background: Bubble continuous positive airway pressure (bCPAP) is used in resource-limited settings for children with respiratory distress. Low-cost modifications of bCPAP use 100% oxygen and may cause morbidity from oxygen toxicity. We sought to test a novel constructible low-cost entrainment syringe system (LESS) oxygen blender with low-cost modified bCPAP in a relevant clinical setting.

Methods: We conducted a clinical trial evaluating safety of the LESS O_2 blender among hospitalized children under five years old in rural Cambodia evaluating the rate of clinical failure within one hour of initiation of the LESS O_2 blender and monitoring for any other blender-related complications.

Findings: Thirty-two patients were included. The primary outcome (clinical failure) occurred in one patient (3.1%, 95% CI = 0.1–16.2%). Clinical failure was defined as intubation, death, transfer to another hospital, or two of the following: oxygen saturation <85% after 30 min of treatment; new signs of respiratory distress; or partial pressure of carbon dioxide ≥60 mmHg and pH <7.2 on a capillary blood gas. Secondary outcomes included average generated FiO_2's with blender use, which were 59% and 52% when a 5 mm entrainment was used vs. a 10 mm entrainment port with 5–7 cm H_2O of CPAP and 1–7 L/min (LPM) of flow; and adverse events including loss of CPAP bubbling (64% of all adverse events), frequency of repair or adjustment (44%), replacement (25%), and median time of respiratory support (44 h).

Interpretation: Overall the LESS O_2 blender was safe for clinical use. The design could be modified for improved performance including less repair needs and improved nasal interface, which requires modification for the blender to function more consistently.

KEYWORDS

pneumonia, bubble CPAP, respiratory support, hyperoxia, global health, pediatrics, medical device

Introduction

Lower respiratory tract infections (LRTIs) continue to be the leading cause of death among children under five years old worldwide (1–4). This burden is particularly significant in low-middle income countries (LMICs) in Sub-Saharan Africa and Southeast Asia (3, 4). Respiratory support is key in decreasing mortality from LRTIs. Unfortunately, many respiratory support modalities, such as ventilators or non-invasive respiratory support devices, have limited availability in LMICs due to high cost, lack of trained staff for device maintenance and repair, reliance on electricity, and lack of specialized materials and parts (5).

Continuous positive airway pressure (CPAP), a form of respiratory support, provides constant airway pressure stenting open alveoli at the end of exhalation, reducing work of breathing and improving oxygenation (6). Commercial CPAP devices cost thousands of dollars and require electricity. In the 1970's, an alternative form of CPAP, called bubble CPAP (bCPAP), was invented for neonatal use (7, 8). BCPAP uses an expiratory limb submerged in a water column which generates CPAP that approximates the pressure at the air water interface assuming minimal resistive pressure losses in the breathing circuit (9, 10). Unlike commercial CPAP, bCPAP circuits can be run without electricity using compressed air or oxygen. In multiple studies, bCPAP has been shown to successfully provide respiratory support and decrease neonatal mortality in both high-income countries (HIC) and LMICs (11–17). To address the burden of LRTI in resource-limited areas, a modified low-cost version of bCPAP has been developed using basic supplies readily found in hospitals in LMIC's (18). Promoted by the World Health Organization (WHO), this version has allowed hospitals to provide effective and safe respiratory support to young children at minimal cost [approximately 5 US dollars (USD) excluding oxygen costs] when the alternative is direct oxygen flow by nasal cannula without pressure support or spending thousands of dollars on an industry-level product (Figure 1).

One opportunity for advancement of this device is titration of the fraction of inspired oxygen (FiO_2) delivered as this low-cost design usually uses 100% oxygen. High concentrations of oxygen can have harmful effects in the brain, lungs, heart, and eyes in neonates (20–22). Indeed, current guidelines for neonatal resuscitation recommend initially using 21% oxygen in term neonates, instead of 100% oxygen in order to avoid oxygen toxicity (23). Additionally, recent data have demonstrated significant associations between increased mortality and high oxygen levels among critically ill children outside of the neonatal period (24, 25). BCPAP has largely been tested in neonates although the burden of pneumonia remains highest in children less than five years old. There is a gap in low-cost, high quality respiratory support that minimizes oxygen toxicity for these children (26). Lastly, current methods of delivering variable concentrations of oxygen are generally expensive (approximately 1,000 USD) and not available to hospitals in LMICs (27).

In 2019, our team successfully developed an oxygen blender prototype utilizing jet mixing principles (Figure 2). By passing a high-velocity fluid jet (i.e., 100% oxygen stream) past quiescent fluid (i.e., 21% oxygen in room air), viscous shear forces promote mixing of the two fluids, allowing a titrated stream (i.e., <100% oxygen) of the two fluids to flow downstream to the patient. This blender, which we have called the LESS (Low-cost Entrainment Syringe System) O_2 blender is designed to complement modified low-cost bCPAP circuit design and, like the bCPAP design, only requires common hospital supplies to build. The total cost of parts per circuit, which includes the blender and the modifications to the circuit, amounts to approximately 1.40 USD (excluding oxygen costs). Based on bench testing, the LESS O_2 blender can decrease FiO_2 to approximately 60%–70% and 40%–50% with 5 mm and 10 mm entrainment ports, respectively (28). We then tested construction among new users, which was performed in the USA and Cambodia, and found that it can be reliably constructed to generate mixed oxygen flows (29). The next step in development of this blender was to test its safety in a relevant clinical setting. We performed a clinical trial to evaluate the safety and feasibility of implementation of the LESS O_2 blender with modified low-cost bCPAP in a children's hospital in rural Cambodia in 2022.

Methods

Device development

A multidisciplinary team (clinical and engineering) began working together in 2019 to design the blender. The LESS O_2 blender utilizes the Venturi effect by funneling oxygen through a hypodermic needle that then exits near an entrainment port exposed to ambient air which facilitates blending of oxygen and room air in the delivered outflow oxygen tubing of the nasal cannula. It is designed to be constructed and assembled on site using two 3 ml syringes with rubber plunger stops, one 22-gauge hypodermic needle, oxygen tubing, super glue or tape, and a blade (i.e., scalpel/razor blade). During bench testing, delivered oxygen concentrations can be approximately 65% or 45% using the 5 mm entrainment port or 10 mm port respectively, and results were published in 2020 in the Journal of Medical Devices (28). For this study, we also used the SEAL-bCPAP modification, which minimizes leak at the nares (Figure 2) (19).

Ethics and institutional approvals

The Institutional Review Boards (IRBs) at the University of Minnesota, Boston Children's Hospital, and Chenla Children's Hospital reviewed and approved this study.

The device was exempt from Food and Drug Administration review since the device is not intended for use in the USA. Additionally, the LESS O_2 blender was given exemption from the determination protocols of the Department of Drugs and Food (DDF) in the Cambodian Ministry of Health given that the device has little to no sale potential, not intended to be sold in

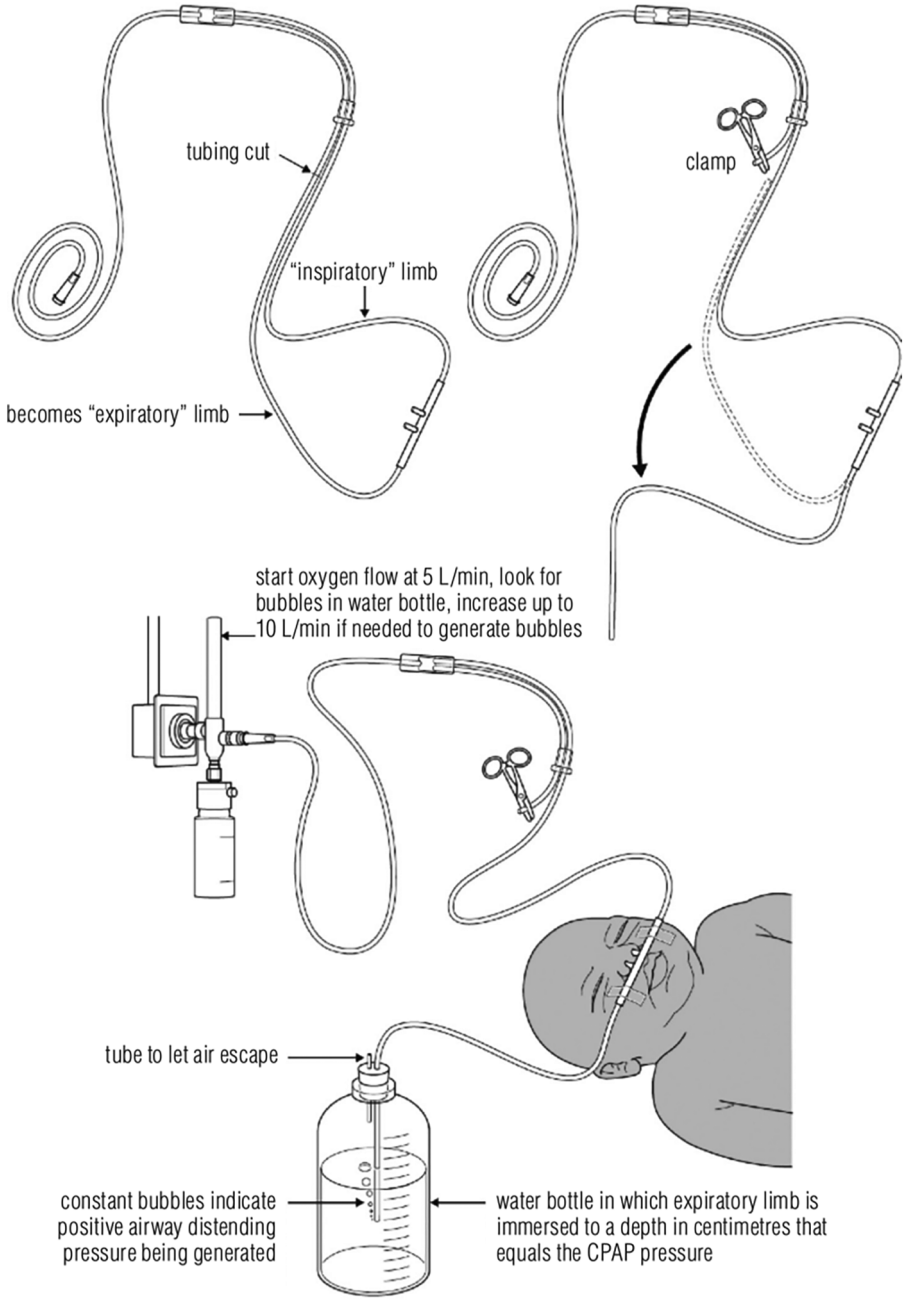

FIGURE 1
Bubble CPAP set-up. Reprinted with permission from the World Health Organization. A modified version of this circuit for older children was safety tested by Bjorklund, et al. that uses ear plugs to decrease nasal leak (19). CPAP, continuous positive airway pressure.

Cambodia; meets criteria for a low-risk device; and has no formal registration certificate from the country of export nor an associated company license given it is constructed on site.

Role of funding source

The study sponsors did not have a role in study design; collection, analysis, or interpretation of data; writing of the report; nor the decision to submit the paper for publication.

Study settings

The study took place at Chenla Children's Healthcare (CCH) located in Kratie, Cambodia, which is primarily rural and heavily affected by poverty. About one third of the residents live on <1 USD a day. Chenla Children's Healthcare runs a 30-bed pediatric ward, including six pediatric intensive care (PICU) beds and ten neonatal intensive care (NICU) beds. At the time of study initiation, there were five ventilators. There are bCPAP machines available but not enough to provide every child who is admitted

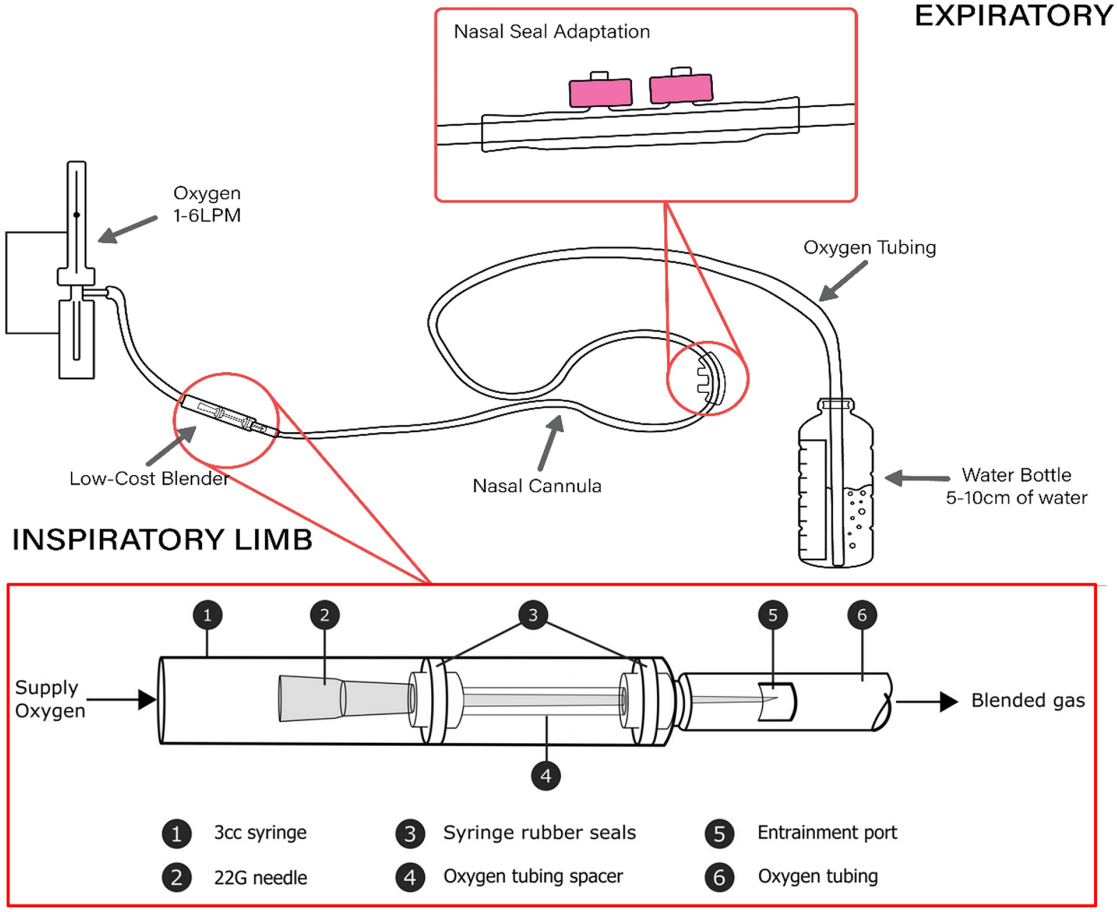

FIGURE 2
Bubble CPAP set-up with syringe oxygen blender in-line. Credit: Mara Halvorson.

for respiratory distress. Of note, in 2020 when the study was planned in pre-COVID pandemic, CCH had five bCPAP machines which increased to 18 in 2022 when the study was launched. Despite this increase, malfunctions in bCPAP machines are common and there are frequently more children requiring bCPAP than machines available.

Device training and teaching

A team of Cambodian ICU nurses was trained on the study protocol and device construction via written instruction, in-person didactics, case discussions and simulated device building prior to study initiation. Constructed blenders that functioned as expected were kept for urgent use during study enrollment. The equipment and parts necessary to construct the low-cost bCPAP circuit and the syringe blender were provided.

Study design

This study was designed as a prospective cohort feasibility and safety pilot study. Patients were enrolled from March 2022 to March 2023. Participants were eligible if they met all criteria in Table 1.

Our target sample size was 50 to obtain preliminary feasibility and safety data. Written consent from parents/guardians was obtained prior to enrollment.

Enrolled patients were initiated on modified low-cost bCPAP without the LESS O_2 blender (Figure 1). Once the patient achieved respiratory stability, which was defined as having an oxygen saturation >90% and capillary refill <2 s, the low-cost bCPAP circuit was replaced with the LESS O_2 blender circuit. Though LESS O_2 blender circuits from the training were available to use, nurses were encouraged to create new syringe blender bCPAP circuits to maximize cleanliness. Circuits were single-patient use. The TAL respiratory score was obtained on enrollment to assess the severity of respiratory distress before initiation of respiratory support (30).

After the LESS O_2 blender circuit was initiated, study nurses assessed the device 30 min later to confirm device function and again at one hour to assess for clinical failure. Nurses evaluated device function every two hours, including measurement of the FiO_2 level at the nasal cannula via an oxygen analyzer placed over one nasal prong (Analytical Industries Palm D Oxygen Analyzer). Vitals and exam findings were documented every four

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria

• 5 years of age or younger
AND
• Admission diagnosis of a lower respiratory tract infection (LRTI) such as pneumonia or bronchiolitis
  ○ For neonates (under 1 month of age), respiratory distress syndrome, transient tachypnea of the newborn, and meconium aspiration qualified for inclusion
AND
• Respiratory distress upon presentation to the hospital, defined as cough or trouble breathing plus at least one of the following
  ○ <92% despite low flow oxygen
  ○ Central cyanosis
  ○ Tachypnea
  ○ Chest indrawing
  ○ Nasal flaring
  ○ Grunting
  ○ Head nodding
  ○ Convulsions
  ○ Lethargy
  ○ Inability to breastfeed or drink
AND
• No bubble continuous positive airway pressure (bCPAP) machine is available for immediate use
	• History of asthma
	• Upper airway obstruction
	• Diaphragmatic hernia
	• Pneumothorax
	• Acute Glasgow Coma score <4
	• Cleft Palate
	• Cyanotic heart disease
	• Congenital lung disease
	• Bleeding disorders
	• Imminent death within 2 h
	• Have had abdominal or thoracic surgery

Eligible patients must have been five years old or younger, have an admission diagnosis of LRTI, and have respiratory distress. If a bCPAP machine was immediately available at the time of enrollment, the patient was not enrolled. If the patient presented with any of the exclusion criterion, the patient was not enrolled.

hours. Due to limited lab availability, the only labs obtained for study purposes were a complete blood count, malaria rapid diagnostic testing (RDT), and a bedside blood gas and electrolyte analyzer, all of which are standard of care at the site. No malaria RDT was required for neonates. Titration of the FiO_2 and CPAP levels were left to the discretion of the ordering physician with use of continuous pulse oximetry, though training was provided for which entrainment port size could be utilized.

If the blender circuit was found to be malfunctioning (e.g., lack of bubbling, twisted tubing, oxygen leak) the patients were assessed for stability. Then the study nurse would troubleshoot the device. If troubleshooting required removal of the circuit from the patient, the patient was placed on low-cost bCPAP without the blender until the blender circuit was repaired or replaced.

Outcomes

The primary study outcome was clinical failure within one hour of changing to the LESS O_2 blender circuit. Clinical failure was defined as intubation, death, transfer to a higher level of care (i.e., another hospital), or two of the following:

- Oxygen saturation <85% after 30 min of treatment
- Signs of respiratory distress, including indrawing, tracheal tugging, nasal flaring, or grunting
- Partial pressure of carbon dioxide ≥60 mmHg and pH <7.2 on a capillary blood gas

The secondary outcomes of the study included the following:

- Number of times no bubbling was noted and/or blender/bCPAP circuit required repair or replacement
- Duration of respiratory support in hours
- Adverse events related to the blender circuit (described below)
- Outcome of hospitalization

Outcomes related to functioning of the LESS O_2 blender included the following:

- Size of entrainment port
- CPAP level
- Oxygen concentration (FiO_2) of nasal cannula outflow
- Flow of oxygen from tank

Adverse events were documented in detail and were defined as either grade I or grade II, with the latter considered serious adverse events (SAE) and characterized by associated clinical decline. Adverse events could be related to the modified circuit (nasal injury, nose bleeding, aerophagia, pneumothorax, device fragmentation at circuit connections) or the blender itself (loss of CPAP, oxygen leak, device fragmentation).

Statistical analysis

Descriptive statistics (means and standard deviations or medians and IQR for continuous variables; counts and percent for categorical variables) were used to summarize patient demographics and outcomes. The clinical failure rate was estimated along with an exact binomial 95% confidence interval. Spearman correlation coefficients, Kruskal–Wallis tests and Wilcoxon rank sum tests were used to compare variables of interest with duration of respiratory support, number of repairs, and number of replacements. A linear mixed effect model was used to compare mean FiO_2 between port sizes while controlling for CPAP level and flow. A random patient effect was included to account for multiple tracking measures per patient. SAS V9.4 (SAS Institute Inc., Cary, NC) was used for the analysis.

Results

Thirty-three patients were enrolled (Figure 3). The majority were male (66.7%), less than three months old (76%), and term gestation (88%). At enrollment, 91% were deemed stable, and 65.2% had moderate respiratory distress (Table 2). The mean respiratory rate on admission was 52 breaths per minute (SD 8) and the mean oxygen saturation on admission was 93.5% (SD 6.6%).

One patient was withdrawn due to the parental request to leave against medical advice and was never placed on the LESS O_2 blender, leaving 32 participants who used the LESS O_2 blender circuit. One patient met criteria for the primary outcome of clinical failure 40 min post initiation of the LESS O_2 blender (3.1%, 95% CI = 0.1%–16.2%). Of note, this patient who failed

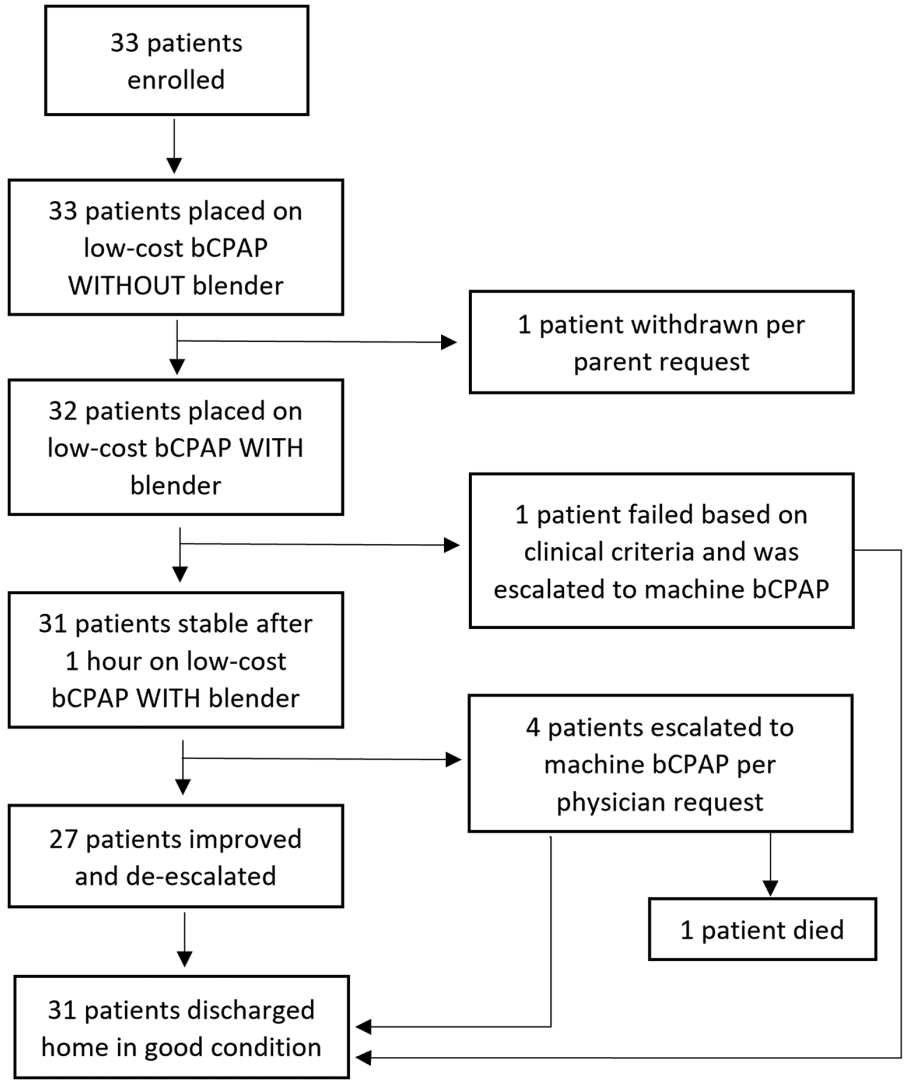

FIGURE 3
Flowchart of enrollment. bCPAP, bubble continuous positive airway pressure.

did not receive 30 min of treatment prior to escalation due to acuity of the clinical situation and physician clinical judgement (i.e., was immediately escalated and eventually intubated). One patient who died during the hospitalization from septic shock (not study related) was escalated to machine bCPAP after eight hours on the LESS O_2 blender circuit due to hypoxemia and central cyanosis felt to be due to disease progression. The remaining 31 patients, including the one who failed the blender, were eventually discharged home. Four patients were escalated to machine bCPAP on request of the physician and these transitions occurred after completing the first hour on the LESS O_2 blender. Capillary gases were obtained on all participants as per hospital protocol, but no patients met clinical failure criteria based on the results.

Most adverse events recorded were due to lack of bubbling, accounting for 64% (18/28 events in 19 patients) of the events (Table 3). Lack of bubbling was caused by leak in the circuit requiring tape or straightening of the entrainment port; incorrect entrainment port size; the expiratory limb accidentally retracting from the water; using nasal prongs too small for the child; and child crying (i.e., leak from mouth). No adverse events were documented as severe. Fourteen patients had their blender circuit repaired at least once with 10/14 requiring only one repair. Examples of repairs included reinforcing circuit leaks with tape or glue, realigning needle, untwisting entrainment port, and re-inserting expiratory limb in the water or adding more water. Eight patients required circuit replacement, with 6/8 requiring only one replacement. Most replacements were done for lack of bubbling, followed by troubleshooting without success and then replacement. Experiencing more repairs or replacements were not significantly correlated with weight, age, gender, gestational age, or TAL respiratory score. There were two nasal septal injuries which were grade I and described as "redness of the nose".

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TABLE 2 Baseline demographics and characteristics.

	$N = 33$
Gender, *n* (%)	
Female	11 (34·4)
Male	22 (68·8)
Age, *n* (%)	
<1 months	15 (45·5)
1–3 months	10 (30·3)
4+ months	8 (24·2)
Stable on enrollment, *n* (%)	30 (90·9)
Gestational age at birth, *n* (%)	
30–36 weeks	4 (12·1)
37–38 weeks	4 (12·1)
39 weeks-Full term	25 (75·8)
Weight (kg), mean (SD)	4·6 (2·0)
Oxygen saturation, mean (SD)	93·5 (6·6)
Respiratory distress based on Tal Score, *n* (%)	
Mild respiratory distress	
Moderate respiratory distress	11 (33·4)
Severe respiratory distress	22 (66·6)
	0 (0·0)
Pediatric Early Warning Sign (PEWS) Score, *n* (%)	
Mild	28 (84·8)
Moderate	5 (15·1)
Severe	0 (0·0)

Data are demonstrated as count and proportions unless otherwise noted.

TABLE 3 Summary of outcomes and adverse events.

	$N = 32$
Clinical failure, *n* (%)	1 (3·1)
Number of times no bubbling/Continuous positive airway pressure (CPAP) failure noted, *n* (%)	
0	15 (46·9)
1	9 (28·1)
2	4 (12·5)
3	4 (12·5)
Number of times blender required repair, *n* (%)	
0	18 (56·3)
1	10 (31·3)
2	3 (9·4)
3	1 (3·1)
Number of times blender required replacement, *n* (%)	
0	24 (75·0)
1	6 (18·8)
2	1 (3·1)
3	1 (3·1)
Number of patients who experienced adverse event(s), *n* (%)	19 (59·4)
Loss of CPAP, *n* (%)	15 (46·9)
Device fragmentation of blender, *n* (%)	5 (15·6)
Nasal septal injury, *n* (%)	2 (6·3)
Other, *n* (%)	6 (18·8)
Duration of respiratory support (hours)	
Median (IQR)	44·0 (13·6–78·0)
Hospitalization outcome, *n* (%)	
Die	1 (3·1)
Discharge	31 (96·9)

Thirty-two patients are represented here instead of 33 as one patient withdrew from the study before initiation of the LESS O_2 blender. Data are demonstrated as count and proportions unless otherwise noted.

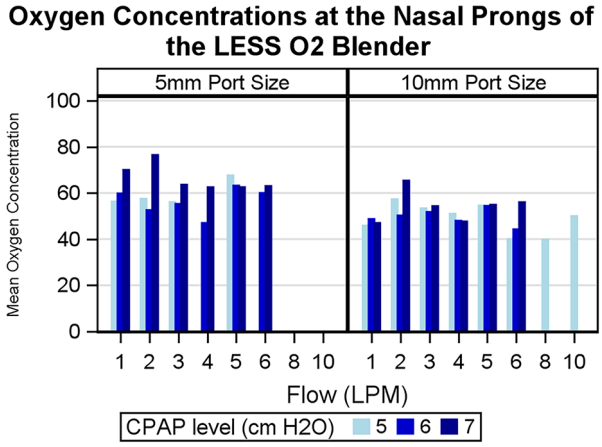

FIGURE 4
Histogram displaying measured oxygen concentrations of the gas mixture at the nasal prongs of the LESS O_2 blender circuit. The left half demonstrates measurements using a 5 mm entrainment port and the right demonstrates measurements using a 10 mm entrainment port. Oxygen concentrations are graphed across flows in liters per minute (LPM) and by CPAP level in cm H_2O. CPAP, continuous positive airway pressure.

The median duration of respiratory support was 44 h (IQR 13.6–78.0 h). The median (IQR) time to CPAP loss was 10.5 h (4.0–28.8). The median duration of support among children who experienced loss of CPAP was the same as the median duration of support among those who did not experience loss of CPAP (44 vs. 44 h, $p = 0.72$). Similarly, duration of support did not differ statistically across weight ($p = 0.27$), gestational age ($p = 0.83$), age at admission ($p = 0.89$), gender ($p = 0.37$), presence of a danger sign (e.g., inability to feed, convulsions, or decreased level of consciousness) ($p = 0.98$), or meeting sepsis criteria ($p = 0.11$).

The average FiO_2 delivered by the syringe blender circuit with any entrainment port size was 54.1% (SD 8.7%). The average minimum FiO_2 was 47.5% (SD 8.6%) and the average maximum was 61.9% (SD 12.1%). The 10 mm entrainment port was used more often than the 5 mm (70% vs. 30% of recorded port lengths, respectively). Figure 4 displays the FiO_2 generated as it varied by flow and CPAP level used. The average FiO_2 of the 5 mm port was 59.0% and the average FiO_2 of the 10 mm port was 52.1% ($p < 0.0001$).

Discussion

Our study sought to test the safety and feasibility of a novel, constructible oxygen blender designed to be used with low-cost, modified bCPAP with the SEAL-bCPAP modification. The burden of pediatric mortality from pneumonia disproportionately occurs in LMICs where respiratory support technology can be very limited. Our device is an additional tool for practitioners caring for sick children in the most resource-limited settings as it can provide both respiratory support with less oxygen toxicity

and without electricity. Overall, we found our device to be safe based on low clinical failure among the population tested, and it provided mixed oxygen concentrations to minimize hyperoxia, though circuit leaks required attention. Nurses were available to troubleshoot the device and continuous pulse oximetry was always used. On average, patients were found to have moderate respiratory distress on enrollment based on increased work of breathing and to a lesser degree, hypoxemia.

A similar study was conducted in a 2016 study in India using an aquarium air pump with bCPAP to deliver mixed oxygen concentrations of 42%–51% (31). No patients decompensated with blender use. Of note, this study has a couple of key differences from our proposed study. First, our study enrolled patients up to 5 years versus only neonates in the Indian study. Second, our device does not require electricity or purchase of a pre-made device, whereas this study in India required a reliable source of electricity and a specific type of aquarium air pump. In recent years, there have also been other groups, such as PATH and Vayu Global Health Innovations, developing low-cost oxygen blenders designed for bCPAP, which is excellent as these open up options for practitioners in LMICs (32, 33). Of note, these devices are usually either 3D-printed or injection molded in the HIC and then transported. In contrast, our blender can be constructed on site with common medical supplies, which provides an avenue for the most resource-restricted areas to have access to methods of reducing oxygen concentrations without additional funding or dependency on high-resource countries for supplies.

We originally hypothesized that the most anticipated concern with the circuit would be leaks of oxygen, leading to loss of bubbling and therefore CPAP, due to the multiple connections required in the blender's construction. Based on our findings, these leaks were largely due to the modified nasal interface. Our design requires the "implantation" of nasal prongs onto oxygen tubing, which allows for CPAP to occur since the tubing is larger bore. However, this design introduces potential leak at the site of implantation. An additional issue was that oxygen tubing is relatively inflexible (compared to smaller, more compliant nasal cannula tubing), which led to prongs repeatedly coming out of the nares when used with a physically active child. Many bCPAP circuits use large bore, high resistance tubing with short binasal prongs or a mask (9). Taken together, the LESS O_2 blender provides the advantage of being constructed on site and therefore an element of self-sufficiency. However, the constructible aspect also introduces a level of imprecision that demands close monitoring of the presence of bubbling. This also translated to increased vigilance and time spent by the nursing and physician teams to monitor the patients very closely. Therefore, use of this device requires enough medical staff to be present and attentive. Of note, six nurses identified by the on-site Cambodia-based investigator (SL) as having exceptional skill in constructing the blenders were deemed "superusers" and tasked with building the circuits if one was needed urgently (i.e., if replacement was required) or if any troubleshooting problems arose. This was a strategy we implemented in order to mitigate mechanical device problems after DSMB review at the mid-point of the study. This device is not intended to supplant a precision manufactured device. The LESS O_2 blender circuit is designed for use where the only other options are either low flow nasal cannula or low-cost, constructible bCPAP using 100% oxygen.

In a previous study, the relationships among FiO_2, flow, and CPAP level in our device were explored. Among circuits with a 10 mm entrainment port, the FiO_2 remained constant across flows 3–10 LPM and varied slightly (±3 points) across CPAP levels (1–8 cm H_2O). Conversely, circuits with a 5 mm entrainment port delivered FiO_2's that were constant unless flows were <4 LPM, at which point the FiO_2 would typically increase by 5–10 points (28). This occurred due to a lower pressure gradient with lower flows, leading to reduced entrainment of room air in the gas mixture. We noted that higher CPAP levels correlated with FiO_2, which was likely from increased back pressure resulting in less entrainment of room air as well. In this clinical study, we found similar patterns—specifically FiO_2 largely remained constant across flow rates and higher CPAP levels were associated with higher delivered FiO_2 in the circuits with only the 5 mm port. For these reasons, we advise practitioners using the LESS O_2 blender be aware that as the CPAP is increased, the FiO_2 will likely increase as well. We limited our CPAP to ≤8 cm H_2O. Flow should be increased just enough to generate gentle bubbling throughout the respiratory cycle (34).

Limitations include the inability to measure either a reduction in oxygen toxicity (i.e., free radicals) or decrease in mortality, both impractical for our purposes. Additionally, our study population was largely term infants with mild-to-moderate respiratory distress. Patients with severe respiratory distress or those >8 months old may not be adequately supported with this device. The target sample size of 50 was not achieved due to lack of enrollment by the pre-determined study end time of March 2023. Despite estimated calculations of an appropriate timeline to reach the target sample size, the COVID19 pandemic caused significant delays in both the USA and Cambodia leading to a delayed study start in 2022, at which time the hospital had acquired many more bCPAP machines which hindered higher enrollment rates. The end time of March 2023 (i.e., one year study duration) was limited by funding. Despite these barriers, the enrolled sample size was adequate and appropriate to provide valuable data about feasibility and safety.

Conclusion

The ability of the LESS O_2 blender to reliably deliver blended oxygen and reduce the burden of hyperoxia is a major benefit of its use. Leaks noted in the circuit were the most frequent issue. If the bubbling is not present constantly (34), practitioners should inspect for leaks at the nasal cannula, the blender housing connections, and/or the entrainment port. The instructions for device use and construction are included with this publication (See Supplementary Materials). The authors intend for the LESS O_2 blender to be open source and available to learn, use, and modify as needed by providers around the world.

As next steps, our team plans on improving the nasal interface and identifying ways to modify the oxygen tubing such that leaks will be minimized but that also less handling by the medical staff during use may be required.

The LESS O_2 blender is ready to use in the field for practitioners caring for children in very resource-limited settings, such as areas without reliable electricity, compressed air, limited international bandwidth, or restricted funding. We emphasize that medical staff should remain attentive to the presence of bubbling and the integrity of the device if it is to be used and that continuous oximetry should be placed on the patient. Additionally, the instructions and guidelines included in this publication should be carefully read before deciding to use (See Supplementary Materials). Currently, there is no low-cost oxygen blender for bubble CPAP that can be assembled on site to our knowledge, allowing the LESS O_2 blender to address this current critical gap.

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 humans were approved by the Boston Children's Hospital Institutional Review Board (IRB), University of Minnesota IRB, and Chenla Children's Ethic Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AW: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SrL: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. TS: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. GF: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. ScL: Formal Analysis, Resources, Software, Writing – review & editing. AB: .

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AW was affiliated with the University of Minnesota during the conception and start of the trial, with Boston Children's Hospital during and at the conclusion of the trial, and with Hennepin Healthcare currently.

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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1313781/full#supplementary-material

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Factors associated with perinatal and neonatal deaths in Sao Tome & Principe: a prospective cohort study

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Background: Neonatal mortality reduction is a global goal, but its factors are seldom studied in most resource-constrained settings. This is the first study conducted to identify the factors affecting perinatal and neonatal deaths in Sao Tome & Principe (STP), the smallest Central Africa country.

Methods: Institution-based prospective cohort study conducted at Hospital Dr. Ayres Menezes. Maternal-neonate dyads enrolled were followed up after the 28th day of life ($n = 194$) for identification of neonatal death-outcome ($n = 22$) and alive-outcome groups ($n = 172$). Data were collected from pregnancy cards, hospital records and face-to-face interviews. After the 28th day of birth, a phone call was made to evaluate the newborn's health status. Crude odds ratios and corresponding 95% confidence intervals were obtained. A p value <0.05 was considered statistically significant.

Results: The mean gestational age of the death-outcome and alive-outcome groups was 36 (SD = 4.8) and 39 (SD = 1.4) weeks, respectively. Death-outcome group ($n = 22$) included sixteen stillbirths, four early and two late neonatal deaths. High-risk pregnancy score [cOR 2.91, 95% CI: 1.18–7.22], meconium-stained fluid [cOR 4.38, 95% CI: 1.74–10.98], prolonged rupture of membranes [cOR 4.84, 95% CI: 1.47–15.93], transfer from another unit [cOR 6.08, 95% CI:1.95–18.90], and instrumental vaginal delivery [cOR 8.90, 95% CI: 1.68–47.21], were factors significantly associated with deaths. The odds of experiencing death were higher for newborns with infectious risk, IUGR, resuscitation maneuvers, fetal distress at birth, birth asphyxia, and unit care admission. Female newborn [cOR 0.37, 95% CI: 0.14–1.00] and birth weight of more than 2,500 g [cOR 0.017, 95% CI: 0.002–0.162] were found to be protective factors.

Conclusion: Factors such as having a high-risk pregnancy score, meconium-stained amniotic fluid, prolonged rupture of membranes, being transferred from another unit, and an instrumental-assisted vaginal delivery increased 4– to 9–fold the risk of stillbirth and neonatal deaths. Thus, avoiding delays in prompt intrapartum care is a key strategy to implement in Sao Tome & Principe.

KEYWORDS

neonatal mortality, perinatal mortality, stillbirth, neonatal death, Sao Tome & Principe

Introduction

The first 28 days of life—the neonatal period—are the most vulnerable days for a child's survival (1, 2). Even nowadays, a significant number of babies die before birth, never having the chance to take their first breath (1, 2). The terminology used depends on the time of death. Perinatal mortality includes stillbirths and early neonatal deaths (ENND), indicating the death of a live newborn before the age of seven completed days (1). Late neonatal deaths (LNNDs) are those that occur after 7 days to 28 completed days of birth (2).

Globally, perinatal mortality accounts for three-fourths of deaths during the neonatal period (3, 4). More than half of the cases of stillbirths occur when pregnant women are in labor, and these deaths are directly related to the lack of skilled care at this critical time (5, 6). On the other hand, the largest contributors to neonatal mortality (ENND plus LNND) are complications of preterm birth, birth asphyxia, infection, and congenital malformations although they can differ depending on the country context (7).

Only in the last two decades, mainly after Lawn et al. published article titled "4 million neonatal deaths: When? Where? Why?" (8), attention started to be given to the neonatal period in developing countries although stillbirths are still invisible and missing from the Sustainable Development Goals (SDG) agenda (5, 9, 10). It urges to highlight that stillbirths and newborn deaths account for twice as many deaths as malaria and human immunodeficiency virus (HIV) infection combined but have received much less awareness and funding in these resource-constrained countries (8, 9).

Understanding the causes of stillbirths (fetal deaths) is also complex, as there are many promoting and interacting factors (11). In most low –to medium—income countries (LMICs), it is difficult to determine the exact reason for the stillbirth; therefore, the cause of death is often classified as "unexplained" (5). The definition of stillbirth used in this study was the WHO/ICD (for international comparison and reporting) as a baby born without any signs of life at or after 28 weeks of gestation or at least 1,000 g in birth weight (9, 12). Intrapartum stillbirth was defined as a dead-born fetus where intrauterine death occurred after the onset of labor and before birth (fresh stillbirth) (9). Antepartum stillbirth is a dead born fetus where intrauterine death occurs before the onset of labor (macerated stillbirth) (9). Researchers report that different risk factors for fetal death, such as maternal factors (advanced maternal age, high pre-pregnancy body mass index, smoking, low socioeconomic status), obstetric history (grand multiparity, previous stillbirth), antepartum factors (fewer than four antenatal visits, fetal growth restriction, maternal anemia, maternal fever and infections, antepartum hemorrhage, hypertension), and intrapartum factors (preterm birth, extremes of neonatal birth weight, cesarean delivery, operative vaginal delivery, and assisted breech delivery), are all factors that have been reported in various studies as causes of stillbirths (6, 11, 13–16).

Sao Tome & Principe (STP) is a LMIC with low HIV/AIDS prevalence and a malaria pre-elimination phase (17, 18). On the other hand, perinatal and neonatal mortality rates are considered a public health problem, given that neonatal deaths account for approximately 43% of all under5 deaths (19). At the time this study was initiated in 2016, there was an annual rate of 22 stillbirths and 22 newborn deaths per 1,000 livebirths (19). There is an established antenatal care (ANC) service in STP, with a 98% rate of women seen at least once by a skilled health provider during pregnancy and a 95.4% rate of deliveries occurring in health units (18). There is no health insurance policy in the country or any private maternity units. In STP, there are three to four obstetricians, one anesthesiologist and one to two general doctors who provide care to the neonates (20). There are no neonatologists in the country. The midwives in the labor ward are responsible for the initial resuscitation of normal deliveries, and doctors from the pediatric department are called to the labor ward to attend babies in distress.

The HAM maternity unit has a facility-based clinical care unit for ill newborn babies, but there is no neonatal or child intensive care unit in the country.

We are aware that the concept of knowing what works in terms of reducing perinatal and neonatal mortality is complicated by a huge diversity of country contexts and of determinants of maternal and neonatal health (21–24). However, according to Lawn and other authors, identifying and addressing avoidable causes of neonatal death is possible even in poorly functioning health systems, justifying our current study (8, 9). Answering—why, when, and where—newborns die in Sao Tome & Principe will enable the design of appropriate planning to prevent this major public health problem since, for appropriate prevention of fetal and newborn mortality, data pertaining to its determinants are important.

To the best of our knowledge, this is the first study to assess perinatal and neonatal deaths in STP, and it was undertaken within the context of a broader project on neonatal adverse birth outcomes (ABOs) and other maternal problems in this LMIC (25–31).

Therefore, we conducted a prospective cohort study to identify the most important factors associated with death among newborns delivered at HAM.

Materials and methods

Study design and period

An institution-based prospective cohort study was conducted at Hospital Dr. Ayres de Menezes (HAM) for mother-neonate dyads followed up until the 28th day after delivery (neonatal period). Recruitment of participants (mother-newborn dyad) occurred from July 2016 to November 2018.

Setting

The archipelago of Sao Tome & Principe is one of the smallest sub-Saharan African (SSA) countries, with approximately 200.000 inhabitants and a total land surface of approximately 1,001 km^2 on two islands (Sao Tome and a smaller island named Principe) (17, 18). As a tertiary healthcare facility, HAM receives the most complicated cases from facilities in lower levels of care. The Neonatal Care Unit (NCU) receives high-risk babies delivered within the institution and referrals from other health facilities or

from home with a total capacity to admit six babies. This unit, like others in SSA settings, is basic and able to manage simple neonatal complications such as hypothermia, feeding problems and sepsis suspicion. Although NCU was rebuilt in 2016, there is still a lack of continuous positive airway pressure therapy, surfactant therapy and enteric feeding for assisting sick babies.

Study population and follow-up

All mother-neonate dyads admitted to the HAM maternity unit for childbirth constituted the source population whereas the study populations were selected neonates delivered in the HAM maternity unit during the study period. During the study period, 4,540 deliveries were recorded, corresponding to 450 cesarean deliveries and 3,740 normal vaginal births.

The inclusion criteria for participants were as follows: (1) all neonates delivered at HAM with a gestational age of 28 weeks or more and (2) newborns who were born outside the hospital but were later admitted at HAM within the first 12 h of life. A total of 535 newborns were initially enrolled.

The exclusion criteria included the following: (1) all neonates delivered at HAM with a gestational age of less than 28 weeks, (2) newborns whose mothers had no antenatal pregnancy card, (3) newborns whose mothers had cognitive impairment. The newborn was also excluded if his health status was unknown at his twenty-eight days of life.

Consenting participants in the sample were followed up (mother-newborn dyad) throughout their stays until hospital discharge. The survival status of neonates after discharge was ascertained by making a follow-up mobile phone call at the end of the neonatal period. Those who could not be reached by phone after four attempts in different weeks were taken as nonrespondents, and the mother-newborn dyad was excluded. A flowchart of participation in the study is shown in Figure 1.

Sampling method

This is a substudy undertaken to estimate adverse birth outcomes (ABOs) and related risk factors in the country.

The sample size initially calculated for the broader project, using Raosoft® (http://www.raosoft.com/samplesize.html), was based on the formula for sample size and margin of error from the software, reaching the minimum sample size of S = 355, with 355 (95%) and 579 (99%) interval confidence. The original study included 537 mother-neonate dyads enrolled based on the following assumptions: two-sided 95% confidence level, power of 80% to detect an odds ratio of at least two for ABO. Since the sample size was not calculated for present outcomes, to assess perinatal and neonatal deaths, a power analysis was performed, varying from 77% to 87% for outcomes such as gestational age (GA < 37) for this study. In this study, 194 mother-neonate dyads were included. Participants were selected through random sampling. Each morning, from the pile of mother's medical folders, every second interval folder was selected and then carried on requesting contentment for enrollment. To guarantee a sample with few biases and effects by means of confounding variables, the study was conducted in different months (two weeks every two other months), avoiding seasonal interference (rain season and malaria period). Women were interviewed only after the delivery, although the invitation and consent were obtained during her admission to the maternity unit before birth (live birth or stillbirth).

Selection of groups: death and alive neonatal outcome

A total of 194 mother-neonate dyads were included and were divided into two groups according to the newborn status (alive vs. dead) at the end of the neonatal period. Newborns who died before the 28th day of life (death-outcome group with stillbirths

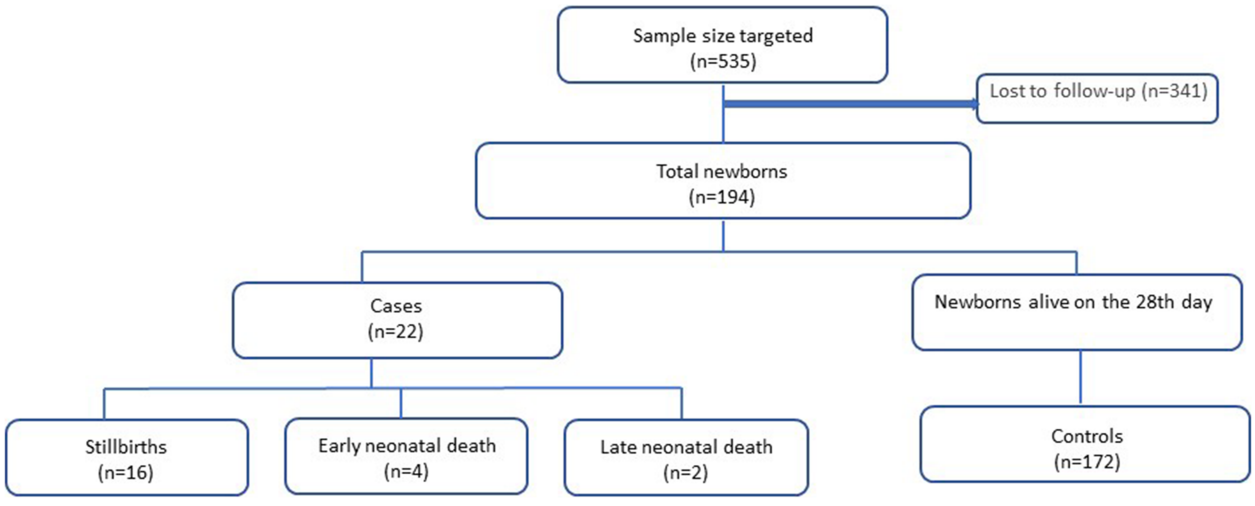

FIGURE 1
Flowchart of participation in the study.

included; $n = 22$) were compared with newborns alive at the 28th day of life (alive-outcome group; $n = 172$) concerning maternal, antepartum, and intrapartum characteristics.

Study variables

The dependent variables for the study were death (stillbirth and neonatal—early and late-death) and live newborns.

For neonates who died at home after discharge, probable causes of death were assigned by the principal investigator (pediatrician) using the International Statistical Classification of Diseases and Related Health Problems ICD-11 coding. For neonates who died in the HAM, the cause of death was assigned by physicians, who work in the hospital, and confirmed by the principal investigator.

The independent variables tested in this study included factors grouped into five categories: (1) newborns' maternal sociodemographic factors (age, educational status, occupation, marital status, partner's education, and residence); (2) preconception factors (previous contraceptive utilization), plus current obstetric condition (gravidity, parity, previous abortion and stillbirth, previous cesarean section and preceding birth interval); (3) ANC service (number of visits, gestational age at first ANC visit, obstetric ultrasound, number of fetuses in the ultrasound) plus antepartum factors as positive ANC screenings [high-pregnancy risk score, maternal anemia as hemoglobin concentration <11 g/dl, bacteriuria, hyperglycemia, Rh incompatibility, intestinal parasitic infection (IPI), malaria, HIV, syphilis, hepatitis B virus and sickle cell]; (4) health facility-related factors (being transferred from another unit, who assisted the delivery and partograph use) plus intrapartum factors as mode of delivery and complications (fetal malpresentation (32), umbilical cord complication (33), prolonged rupture of membranes (PROM) (34, 35), meconium-stained amniotic fluid (36), postpartum hemorrhage as bleeding >500 ml, preeclampsia defined as hypertension ≥140/90 mmHg and proteinuria in dipsticks in women who were normotensive at ANC, and obstructed labor (37); (5) newborns characteristics as (gestational age, sex, birth weight) and complications [intrauterine growth restriction (IUGR), congenital anomalies, infectious risk, neonatal resuscitation, fetal distress at birth, birth asphyxia and admission at NCU] (38–40).

Data collection

Data on antepartum, intrapartum, and postpartum characteristics of participants were gathered and collected from ANC pregnancy cards, obstetric maternal and newborn clinical records. For antepartum data, relevant details of the perinatal history and antenatal period were collected systematically from the ANC pregnancy card. Intrapartum data were collected from labor follow-up sheets, delivery summaries and maternal medical records. Postpartum data were abstracted from newborn birth charts and/or newborn medical records if admitted to the NCU.

Maternal sociodemographic characteristics were supplemented with a structured administered questionnaire through a face-to-face interview of the mothers 12–24 h after delivery, similar to other studies from LMICs (41).

Data quality alive-outcome group

The questionnaires were administered in Portuguese, the country national language. The questionnaire was pretested at HAM one month before data collection in 23 mothers, and modification was made based on the pretest result, mainly adjusting terminology for more culturally friendly terms. Womeńs consent to participate in the study was obtained at the time of admission at HAM, but the interview was held after a woman was stabilized and ready to be discharged. Continuous follow-up and supervision of data collection were made by the supervisors. The collected data were checked daily for completeness. The principal investigator (pediatrician) executed and was responsible for all main activities as follows: (1) obtaining consent and enrollment of the participants, (2) data collection from antenatal cards plus maternal clinical and newborns' records, (3) newborns' clinical observation (for diagnosis confirmation), (4) face-to-face interviews, (5) administering all phone interviews and (6) data collection entry into the database.

Data management

The anonymity and safety of the participants were ensured. Data were secured in a confidential and private location. Participants were referred to by identification numbers, and the informed consent forms were kept separate from the questionnaires. Both could only be linked by a coding sheet available only to the principal investigator.

Data analysis

Data were entered into the QuickTapSurvey app (©2010–2021 Formstack), and the dataset was exported to Excel for cleaning and further analysis using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and Stata 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). All data were checked for completeness and accuracy by the principal investigator and a qualified biostatistician.

Descriptive statistics, namely, frequencies and percentages were estimated. For binary variables, crude odds ratios estimates with 95% confidence intervals (95% CI) were obtained from corresponding contingency tables, and for categorical variables with more than two categories, exact logistic regression was used. In this study, the neonatal death-

outcome group was coded as 1, and the neonatal alive-outcome group was coded as 0. The proportion of missing data ranged from 0.8 to 10% across variables, and missing values higher than 10% were described in the analysis. A level of significance $\alpha = 0.05$ was considered.

Results

A total of 194 newborns were followed up during their first 28 days of life. In this study, the newborn's mean gestational age (GA) was 38.86 weeks with a standard deviation (SD) of 2.26 (minimum 28–maximum 42 weeks). The death-outcome group ($n = 22$) had a mean GA and birth weight of 36 (SD = 4.83) and 2,515 (SD = 997) g, respectively, while their counterparts (172 in the alive-outcome group) had 39 (SD = 1.41) weeks and 3,209 (SD = 507) g, respectively. The mean maternal age was 27.14 years, with a SD of 6.86 (minimum 15–maximum 43) years old. The mean maternal age for the death-outcome group and alive-outcome group was 30.73 (SD = 7.45) and 26.68 (SD = 6.66) years, respectively.

The death-outcome group under-study included 16 stillbirths (72.7%), four (18%) ENND and two (9%) LNND. Stillbirths were 69% intrapartum stillbirths (fresh stillbirths), and 31% were antepartum stillbirths (macerated stillbirths). Stillbirth characteristics are further described in Supplementary Additional File S1, and the early and late neonatal deaths (ENND and LNND) are described in Supplementary Additional File S2.

The maternal characteristics as well as antepartum, intrapartum, and postpartum factors for the total of the participants and for the death-outcome group vs. the alive-outcome group are described in Tables 1, 2.

There were no maternal deaths in this study, with a total of 2 maternal near-misses occurring in the stillbirths' mother's death-outcome group numbers 5 and 11 that needed hysterectomy intervention due to atonic uterus with major obstetric hemorrhage.

Factors associated with perinatal and neonatal deaths

Crude odds ratios were estimated to assess the association of perinatal and neonatal deaths with several characteristics (Tables 1, 2). Results of this analysis showed that meconium-stained amniotic fluid, prolonged rupture of membranes, transfer from another unit, and instrumental vaginal delivery were significantly associated with perinatal and neonatal deaths.

Sociodemographic factors

A maternal secondary education level (cOR 0.162, 95% CI 0.46–0.566, $p = 0.002$) and a baby's father secondary education level (cOR 0.140, 95% CI 0.029–0.67, $p = 0.006$) were found to be protective factors for perinatal and neonatal deaths.

Antepartum factors

The odds of perinatal and neonatal deaths were three times higher among mothers classified as having a high-pregnancy risk (cOR 2.91, 95% CI 1.18–7.22, $p = 0.017$). Mothers without hemoglobin test during the ANC follow-up had a higher risk of having a perinatal and neonatal death (cOR 5.68, 95% CI 1.89–17.05, $p = 0.004$) than those without anemia.

Health facility-related factors

The odds of perinatal and neonatal deaths were six times higher among mothers transferred from another unit compared to those directly admitted at HAM maternity (cOR 6.08, 95% CI 1.95–18.90, $p = 0.004$).

Intrapartum factors

PROM as well as meconium-stained amniotic fluid were other intrapartum factors, with the odds of deaths being almost five times higher for newborns whose mothers had a PROM (cOR 4.84, 95% CI 1.47–15.93, $p = 0.016$), and four times higher for those with a meconium-stained amniotic fluid (cOR 4.38, 95% CI 1.74–10.98, $p = 0.002$).

For the mode of delivery, having an instrumental assisted delivery was associated with an eightfold higher risk of perinatal and neonatal death (cOR 8.90, 95% CI 1.68–47.21, $p = 0.020$).

Newborns' factors

Newborns with intrauterine growth restriction had a twenty-one-fold higher risk of death (cOR 21.13, 95% CI 4.82–92.59, $p < 0.001$), and newborns with an infectious risk had almost sevenfold higher odds of dying (cOR 6.61, 95% CI 2.57–16.98, $p < 0.001$). Regarding newborn characteristics, female neonates (cOR 0.38, 95% CI 0.14–1.00, $p = 0.044$) and birth weight greater than 2,500 g and lower than 3,999 g (cOR 0.017, 95% CI 0.002–0.162, $p < 0.001$), and greater than 4,000 g (cOR 0.028, 95% CI 0.001–0.564, $p = 0.034$) were protective factors against perinatal and neonataldeaths.

Postpartum characteristics were only assessed for a total of six death-outcome group since sixteen stillbirths were not further included for analysis. Performance of neonatal resuscitation, fetal distress at birth (APGAR score at first-minute inferior to seven), birth asphyxia, and admission to the neonatal care unit were all related to an increased risk for neonatal death (Table 2).

TABLE 1 Univariable analysis of perinatal and neonatal deaths among newborns admitted at HAM, Sao Tome & Principe ($n = 194$; death-outcome group = 22 and alive-outcome group = 172).

Variables	Categories	Total	Death-outcome group	Alive-outcome group	cOR	(95%) CI	*p* value
		n = 194	*n* = 22	*n* = 172			
			n (%)	*n* (%)			
Sociodemographic characteristics							
Mother's age	14–19	28 (14.4)	3 (13.6)	25 (14.5)	1		
	20–34	131 (67.5)	11 (50.0)	120 (69.8)	0.765	0.183–4.578	0.925
	≥35	35 (18)	8 (36.4)	27 (15.7)	2.436	0.510–15.842	0.355
Mother's education	None + primary	106 (54.6)	19 (86.4)	87 (50.6)	1		
	Secondary	88 (45.4)	3 (13.6)	85 (45.4)	0.162	0.046–0.566	**0.002**
Mother's occupation	Unemployed	139 (72.0)	16 (72.7)	123 (71.9)	1		
	Employed	54 (28)	6 (27.3)	48 (28.1)	0.961	0.355–2.601	0.937
Marital status	Union/married	124 (63.9)	14 (63.6)	110 (64)	0.986	0.392–2.482	0.977
	Single	70 (36.1)	8 (36.4)	62 (36)	1		
Baby's father education	None + primary	63 (41.7)	9 (81.8)	54 (38.6)	1		
	Secondary	88 (58.3)	2 (18.2)	86 (61.4)	0.140	0.029–0.67	**0.006**
Residence[a]	Urban	92 (48.2)	9 (45)	83 (48.5)	0.867	0.342–2.200	0.817
	Rural	99 (51.8)	11 (55)	88 (51.5)	1		
Preconceptional							
Contraception previous use	Yes	38 (24.8)	3 (20)	35 (25.4)	0.736	0.196–2.760	0.763
	No	115 (75.2)	12 (80)	103 (74.6)	1		
Obstetric history							
Gravidity	1	42 (21.6)	4 (18.2)	38 (22.1)	1		
	2–5	100 (51.5)	8 (36.4)	92 (53.5)	0.827	0.206–3.981	0.995
	≥5	52 (26.8)	10 (45.5)	42 (24.4)	2.243	0.585–10.628	0.306
Parity	0	53 (27.3)	5 (22.7)	48 (27.9)	1		
	1–4	121 (62.4)	12 (54.5)	109 (63.4)	1.057	0.324–4.045	1.000
	≥5	20 (10.3)	5 (22.7)	15 (8.7)	3.140	0.631–15.764	0.186
Previous abortion	Yes	59 (30.4)	6 (27.3)	53 (30.8)	0.842	0.312–2.272	0.734
	No	135 (69.6)	16 (72.7)	119 (69.2)	1		
Previous stillbirth	Yes	17 (8.8)	4 (18.2)	13 (7.6)	2.718	0.801–9.225	0.109
	No	177 (91.2)	18 (81.8)	159 (92.4)	1		
Poor birth spacing[b]	Yes	39 (20.1)	6 (27.3)	33 (19.2)	1.580	0.574–4.346	0.399
	No	155 (79.9)	16 (72.7)	139 (80.8)	1		
Antenatal care							
GA at first ANC visit	≤12	98 (60.5)	6 (27.3)	92 (53.5)	1		
	>12	58 (35.8)	9 (40.9)	55 (32)	2.509	0.847–7.430	0.088
Number of ANC visits	1–4	19 (10.1)	2 (10)	17 (10.1)	1		
	5–7	84 (44.4)	16 (80)	68 (40.2)	1.988	0.402–19.493	0.609
	≥8	86 (45.5)	2 (10)	84 (49.7)	0.207	0.014–3.035	0.298
Obstetric ultrasound	0	73 (38.4)	7 (35)	66 (38.8)	1		
	1	87 (45.8)	12 (60)	75 (44.1)	1.505	0.511–4.792	0.570
	2	30 (15.8)	1 (5)	29 (17.1)	0.328	0.007–2.745	0.524
Twin pregnancy	Yes	14 (7.2)	0	14 (8.1)	-	-	0.375
	No	180 (92.8)	22 (100)	158 (91.9)	1		
Antenatal care screenings							
High-pregnancy risk[c]	Yes	70 (36.1)	13 (59.1)	57 (33.1)	2.914	1.176–7.220	**0.017**
	No	124 (63.9)	9 (40.9)	115 (66.9)	1		
Maternal disease during pregnancy[d]	Yes	123 (63.4)	11 (50)	112 (65.1)	0.624	0.220–1.809	0.448
	No	66 (34)	9 (40.9)	57 (33.1)	1		
	Missing	5 (2.6)	2 (9.1)	3 (1.7)	4.100	0.304–41.348	0.337
Maternal anaemia[e]	Yes	59 (30.4)	6 (27.3)	53 (30.8)	1.729	0.438–6.830	0.531
	No	98 (50.5)	6 (27.3)	92 (53.5)	1		
	Not tested	37 (19.1)	10 (45.5)	27 (15.7)	5.588	1.666–20.543	0.004
Bacteriuria	Yes	62 (32)	5 (22.7)	57 (33.1)	0.593	0.208–1.690	0.324
	No	132 (68)	17 (77.3)	115 (66.9)	1		

(*Continued*)

TABLE 1 Continued

Variables	Categories	Total	Death-outcome group	Alive-outcome group	cOR	(95%) CI	*p* value
		n = 194	*n* = 22	*n* = 172			
			n (%)	*n* (%)			
Hyperglycaemia[f]	Yes	8 (4.1)	1 (4.5)	7 (4.1)	1.122	0.132–9.578	1.000
	No	186 (95.9)	21 (95.5)	165 (95.9)	1		
Rh incompatibility	Yes	7 (3.6)	0	7 (4.1)	-	-	1.000
	No	187 (96.4)	22 (100)	165 (95.9)	1		
IPIs	Yes	98 (50.5)	8 (36.4)	90 (52.3)	0.521	0.208–1.305	0.159
	No	96 (49.5)	14 (63.6)	82 (47.7)	1		
Malaria	Yes	1 (0.5)	0	1 (0.6)	-	-	1.000
	No	193 (99.5)	22 (100)	171 (99.4)	1		
HIV	Yes	2 (1.0)	1 (5.0)	1 (0.6)	1		
	No	192 (99)	19 (95)	163 (99.4)	0.123	0.007–2.037	0.206
HsAg positive	Yes	6 (3.1)	2 (9.1)	4 (2.3)	1		
	No	113 (58.2)	10 (45.5)	103 (59.9)	0.194	0.032–1.195	0.112
Sickle cell positivity[g]	Yes	13 (6.8)	1 (4.5)	12 (7.0)	0.631	0.078–5.102	1.000
	No	181 (93.2)	21 (95.5)	160 (93)	1		
Health facility-related factors							
Baby delivered at HAM	Yes	188 (96.9)	21 (95.5)	167 (97.1)	1.590	0.177–14.275	0.519
	No	6 (3.1)	1 (4.5)	5 (2.9)	1		
Transferred from another unit*	Yes	16 (8.2)	6 (27.3)	10 (5.8)	6.075	1.953–18.900	**0.004**
	No	178 (91.8)	16 (72.7)	162 (94.2)	1		
Delivery assisted by	Obstetrician	36 (18.6)	5 (22.7)	31 (18)	1		
	Midwife	153 (78.9)	16 (72.7)	137 (79.7)	0.725	0.231–2.726	0.736
	Home labor	5 (2.6)	1 (4.5)	4 (2.3)	1.532	0.026–20.683	1.000
Partograph use	Yes	76 (39.2)	9 (40.9)	67 (39)	1.085	0.440–2.678	1.000
	No	118 (60.8)	13 (59.1)	105 (61)	1		
Fetal malpresentation[h]	Yes	2 (1)	0	2 (1.2)	-	-	1.000
	No	192 (99)	22 (100)	170 (98.8)			
PROM[i]	Yes	15 (8.1)	5 (23.8)	10 (6.1)	4.844	1.473–15.930	**0.016**
	No	171 (91.9)	16 (76.2)	155 (93.9)	1		
Pre/Eclampsia[j]	Yes	17 (8.8)	2 (9.1)	15 (8.7)	1.047	0.223–4.917	1.000
	No	177 (91.2)	20 (90.9)	157 (91.3)	1		
Obstructed labour[k]	Yes	22 (11.3)	4 (18.2)	18 (10.5)	1.901	0.579–6.239	0.286
	No	172 (88.7)	18 (81.8)	154 (89.5)	1		
Postpartum haemorrhage[l]	Yes	2 (1)	0	2 (1.2)	-	-	1.000
	No	192 (99)	22 (100)	170 (98.8)	1		
Normal Vaginal delivery	Yes	155 (79.9)	15 (68.2)	140 (81.4)	0.490	0.185–1.300	0.161
	No	39 (20.1)	7 (31.8)	32 (18.6)	1		
Caesarean section	Yes	33 (17)	4 (18.2)	29 (16.9)	1.096	0.345–3.477	0.772
	No	161 (83)	18 (81.8)	143 (83.1)	1		
Previous caesarean	Yes	10 (5.2)	2 (9.1)	8 (4.7)	2.050	0.407–10.333	0.316
	No	184 (94.8)	20 (90.9)	164 (95.3)	1		
Instrumental vaginal delivery[m]	Yes	6 (3.1)	3 (13.6)	3 (1.7)	8.895	1.676–47.208	**0.020**
	No	188 (96.9)	19 (86.4)	169 (98.3)	1		
Meconium-stained amniotic fluid	Yes	43 (22.2)	11 (50)	32 (18.6)	4.375	1.744–10.975	**0.002**
	No	151 (77.8)	11 (50)	140 (81.4)	1		
Umbilical cord complication	Yes	8 (4.1)	1 (4.5)	7 (4.1)	1.122	0.132–9.578	1.000
	No	186 (95.9)	21 (95.5)	165 (95.9)	1		
Newborn's characteristics							
Gestational Age[n]	28–31	3 (1.5)	3 (13.6)	0	1		<0.001
	32–36	8 (4.1)	4 (18.2)	4 (2.3)	-	-	
	37–41	176 (90.7)	15 (68.2)	161 (93.6)	-	-	
	≥42	7 (3.6)	0	7 (4.1)	-	-	
Sex	Feminine	92 (47.4)	6 (27.3)	86 (50)	0.375	0.140–1.004	**0.044**
	Masculine	102 (52.6)	16 (72.7)	86 (50)	1		

(*Continued*)

TABLE 1 Continued

Variables	Categories	Total	Death-outcome group	Alive-outcome group	cOR	(95%) CI	*p* value
		n = 194	*n* = 22	*n* = 172			
			n (%)	*n* (%)			
Birth weight[o]	<1,500 g	5 (2.6)	4 (18.2)	1 (0.6)	1		
	1,500–2,499 g	18 (9.3)	7 (31.8)	11 (6.4)	0.172	0.003–2.220	0.263
	2,500 g–3,999 g	161 (83)	10 (45.5)	151 (87.8)	0.018	0.001–0.200	**<0.001**
	≥4,000 g	10 (5.2)	1 (4.5)	9 (5.2)	0.034	0.001–0.844	**0.034**
IUGR[p]	Yes	9 (4.6)	6 (27.3)	3 (1.7)	21.125	4.82–92.586	**<0.001**
	No	185 (95.4)	16 (72.7)	169 (98.3)	1		
Infectious risk[q]	Yes	50 (25.8)	14 (63.6)	36 (20.9)	6.611	2.574–16.978	**<0.001**
	No	144 (74.2)	8 (36.4)	136 (79.1)			
Congenital malformation	Yes	4 (2.1)	4 (18.2)	0	-	-	<0.001
	No	190 (97.9)	18 (81.8)	172 (100)	-	-	

ANC, antenatal care; CI, confidence interval; cOR: crude odds ratio; GA, gestational age; HAM: Hospital Dr. Ayres de Menezes; IPI, intestinal parasitic infection; IUGR, intrauterine growth restriction; PROM, prolonged rupture of membranes.
Bold values indicate significant *p*-value ≤0.05.
[a]Urban residence for women living in the capital city (Água Grande) and rural areas in all other districts (Mé-Zochi, Cantagalo, Lobata, Lembá, Caué and Principe Island).
[b]Poor birth spacing birth intervals of less than 2 years (42).
[c]High-pregnancy risk is registered in the ANC pregnancy card if the current pregnancy is defined as one or more of the following: 1) pregnant women age less than 15 years old or greater than 35, 2) grand multipara for women with six or more labors, 3) previous history of a stillbirth or early neonatal death, 6) previous caesarean section, and 7) previous hemorrhagic complication.
[d]Maternal disease was operationally defined as one or more of the following conditions during the current pregnancy: pre/eclampsia, gestational diabetes, malaria, bacteriuria, anemia, and intestinal parasitic infection.
[e]Anaemia during pregnancy as a hemoglobin concentration <11 g/dl.
[f]Glycaemia >105 mg/dl,.
[g]Through a sickle cell solubility test, which involves treating a thin blood film with sodium dithionate under hypoxic conditions and observing for sickling under a light microscope, that is the screening technique available in STP and performed to pregnant women with anemia or clinical suspicion. A positive result can suggest either sickle cell anemia or the sickle cell trait (43).
[h]Foetal malpresentation was determined if the presenting fetal part was noncephalic (e.g. breech, transverse, oblique) (32).
[i]Prolonged rupture of membrane (PROM) was defined as a rupture of membrane lasting longer than 18 hours before labor began (34, 35).
[j]Preeclampsia (hypertension ≥140/90 mmHg and proteinuria in dipsticks in women who were normotensive at ANC).
[k]Obstructed labor was operationally defined as the sum of all cesarean sections due to mechanical problems or fetal distress and all instrumental delivery (37).
[l]Postpartum hemorrhage was defined as >500 ml bleeding.
[m]IVD in STP is only performed by vacuum.
[n]Gestational age was estimated from the date of onset of the last normal menstrual period or through ultrasound dating of pregnancy. Prematurity was defined as a delivery before 37 complete weeks of gestation from the date of onset of the last normal menstrual period and subcategorized as very preterm (28 to 31 weeks) and moderate to late preterm (32 to 37 weeks).
[o]Low birth weight was defined as a newborn weight less than 2,500 grams (up to and including 2,499 g) at birth regardless of gestational age (44). Low birth weight was further categorized into very low birth weight (VLBW, <1,500 g) (45). Low birth weight is a result of preterm birth, intrauterine growth restriction or both (45).
Large birth weight when ≥4,000 g (macrosomia) irrespective of gestational age.
[p]There is still no consensual definition for intrauterine growth restriction (IUGR) or fetal growth restriction in Africa (46). In this study, it was defined as the term LBW (i.e., birthweight <2,500 g and gestational age ≥37 weeks of gestation) due to low *in utero* measurements through obstetric ultrasounds in the country (46).
[q]Infectious risk was operationally defined as the sum of all the following risk factors: (1) maternal fever (axillary temperature >37.9 C) at the time of delivery, (2) prolonged rupture of membrane (≥18 h), and/or (3) foul-smelling amniotic fluid (47).

TABLE 2 Univariable logistic regression analysis of neonatal deaths among newborns who were live births *n* = 178 [death-outcome group: 6 and alive-outcome group: 172].

Variables	Categories	Total	Death-outcome group	Alive-outcome group	cOR	(95%) CI	*p* value
		n = 178[a]	*n* = 6[a]	*n* = 172			
			n (%)	*n* (%)			
Neonatal resuscitation	Yes	7 (3.9)	2 (33.3)	5 (2.9)	16.700	2.457–113.495	**0.004**
	No	171 (96.1)	4 (66.7)	167 (97.1)	1		
Fetal distress at birth[b]	Yes	26 (14.6)	5 (83.3)	21 (12.2)	35.952	4.004–322.859	**0.001**
	No	152 (85.4)	1 (16.7)	151 (87.8)	1		
Birth asphyxia[c]	Yes	10 (5.6)	4 (66.7)	6 (3.5)	55.333	8.421–363.600	**<0.001**
	No	168 (94.4)	2 (33.3)	166 (96.5)	1		
Admission at NCU	Yes	15 (8.4)	3 (50)	12 (7)	13.333	2.425–73.310	**0.003**
	No	163 (91.6)	3 (50)	160 (93)	1		

CI, confidence interval; cOR, crude odds ratio; NCU, neonatal care unit.
Bold values indicate significant *p*-value ≤0.05.
[a]Stillbirths excluded.
[b]Fetal distress was defined as a low Apgar score <7 at the first minute of life (score from 0 to <7) (26, 48).
[c]Birth asphyxia was defined as a low Apgar score <7 at the fifth minute of life (score from 0 to <7) (26, 48).

Discussion

In this prospective cohort study, the main aim was to identify associated factors with perinatal and neonatal death. The most vulnerable period for death—partum, early or late neonatal period—and to identify where they die—in the maternity, at home or in the pediatric ward—was also possible as we were able to follow newborns up until their 28th day of life. In this study, we found that 90% died in HAM maternity before the 7th day of life, that is, during the perinatal period, with mainly being stillborn (73%). The magnitude of stillbirths observed in this study (3%) is in line with the studies conducted in Nigeria (4.8%) (49) and Tanzania (3.5%) (50) and lower compared with studies from Ethiopia (6.7%) (51). Most stillbirths were intrapartum deaths, as also identified in LMICs similar to STP, and most could have been prevented (52, 53).

Thus, this study indicates a probability of a stillbirth in 30 per 1,000 liverbirths, and a probability of neonatal death rate of 11 per 1,000 livebirths. The value found for the perinatal mortality is two times higher than the rates estimated for the country (18, 19).

In this study, intrapartum characteristics, such as pregnant women with meconium-stained amniotic fluid, prolonged rupture of membranes, and instrumental vaginal delivery, were the main factors significantly associated with perinatal and neonatal death. Health facility-related factors, as pregnant women transferred from another unit were also at a significant risk.

High-pregnancy risk score notification was the only antepartum factor significantly associated with perinatal and neonatal deaths. For newborns, experiencing fetal distress at birth, needing resuscitation maneuvers, having birth asphyxia and admission to the neonatal unit were identified as high-risk factors for death. Being a female newborn and having a birth weight greater than 2,500 grams were found to be protective factors.

Odds of experiencing death were identified as four times higher among newborns from mothers with meconium-stained amniotic fluid. This finding is consistent with studies from Ethiopia (6, 54) and Yemen (13) that also reported higher rates of fetal death due to intrauterine passage of meconium into amniotic fluid and a fivefold increase in perinatal mortality compared with low-risk patients with clear amniotic fluid (55). Meconium-stained amniotic fluid is associated with fetal distress since the fetus, in response, inhales the meconium, which in turn leads to airway obstruction, surfactant dysfunction and pneumonitis, which leads to loss of the fetus (6).

PROM was also a significant factor associated with neonatal deaths in this study, showing fivefold higher odds for the death-outcome group. This association was also identified in other studies from low-resource constrained countries reporting one-third of stillbirths occurring during labor as a result of prolonged labor or obstructed labor not attended to promptly (38, 39, 41, 56, 57). The reason for this might be because PROM is a risk factor for early-onset neonatal sepsis as well as a high risk of fetal distress, respiratory distress syndrome, intraventricular hemorrhage, and death (34, 35, 58). In this study we found an overall prevalence of PROM of 8.1%, which is in accordance with the global incidence that ranges from approximately 5% to 10% of all deliveries in the world (59, 60).

Lack of emergency obstetric care (EmOC) is well-known to increase the risk of neonatal mortality, as laboring mothers with complications cannot immediately receive appropriate health services, such as access to a cesarean section (39). In this study, mothers who needed to be transferred from another health unit for delivery at HAM had a sixfold higher risk of having a neonatal death outcome than mothers directly admitted at HAM. Half the mothers who were transferred from the death-outcome group had to do a 60 -kilometer journey that took approximately two to three hours until reaching HAM maternity in the capital city. Distance from a health facility with EmOC and the considerable travel times are well-known barriers and influential factors of birth adverse outcomes also found in other studies in sub-Saharan Africa (58, 61).

In this study, the overall rate of 3.1% of instrumental assisted vaginal birth deliveries was found to be lower compared to 17% of births by cesarean section and 79.9% of normal vaginal deliveries. Instrumental-assisted deliveries are an effective intervention for deliveries complicated by prolonged labor or fetal distress but are also related to adverse outcomes since fetal distress or cephalopelvic disproportion are more frequently the motive to use this technique. Therefore, the ninefold higher risk of death outcome found in this study, similar to other researchers reporting (14, 62, 63), relates to late appropriate intrapartum care intervention with subsequently higher rates of fetal distress and risk of an intrapartum stillbirth.

Antenatal care health services in STP follow a high-risk stratification for each pregnancy and, in this study, this notification of a high-risk pregnancy in the pregnant women antenatal pregnancy card was significantly associated with a threefold higher risk for fetal and neonatal death than alive-outcome group. High-pregnancy risk was operationally defined as one or more of the following according to STP national practice, namely, age as inferior to 15 years old or superior to 35, grand multipara, previous history of a stillbirth or early neonatal death, previous cesarean section, and previous hemorrhagic complication. This is consistent with other studies that reported higher rates of perinatal and neonatal mortality with extreme maternal ages and previous adverse obstetric history (grand multipara, previous stillbirth, or early neonatal death) (1, 13). However, in this study, we could not find a statistically significant difference between groups when each of these variables were independently analyzed.

Regarding the newborns' characteristics, the overall sex ratio at birth was 52.6% for males and 47.4% for females. The death rate was higher in male neonates (72%) than in the female death-outcome group (27.3%), with female sex being a protective factor. Sex variations are frequently reported, with a highly consistent pattern of excess male mortality across different populations and income groups (64). Male infants are more vulnerable to fetal and early neonatal death, with most studies reporting no gender difference in mortality after 7 days of age (64). This sex difference may be explained by a sex-specific difference in the growth and function of male and female placentae, making boys more vulnerable to different adverse outcomes (64–66).

Birth weights of more than 2,500 g were protective factors for death outcome in this study. This finding is comparable with

different research on other African countries that associates a birth weight of less than 2,500 g (LBW) with higher rates of stillbirth and neonatal death (1). Additionally, the odds of experiencing death were 21 times higher for babies with IUGR or fetal growth restriction defined, in this study, as a term LBW (birthweight <2,500 g and gestational age ≥37 weeks) (46). Low birth weight is a worldwide recognized important multifaceted public health problem since LBW infants are 20 times more likely to develop complications and die than normal weight infants (6, 67).

We found that the odds of death were six times higher for newborns with maternal infectious risk. This finding is in agreement with previous studies conducted in SSA, as neonatal infectious risk is linked to amniotic fluid contamination that can cause intrapartum fetal infection or early postpartum neonatal infection with sepsis complicated with septic shock and multiple organ dysfunction, in which both are the most common causes of death in the perinatal period (38, 47). Infection is an important cause of stillbirth and neonatal death in LMICs, although there is a lack of overall information regarding the organisms involved, the types of transmission, and the mechanisms of death in these constrained countries (68). In Sao Tome & Principe, malaria and syphilis are no longer an infection-burden and cause of stillbirth or neonatal death; therefore, other bacterial and viral maternal infections should be linked to stillbirth and ENND (68). In STP, there are no means to establish a neonatal infection through blood cultures; that is, neonatal infection is based only on clinical signs with no bacteriological documentation. Additionally, nothing is known about the rate of vertical transmission of Streptococcus Group B (GBS) from colonized mothers at birth in the country. Therefore, there is a current gap in the knowledge, capability of making diagnosis and prevention and treatment of neonatal infections in STP. For instance, a study from Ethiopia (68) detected that the rate of vertical transmission of GBS from colonized mothers at birth was as high as 45.02% due to term PROM, PROM ≥18 h before delivery and mothers having fever during labor. Detecting the risk for vertical transmission of GBS and implementing prevention methods such as adequate intrapartum administration of antibiotics are recognized as easy and affordable practices for reducing mortality due to infectious causes and should be implemented in the country along with culture techniques (47).

All four congenital major malformations detected in this study resulted in a perinataldeath, although due to the low number of newborns enrolled it was not possible to establish a statistically significant difference. Congenital malformations are known to be associated with poor outcomes for newborns, and 10%–20% of stillbirths are attributed to intrinsic fetal anomalies (57). Studies from Zimbabwe (69), Ethiopia (1) and Yemen (13) found that congenital anomalies among stillbirths were associated with a 5-fold (69), 34-fold (1) and 40-fold (13) higher risk than those among live births. Another important consideration regarding congenital anomalies is the type of malformation, since some, such as neural tube defects, are preventable and can be reduced by 30 to 50% by folic acid supplementation in pregnant women and have been estimated to cause 29% of deaths related to congenital anomalies in LMICs (4). In this study, three out of the four major anomalies were neural tube defects, highlighting the need to enhance proper supplementation to preconceptional women in the country.

In this study, we were not able to find a higher risk associated with newborn gestational age. The high rate of stillbirths found in our study as well as the low number of preterm babies enrolled (5.6%) explain the lack of association. Stillbirths are among the most common pregnancy-related adverse outcomes worldwide, but they differ between low- and high-income countries. In high-income countries, most stillbirths occur early in the preterm period, whereas in low-resource constrained countries, most occur in term or in late preterm births, as found in our study (70). Additionally, the neonatal deathis higher in babies born between 37 and 38 weeks of gestation than in those born between 39 and weeks (4).

From stillbirths in this study, 69% occurred during the intrapartum period, in accordance with other studies from LMICs (5). These intrapartum stillbirths mean that intrauterine death occurred after the onset of labor and before birth (fresh stillbirth). We can also guess that some of them could be early neonatal deaths, as there are known barriers and difficulties in these contexts to establish whether a fetus or motionless newborn is living or dead after its delivery. For instance, information on some Apgar scores in these death-outcome group was not recorded, perhaps because of lack of time, especially when the neonates had to be rushed to receive resuscitation maneuvers. Studies from SSA highlight that it is very frequent that some depressed but living fetuses with a possible heartbeat do not receive resuscitation maneuvers and are prompt classified as stillbirths (1, 70). This is supported by a systematic review of sixteen hospitals and community-based perinatal mortality studies (71, 72).

In this study, newborns who needed resuscitation maneuvers were at a 16-fold higher risk of dying. Additionally, the odds of neonatal death from fetal distress at birth and birth asphyxia were 36 and 55 times higher, respectively. These results are in line with studies conducted in Cameroon (34) and Ethiopia (39) as well as published literature that suggests that lower APGAR scores are associated with severe multiorgan damage resulting in brain damage, lung dysfunction, cardiomyopathy, renal failure, hepatic failure, necrotizing enterocolitis and consequently death (73). Previous studies conducted by the authors, that compared outcomes between adolescent pregnant girls and older counterparts identified that adverse outcomes imputable to adolescent births were fetal distress and performance of neonatal resuscitation maneuvers, highlighting the risks surrounding this period among deliveries at HAM maternity unit (25, 26).

Perinatal asphyxia can be caused by factors grouped according to whether they are before birth (antepartum risk actors), during birth (intrapartum risk factors), or after birth (postpartum or fetal risk factors) (48, 73). Nonetheless, the single most important predictor is, undoubtedly, the quality of intrapartum care during labor and delivery.

The most important aspect of this study for public health is that it identifies potential characteristics that predispose newborns to life-threatening conditions, which is critical to address the underlying causes and provide prompt interventions by various stakeholders in the healthcare system (74).

This study allows us to perceive how to answer our question "when, where and why do newborns die in STP?" as "when": mostly during labor, "where": in uterus and "why": mainly due to fetal distress and intrapartum-related deaths probably due to low quality and constraints of care during labor and delivery. Ending preventable stillbirths and neonatal deaths does not necessarily require new or innovative interventions. Most modifiable risk factors identified in this study can be addressed and prevented with timely, quality care during childbirth, including ongoing intrapartum monitoring and opportune intervention in case of complications (5). Some interventions, such as cardiotocography to monitor a baby's well-being in the womb by measuring contractions, are estimated to reduce the rate of infant deaths around the time of birth by 80% (75). Thus, according to this study results, the priority for STP is to prevent stillbirths through proper fetal surveillance, therefore, measures such as, the implementation of simple techniques in all maternity units, namely foetal heart rate monitoring and to provide algorithms to deliver prompt interventions when needed are essential.

In summary, the findings of this study will be useful to health policymakers and program developers in implementing appropriate interventions to achieve the newborn health post-2015 Sustainable Development Goals of no more than 12 neonatal deaths per 1,000 live births in Sao Tome & Principe by 2030 (76).

Strengths and limitations

In this study, the researcher retrieved maternal and neonatal data directly from ANC cards and maternity registers to limit recall bias. The selection of the death-outcome group and alive-outcome group was based on the records of maternal and neonatal registers; therefore, it is less likely that this study has misclassification biases both in the exposure and death-outcome group -alive-outcome group categories (44, 67).

Regarding the limitations, this is a relatively small study aiming to identify factors associated with perinatal and neonatal deaths in Sao Tome & Principe with a cohort of 194 newborns that were followed up until 28th days of age, 22 died and 172 survived. Thus, this study results cannot be generalized.

Another limitation is that some of the variables mentioned in the univariable analysis had wide confidence intervals and high odds ratios due to the low number of newborns in the death-outcome group enrolled in this study.

Nonetheless, the current study can assist Sao Tome & Principe policy makers and stakeholders in designing new policies for the country to improve maternal and neonatal health outcomes.

Conclusions

Perinatal mortality is a major public health problem in Sao Tome & Principe, as reinforced by this study, indicating a probability of a stillbirth in 30 per 1,000 liverbirths, and a probability of neonatal death rate of 11 per 1,000 livebirths, values higher than the rates estimated for the country.

Complications such as a high-risk pregnancy score, meconium-stained amniotic fluid, prolonged rupture of membranes, being transferred from another unit, and an instrumental-assisted vaginal delivery increased the risk of stillbirth and neonatal death between 4– and 9–fold, and 90% of all these deaths occurred in the perinatal period.

Newborns with an infectious risk, intrauterine growth restriction, fetal distress at birth, who needed resuscitation maneuvers, birth asphyxia, and those admitted to the neonatal unit had a 3- to 55-fold higher risk for dying than the alive-outcome group. Female newborn and birth weight of more than 2,500 g were found to be protective factors.

Thus, the priority for STP is to prevent stillbirths through proper fetal surveillance. Measures such as, the implementation of simple techniques in all maternity units, namely fetal heart rate monitoring and to provide algorithms to deliver prompt interventions when needed will improve perinatal and neonatal outcomes and survival in Sao Tome & Principe.

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 study complies with the Declaration of Helsinki and was approved and consented to by the Ministry of Health of Sao Tome & Principe and by the main board of Hospital Dr. Ayres de Menezes, since at the time the study protocol was submitted there was no ethics committee in STP. Only recently has the country's National Ethics Committee been appointed. Previously, study analysis and approval were performed by dedicated ethics oversight bodies, such as the Ministry of Health of Sao Tome & Principe and the main board of the Hospital Dr. Ayres de Menezes, and both approved this study.

Moreover, all methods in our study were performed in accordance with the relevant guidelines and regulations in practice.

Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants parents or legal guardians was asked in the case of adolescents under 16 years of age or for illiterate women.

The participants or their legal representatives also consented to have the results of this research work to be published. Participation in the survey was voluntary, as participants could decline to participate at any time during the study.

The studies involving humans were approved by dedicated ethics oversight bodies such as the Ministry of Health of Sao Tome and Principe and by the main board of Hospital Dr. Ayres de Menezes. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in

this study was provided by the participants' legal guardians/ next of kin.

Author contributions

AV: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. SS: Resources, Visualization, Writing – review & editing. NB: Resources, Visualization, Writing – review & editing. MA: Data curation, Formal Analysis, Software, Writing – review & editing. AP: Formal Analysis, Methodology, Software, Supervision, Validation, Writing – review & editing. FP: Conceptualization, Methodology, Supervision, Writing – review & editing. MM: Conceptualization, Methodology, Supervision, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1335926/full#supplementary-material

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Preclinical validation of NeoWarm, a low-cost infant warmer and carrier device, to ameliorate induced hypothermia in newborn piglets as models for human neonates

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Introduction: Approximately 1.5 million neonatal deaths occur among premature and small (low birthweight or small-for gestational age) neonates annually, with a disproportionate amount of this mortality occurring in low- and middle-income countries (LMICs). Hypothermia, the inability of newborns to regulate their body temperature, is common among prematurely born and small babies, and often underlies high rates of mortality in this population. In high-resource settings, incubators and radiant warmers are the gold standard for hypothermia, but this equipment is often scarce in LMICs. Kangaroo Mother Care/Skin-to-skin care (KMC/STS) is an evidence-based intervention that has been targeted for scale-up among premature and small neonates. However, KMC/STS requires hours of daily contact between a neonate and an able adult caregiver, leaving little time for the caregiver to care for themselves. To address this, we created a novel self-warming biomedical device, NeoWarm, to augment KMC/STS. The present study aimed to validate the safety and efficacy of NeoWarm.

Methods: Sixteen, 0-to-5-day-old piglets were used as an animal model due to similarities in their thermoregulatory capabilities, circulatory systems, and approximate skin composition to human neonates. The piglets were placed in an engineered cooling box to drop their core temperature below 36.5°C, the World Health Organizations definition of hypothermia for human neonates. The piglets were then warmed in NeoWarm ($n = 6$) or placed in the ambient 17.8°C $\pm$ 0.6°C lab environment ($n = 5$) as a control to assess the efficacy of NeoWarm in regulating their core body temperature.

Results: All 6 piglets placed in NeoWarm recovered from hypothermia, while none of the 5 piglets in the ambient environment recovered. The piglets warmed in NeoWarm reached a significantly higher core body temperature (39.2°C $\pm$ 0.4°C, $n = 6$) than the piglets that were warmed in the ambient

environment (37.9°C ± 0.4°C, $n = 5$) ($p < 0.001$). No piglet in the NeoWarm group suffered signs of burns or skin abrasions.
Discussion: Our results in this pilot study indicate that NeoWarm can safely and effectively warm hypothermic piglets to a normal core body temperature and, with additional validation, shows promise for potential use among human premature and small neonates.

KEYWORDS

low to middle income country (LMIC), neonatal hypothermia, thermal model, piglet model, kangaroo mother care (KMC), vital signs monitoring system (VSMS), neonatal mortality and morbidity

Introduction

There are nearly 15 million premature (babies born <37 weeks gestation) and low-birthweight (less than 2.5 kg) babies born each year (1, 2). 1.5 million of these neonates will not survive, with the vast majority of these deaths occurring in low and middle income countries (LMICs), a staggering—and unacceptable trend—that has persisted for decades (3–8). One of the main contributing factors which underlies high rates of preventable neonatal mortality is hypothermia (9–12). For a variety of reasons related to underdeveloped physiology, as well as environmental conditions both within health facilities and in the home and community settings, premature, low birthweight, and small-for-gestational age newborns struggle to maintain a normal body temperature, defined as 36.5°C–37.5°C (13–15). Newborns have a greater surface area-to-weight ratio, larger head-to-body ratio, and less adipose tissue for insulation, predisposing them to heat loss without appropriate thermal care interventions (16).

In high-resource settings, hypothermia is most often prevented, or treated, through the use of incubators and radiant warmers (17). However, in low-resource settings, incubators and radiant warmers may not be readily available due to scarcity (e.g., high cost or lack of resources to repair broken machines) or unreliable power grids (18). Kangaroo Mother Care/Skin-to-skin care (KMC/STS), in which an adult caregiver holds the newborn bare skin-to-bare skin, thereby transferring warmth to the neonate, preventing hypothermia, is a newborn care initiative that has been targeted for global scale up by a number of international partners. KMC/STS has been shown to be a low-cost and effective solution to prevent neonatal hypothermia, as well to provide numerous other benefits for both the neonate and the primary caregiver such as supporting improved breastfeeding and bonding between caregiver and child (19–22). However, KMC/STS has faced challenges in regards to widescale adoption and scale-up (23–26). For healthcare providers, it can be perceived that KMC/STS interferes with the regular flow of clinical care and monitoring, such as for vital signs. For adult caregivers serving as the KMC/STS partner to the premature/small baby, KMC/STS can be physically demanding, leading to exhaustion and fatigue, and limiting the caregiver from taking a break and caring for themselves (20, 27–29).

Other devices that aim to address neonatal hypothermia have been developed (30–46); however, they are either incompatible with KMC/STS or vital signs monitoring. There remains a need for a low-cost solution for prevention of neonatal hypothermia that is both compatible with KMC/STS and has the capability to be integrated with evidence-based recommendations for regular measurement of key neonatal vital signs to detect common complications of prematurity such as apnea. As a result, we have developed NeoWarm, a sensor-enabled carrier and swaddling device that both allows for KMC/STS and integrates temperature sensing and key vital signs into a single carrier (47–52). Our device will not reduce time spent in KMC/STS, but support and augment KMC/STS. Our previous studies have validated the ability of NeoWarm to warm hypothermic (35°C) tissue phantoms (bottle filled with water) to 37°C (normal human body temperature) and maintain this temperature for 2 h with no overheating (47, 48). These studies have also validated our ability to miniaturize our vital signs monitoring technology into a package that can be integrated into the neonatal carrier (53–58).

Aside from tissue phantoms, which we used in our previous work, current neonatal models for evaluating thermal care focus primarily on thermal manikins which have integrated heating elements and other electronics to mimic heat transfer and flow in the human body. However, while thermal manikins can mimic total heat loss (59, 60), they cannot simulate safety issues such as tissue response and burning. Therefore, a living biological model is necessary to evaluate NeoWarm's ability to safely warm a neonate without causing burns or visible discomfort, which is particularly important as premature neonates have significantly thinner and more fragile skin (61). Currently, there is no standard animal model specifically for neonatal hypothermia. Neonatal piglets are a promising model for neonatal hypothermia as they are of the approximate size and weight of prematurely born/small human neonates (1–2.5 kg), have similar cardiovascular systems, approximate skin composition, and similar core body temperatures (38.6°C–39.7°C in piglets vs. 36.5°C–37.5°C in humans) (13–15, 62, 63). Combined, these characteristics result in humans and piglets having similar thermoregulatory capabilities (64–70). Thus, for the current study, neonatal piglets were selected as a pre-clinical model to test the safety and efficacy of NeoWarm to ameliorate induced hypothermia.

Materials and methods

This study was approved by the Purdue University Institutional Animal Care and Use Committee (PACUC) under protocol #2008002063. Veterinary technicians monitored the piglets during the entire experiment via visual inspection and palpitation to ensure the piglets' well-being.

Inclusion criteria

Piglets were acquired from the Purdue Animal Sciences Research and Education Center (ASREC) farm. Inclusion criteria were that piglets were less than 120 h old, greater than 0.75 kg, less than 2.5 kg, and were within 1°C of a healthy initial core temperature (38.6°C–39.7°C) when they arrived our facility as measured using a commercial rectal thermometer (Part Number: VET-TEMP® DT-10, Advanced Monitors Corporation, San Diego, California, USA). For our study, we utilized convenience sampling, and thus, did not select based on sex. When two trials were able to be run on the same day, we selected litter mates, when possible, to minimize variability between piglets.

Acquiring piglets from the ASREC farm

Piglets were obtained from their birthing pen at the farm to start each day. Most days, two piglets were available from the same litter, allowing us to run two trials concurrently. Birthweight and initial temperature were acquired for each piglet at the farm. The piglets were then transported 30 min to the testing facility in separate travel crates in the back of an air-conditioned van. Temperature and weight were collected upon arrival at the testing facility.

Pen setup

As shown in Figure 1A, a roughly 4-ft diameter soft-sided pen was chosen to allow the piglets mobility while keeping them contained. A sheet of cardboard was placed underneath the pen to insulate the bottom of the pen from the cold laboratory floor. Additionally, the inside of the pen was lined with a layer of fleece blankets and absorbent pads to provide more insulation from the cold floor, give the piglets a more comfortable surface to lay on, and to make cleanup easier. Importantly, the piglets were not able to snuggle into the blankets, preventing them from getting additional warmth from their environment. Care was taken so that there were no drafts in the 17.8°C ± 0.6°C room. To prepare for the risk of dangerous levels of hypothermia or deleterious health impacts as determined by the veterinary technicians monitoring the study, we had a heat lamp fixed above the pen (turned off), warm rice pillows, a warm air blower, and additional fleece blankets on standby.

Temperature phase: cooling

Most days, two piglets were available from the same litter from the farm at a time. Both piglets were placed into a 27-gallon plastic tub lined with ice water-soaked towels and cold water-filled balloons as shown in Figure 1B. Small fans were positioned to blow air into the tub and onto the piglets. The piglets were left in the tub until they reached a core body temperature below 36.5°C or three hours had passed without their temperature dropping below 36.5°C.

Temperature phase: heating

Piglets were divided into "NeoWarm" or "ambient environment" groups based on three distinct scenarios. (1) The

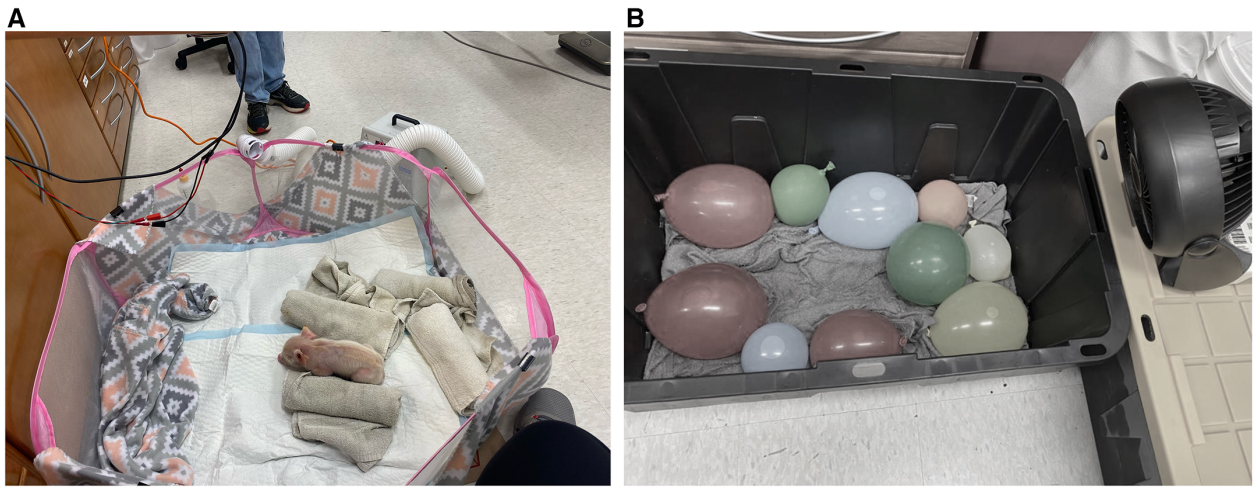

FIGURE 1
(A) Image of neonatal piglet in the pen. (B) Image of the cooling box with cold water-soaked towels, cold water-filled balloons and small fan.

first of the two litter mates to drop below 36.5°C was placed in NeoWarm with the heating pads set to 40°C. The other piglet was placed back into its original pen to warm itself as a control. (2) If both piglets dropped below 36.5°C at the same time or (3) neither piglet dropped below 36.5°C, the piglet with the lower core temperature was placed inside NeoWarm and the other piglet was placed into the 17.8°C ± 0.6°C pen in the ambient environment group.

Data collection

Piglet core temperature was collected with a rectal thermometer every 15–45 min after their arrival at the testing facility. The veterinary technicians continually monitored the piglets and fed them when their behavior indicated they were hungry. The ambient temperature of the room was set at the beginning of the day, recorded at the beginning of each trial, and verified at least twice throughout the trial, once in the middle and once at the end. The trial was concluded when the piglets' rectal temperature was stable and did not vary more than 1°C in approximately two and a half hours.

Euthanasia

Piglets were anesthetized with nitrogen gas, and then Euthasol was used by the veterinary technicians to humanely euthanize the piglets at the end of each trial according to approved animal safety and welfare protocols. Fifteen (15) piglets were euthanized via the intravenous route. One (1) piglet was euthanized via the intracardiac route after two separate veterinary technicians were unable to obtain intravenous access. Prior to euthanasia, a final temperature was taken.

Data analysis

Once the data points were collected, final temperatures were compared between the NeoWarm group and the ambient environment group. Student's *t*-test was used to compare averages across the two groups. Plots were generated using MATLAB (71) and statistics were computed in MATLAB (R2020b, MathWorks, Natick, Massachusetts, United States) or Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States).

Results

Piglets

Sixteen (16) piglets were initially acquired from the ASREC Farm (Figure 2). Four (4) were used to help develop the experimental design and were excluded from final analysis. One (1) additional piglet was removed from analysis as it did not meet the inclusion criteria of having a healthy starting temperature at our facility within 1°C of 38.6°C, with its starting temperature being 32.4°C.

The remaining 11 piglets were enrolled in the study. There were five male piglets and six female piglets in this study. The piglets weighed an average of 1.17 ± 0.16 kg, were all younger than 120 h (five days) old and were within 1°C of a healthy initial core temperature (38.6°C–39.7°C) (62, 63) when they arrived our facility as measured using a commercial rectal thermometer.

Temperature phase: cooling

The average final temperature at the end of the cooling phase of all the piglets was 36.4°C ± 1.1°C ($n = 11$). Six (6) out of 11 piglets fell below 36.5°C within an average time of 73.2 ± 35.4 min ($n = 6$). Five (5) piglets never dropped below 36.5°C even after three hours in the cold tub. The average final temperature at the end of the cooling phase of the six piglets that did drop below 36.5°C was 35.6°C ± 0.8°C ($n = 6$), while the average final temperature at the end of the cooling phase of the five piglets that did not drop below 36.5°C was 37.2°C ± 0.6°C ($n = 5$). The Student's *t*-test indicates that the difference in final temperature between the six piglets that did drop below 36.5°C and the five piglets that did not drop below 36.5°C is statistically significant ($p < 0.0051$).

Of the six piglets that had final temperatures below 36.5°C at the end of the cooling phase, four of them were placed in NeoWarm, along with two piglets that did not have a final temperature below 36.5°C. The average final temperature of the six piglets placed in NeoWarm at the end of the cooling phase was 36.0°C ± 0.9°C ($n = 6$), while the average final temperature of the five piglets that were not placed in NeoWarm at the end of the cooling phase was 36.8°C ± 1.2°C ($n = 5$). The Student's *t*-test indicates that the difference in final temperature between the six piglets that were placed in NeoWarm and the five piglets that were not placed in NeoWarm at the end of the cooling phase was not statistically significant ($p = 0.24$). We do note that piglet A4 dropped below 36.5°C after the cooling phase. This piglet was not included in the statistics above since it dropped below 36.5°C in the warming phase, not the cooling phase.

All 11 piglets fell below 38.6°C after being in the cooling box.

Temperature phase: warming (NeoWarm or ambient environment)

The average final temperature of all 11 piglets at the end of the heating phase was 38.6°C ± 0.8°C ($n = 11$). The average final temperature of the six piglets that were placed in NeoWarm was 39.2°C ± 0.4°C ($n = 6$) after an average time of 183.8 ± 71.2 min ($n = 6$). As shown in Figure 3B, of the six piglets placed in NeoWarm, the highest final temperature of 39.9°C was observed in piglet B6, and the lowest final temperature of 38.7°C was observed in piglet B1. Piglet B6 exceeded the normothermic cutoff of 39.7°C by 0.2°C, having a final temperature of 39.9°C at the end of the heating phase. NeoWarm warmed the piglets up

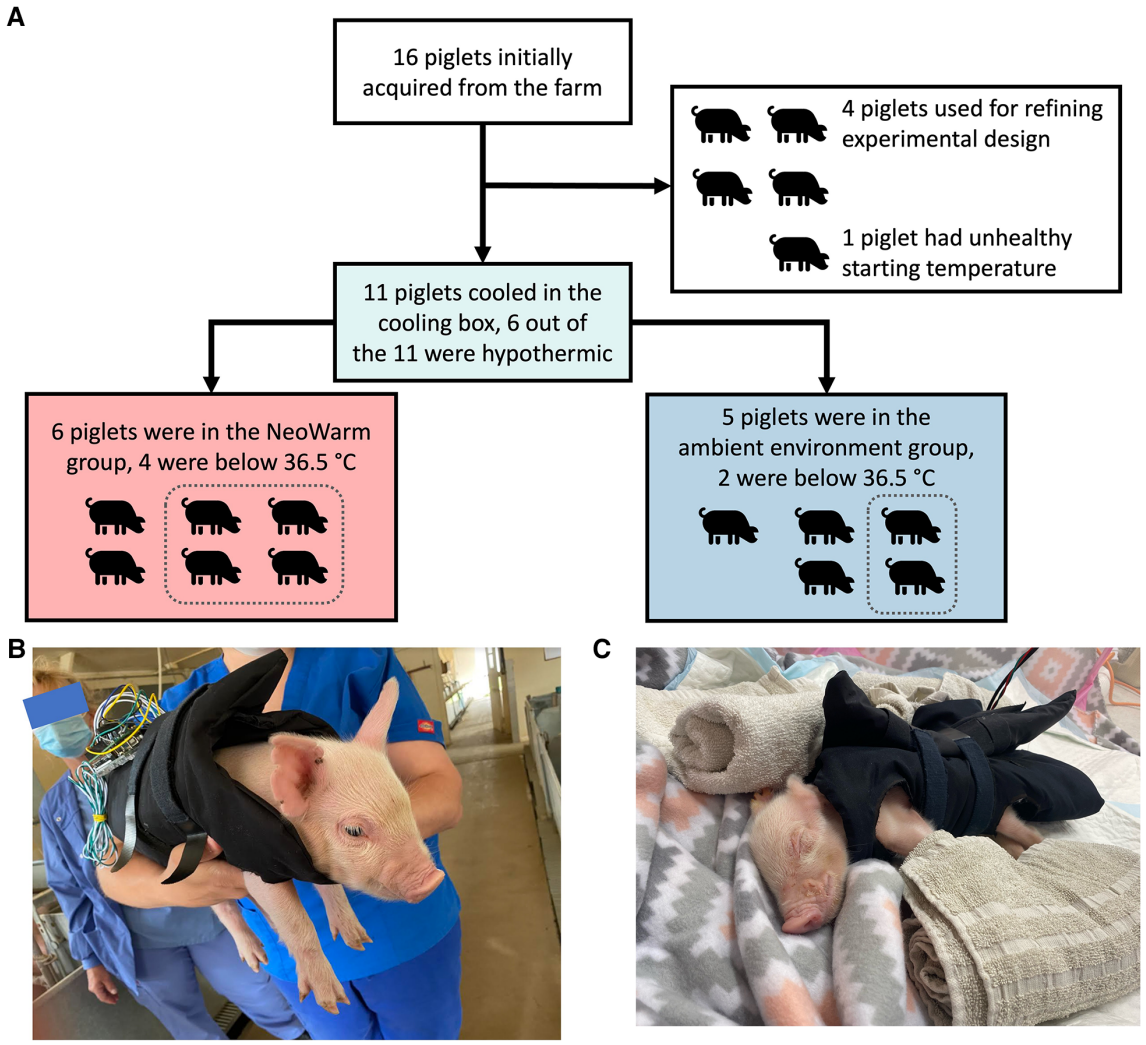

FIGURE 2
(A) Flow chart detailing how pigs were grouped for each stage of the experiment. Images of piglet snuggled in NeoWarm (B) at the farm and (C) in the pop-up pen.

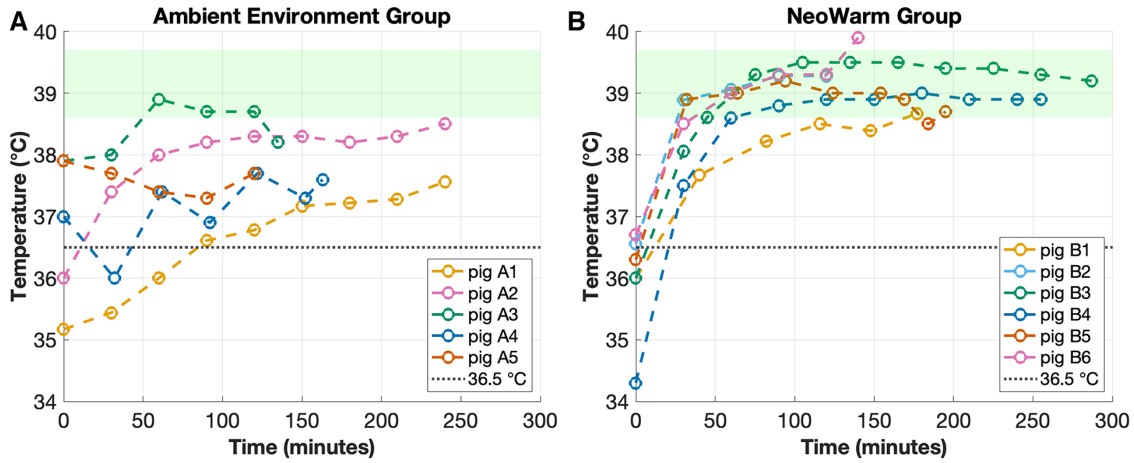

FIGURE 3
(A) Temperature of piglets that were in the ambient environment group vs. (B) piglets that were in the NeoWarm group. The dashed line depicts the 36.5°C cooling box threshold and the green shaded region highlights the normothermic temperature range for piglets (38.6°C–39.7°C).

to 38.6°C at a rate of +3.42°C/min. All six piglets that were placed in NeoWarm reached normothermic temperatures at the end of the heating phase, having final temperatures equal to or above 38.6°C (Figure 3B).

The average final temperature of the five piglets in the ambient environment group was 37.9°C ± 0.4°C ($n = 5$) after an average time of 179.6 ± 57.3 min ($n = 5$). As shown in Figure 3A, of the five piglets, the highest final temperature of 38.5°C was observed in piglet A2, and the lowest final temperature of 37.6°C was observed in piglets A1 and A4. None of the five piglets in the ambient environment group had final temperatures in the normothermic range (Figure 3A). Piglet A3 had a peak temperature within the normothermic range, but it was not maintained. Its final temperature dropped below 38.6°C at the conclusion of the trial.

The Student's *t*-test indicates that NeoWarm did warm the piglets to a statistically significant higher core body temperature than the piglets in the ambient environment group ($p < 0.001$). No piglet in either group had any observable burns or skin irritations, as visually and physically assessed by the veterinary technicians.

Critically, all six piglets that were placed in NeoWarm reached normothermic temperatures at the end of the heating phase, having final temperatures equal to or above 38.6°C, while none of the five piglets in the ambient environment group reached normothermia, having final core body temperatures less than 38.6°C (Figure 3). The Pearson's correlation coefficient indicated that there was no significant correlation between weight and final temperature for piglets in the NeoWarm ($r = -0.35$, $p = 0.50$) or ambient environment groups ($r = -0.01$, $p = 0.99$) (Table 1).

Discussion

Defining normothermia and hypothermia for this study

The reported normal core body temperature (normothermia) for piglets varies, but the most reliable range we found in the literature was 38.6°C–39.7°C (62, 63). We found additional sources that suggest that a temperature range of 38°C–40°C was acceptable, but those metrics were less commonly reported in the literature (72, 73). Therefore, we used the temperature range of 38.6°C–39.7°C as our normothermic range for the piglets in this study. Consequently, below 38.6°C was considered hypothermic for the piglets. For comparison, the normothermic range for newborn humans is 36.5°C–37.5°C with hypothermia defined as core body temperature below 36.5°C (16).

We cooled the piglets below 36.5°C, instead of simply below 38.6°C, to show direct translatability of NeoWarm's performance in this pilot study to the human use-case and to demonstrate NeoWarm's warming capabilities from moderate hypothermia to normal body temperature. We also note that NeoWarm was modified to warm the piglets to their normothermic temperatures of 38.6°C–39.7°C, not the human normothermic temperature of 36.5°C–37.5°C. Human normothermic temperatures would still be severely hypothermic for the piglet and would not allow us to compare NeoWarm's effectiveness to the piglets' own thermoregulatory capabilities as the piglets would naturally try to warm themselves up to 38.6°C–39.7°C. However, NeoWarm can be readily modified in software to regulate to 36.5°C–37.5°C for the human use-case as we have demonstrated in our previous work using tissue phantoms (48).

Neowarm's device modifications

We modified NeoWarm from our previously published version (48) in order to accommodate some of the significant differences between piglets and human newborns. An obvious difference affecting form factor is that piglets are four-legged animals while humans walk upright on two legs. Also, critical for this study, piglets are mobile at (or very near) birth. Our prior form factor, resembling more of an infant carrier or baby wrap (48), impeded the piglets' ability to walk, resulting in distress. Therefore, to allow the piglets to walk and sleep in NeoWarm while remaining thermally insulated, we redesigned the form factor to incorporate holes for the piglets' legs. We used the same heating pads and microcircuitry that we used in the previous version of NeoWarm. Re-configuring NeoWarm with holes for the piglets' legs allowed the piglets to walk freely around the pen. To further accommodate their need to walk, we ran NeoWarm from a benchtop power supply, with lightweight cables extending from the power supply to NeoWarm, rather than battery packs, as the weight of the batteries was too heavy for the piglets to move around comfortably. Future work will focus on making NeoWarm more power efficient, so that we can ultimately run the device using lightweight battery packs.

Modified temperature control algorithm

In our previous iteration of NeoWarm, we monitored the temperature of the heaters as well as the temperature of the

TABLE 1 Piglet demographic information and temperatures at the end of each temperature phase.

			Cooling		Warming	
	Gender: M/F	Weight: Avg ± Std	Avg ± Std	Min to max	Avg ± std	Min to max
Total $n = 11$	5/6	1.17 ± 0.16	36.4 ± 1.1	34.3–37.9	38.6 ± 0.8	37.6–39.9
NeoWarm $n = 6$	4/2	1.17 ± 0.12	36.0 ± 0.9	34.3–36.7	39.2 ± 0.4	38.7–39.9
Ambient $n = 5$	1/4	1.17 ± 0.21	36.8 ± 1.2	35.2–37.9	37.9 ± 0.4	37.6–38.5
p-value (NeoWarm vs. ambient)		0.99	0.24		<0.001	

All weights are in grams (g) and all temperatures are in degrees Celsius (°C).

tissue phantom using separate temperature sensors (48). Monitoring the temperature of the heaters allowed us to ensure the heaters did not exceed 38°C, the maximum recommended water bath temperature for newborns (16, 74, 75). Monitoring the temperature of the tissue phantom allowed our algorithm to regulate power delivered to the heaters such that the tissue phantom did not exceed the desired setpoint of 37°C, the average human neonatal core body temperature (16).

However, in our present study with piglets, we were unable to continuously monitor the temperature of the piglets using NeoWarm. We utilized intermittent measurements (every 15–45 min) of core body temperature, via a rectal thermometer. Unlike human newborns where we can measure skin temperature at several locations (abdomen, axilla, etc.) to reliably estimate core body temperature (76–80), core body temperature in piglets can only be reliably measured from the rectum (81). Infrared thermometers have been demonstrated to show errors of up to 2°C when estimating core body temperature from the forehead, abdomen, or other locations on the skin. We attempted to continuously monitor both the heater temperature and the piglet's instantaneous rectal temperature in this study; however, the piglets found the temperature sensor very uncomfortable and restrictive even though the sensor was very small (1 mm in diameter). Therefore, we were not able to continuously monitor the piglet's rectal temperature. Consequently, we modified our algorithm to regulate the temperature of the heating pad at 40°C, just slightly above the maximum normothermic temperature of the piglets (38.6°C–39.7°C) (62, 63). We chose a setpoint slightly above 39.7°C to help account for any normally occurring heat loss through the material and to the environment. Our modified algorithm does not incorporate instantaneous temperature measurements from the piglet, since we were unable to continuously measure the piglets' rectal temperatures using NeoWarm. Nonetheless, regulating the temperature of the warmer, without incorporating feedback from the continuous temperature of the neonate is an acceptable approach that has been demonstrated by others in the literature and in commercially available neonatal warmers (34, 43, 44). This approach is only a necessary modification implemented in this study and will likely not be translated to the human use-case since we can reliably measure the temperature of the newborn from various locations on the skin without causing undue distress to the newborn. However, the results from the current study suggest that our modified approach could be employed in the human use case as well, albeit at a lower set temperature.

Piglets may have better thermoregulatory capabilities than previously thought

This study suggests several potential considerations in utilizing the neonatal pig as an animal model for human neonatal thermoregulatory capabilities. Based on the literature and the experience of the veterinary technicians, we expected that the piglets would be thermally compromised and rapidly enter hypothermia without external intervention while in the 17.8°C ± 0.6°C laboratory environment (82–84). We observed that this was not the case. Two of the four piglets used in development of the experimental design were left in the ambient environment (not being placed in the cooling box or in NeoWarm). These piglets lost heat at a rate of less than 0.01°C/min. Human premature neonates could lose up to 0.3°C/min in cold environments (85), and this was expected to be the case for the piglets as well without any thermal support. The piglets core temperatures were dropping throughout the experiment (<−0.01°C/min), but much more slowly than human neonates [−0.3°C/min for human neonates (85)]. Also, one of these two piglets kept its internal temperature above 38.6°C, never becoming hypothermic even after six hours in the 17.8°C ± 0.6°C laboratory environment. These preliminary trials led us to use the cooling box to more rapidly cool the piglets below hypothermic temperatures within a reasonable time frame and to demonstrate the warming capabilities of NeoWarm. However, with only two piglets used for these preliminary trials, we cannot make any statistically significant claims regarding piglets' baseline thermoregulatory capabilities, and we suggest further studies into this matter.

Neowarm is effective at regulating core body temperature

Our results indicate that NeoWarm is effective as a thermoregulatory solution for hypothermic piglets. Our study has demonstrated that NeoWarm can successfully maintain piglets at a safe core body temperature of 38.6°C–39.7°C, indicating NeoWarm can maintain the piglets' body temperatures without inducing hyperthermia. Only one piglet, piglet B6, exceeded 39.7°C at any point in the study, having a final temperature of 39.9°C. However, we found reports indicating that a core temperature of up to 40°C (72) or even 41°C (86) could also be observed in piglets. Therefore, we deduce that a 0.2°C overshoot would not be a cause for undue concern. All six piglets that were placed inside NeoWarm were warmed to normothermic temperatures (38.6°C–39.7°C) within 67.3 ± 55.3 min ($n = 6$), while none of the five piglets in the ambient environment group had a final temperature equal to above 38.6°C, and only two of the five even reached the broader definition of normothermia of 38°C–40°C reported by other sources (72, 73, 86). Piglet A3 had a peak temperature within the normothermic range, but it was not maintained. Its final temperature dropped below 38.6°C at the conclusion of the trial, indicating that the piglet was not able to properly maintain its temperature on its own.

Neowarm is safe

Our study demonstrated that NeoWarm is safe. No piglet demonstrated evidence of burns or skin injury by NeoWarm, as visually assessed by veterinary technicians at the end of each trial, and only one piglet overshot the high end of

normothermia (39.7°C) and did so only by 0.2°C. Furthermore, we informally observed that the piglets seemed to be very comfortable inside NeoWarm. Piglets inside NeoWarm slept comfortably, while piglets that were left to warm themselves continued to shiver and roam around the pen seemingly looking for warmth. We did observe that piglets tried to wriggle themselves out of NeoWarm when they were at normothermic temperatures (38.6°C–39.7°C); however, piglets also tried to wriggle themselves away from the veterinary technicians when being held.

Limitations of the study

Due to convenience sampling, our study was limited to only one breed of piglets, and we were not able to match weight, sex, and litter. Our sample size was also small, having only 11 piglets in the study. It was difficult to acquire a large number of piglets for testing, as piglets are not selectively bred year-round. Given that our access was limited to only a few sows and our testing facility could only manage two piglets per weekday, inclusion criteria provided for enrollment of piglets at ages up to 120 h. However, we aimed to enroll piglets in our study within 24 h whenever possible. Additionally, although trained veterinary technicians reviewed the animals and concluded no damage or harm was done to the animal, skin samples were not taken to experimentally confirm their visual inspection.

Summary

This pilot study presented thermal monitoring and regulation of 11 piglets to demonstrate safety and preliminary thermoregulatory efficacy in a pre-clinical animal model for a novel biomedical device, NeoWarm. Our studies have shown that NeoWarm is able to warm hypothermic piglets to normothermic temperatures (38.6°C–39.7°C) with no more than 0.2°C overshoot. Not only is NeoWarm effective at warming the piglets, but it is also safe. Our study also suggests that neonatal piglets have more mature thermoregulatory capabilities than as might be expected by review of the literature and by seasoned veterinary professionals. In order to better define neonatal piglets as a standard for neonatal human thermoregulation, further studies would be required to define the limits of neonatal piglet thermoregulatory capabilities.

While safety was effectively demonstrated, form factor modifications that were necessary for this study may alter the thermoregulatory capabilities of the device between neonatal humans and piglets. Studies demonstrating NeoWarm efficacy in human neonates will be completed in future work. Future work will also focus on making NeoWarm more power efficient, removing the need of a benchtop power supply, using small, lightweight battery packs instead.

Author's note

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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 animal study was approved by Purdue University Institutional Animal Care and Use Committee. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

NB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft. GT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. OH: Formal Analysis, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. EL: Data curation, Formal Analysis, Software, Writing – original draft, Writing – review & editing. BW: Conceptualization, Investigation, Software, Writing – review & editing. AP: Conceptualization, Investigation, Writing – review & editing. KB: Conceptualization, Investigation, Writing – review & editing. SB: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. JL: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

OH is a co-founder of Predictive Wear, Inc. JL is a co-founder of Rescue Biomedical, LLC. SB is the inventor on patent #US10390630B2; International Patent (ARIPO): PCT/US2016/053394 – Infant thermoregulation and monitoring support system (issued February 4, 2022: and Nigeria Patent RP:NG/PT/C/2018/2802 – Infant thermoregulation and monitoring support system (issued March 20, 2019) issued to SB. OH, JL, and BW are co-inventors on patent #US11633152B2 issued to Purdue Research Foundation. OH and JL are co-inventors on patent #US10786201B2 issued to Purdue Research Foundation. OH and JL are co-inventors on patent #US20210022675A1 pending to Purdue Research Foundation.

The remaining 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 case of the neonate vs. LMIC medical academia—a jury-style systematic review of 32 years of literature without significant mortality reduction

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Introduction: The high neonatal mortality rate in low- and middle-income countries (LMICs) such as Nigeria has lasted for more than 30 years to date with associated nursing fatigue. Despite prominent hard work, technological improvements, and many publications released from the country since 1990, the problem has persisted, perhaps due to a lack of intervention scale-up. Could there be neglected discoveries unwittingly abandoned by Nigerian policymakers over the years, perhaps locked up in previous publications? A careful review may reveal these insights to alert policymakers, inspire researchers, and refocus in-country research efforts towards impactful directions for improving neonatal survival rates. The focus was to determine the prevailed effectiveness of LMIC medical academia in creating solutions to end the high neonatal mortality rate.

Methods: An unconventional systematic review protocol structure following the PRISMA 2020 checklist was designed and registered at INPLASY (registration number: INPLASY202380096, doi: 10.37766/inplasy2023.8.0096). A jury of paediatricians was assembled and observed by a team of legal professionals. The jury searched the literature from 1990 to the end of 2022, extracted newborn-related articles about Nigeria, and assessed and debated them against expected criteria for solution creation, translation, scale-up, sustainability, and national coverage. Each juror used preset criteria to produce a verdict on the possibility of a published novel idea being a potential game-changer for improving the survival rate of Nigerian neonates.

Results: A summation of the results showed that 19 out of 4,286 publications were assessed to possess potential strategies or interventions to reduce neonatal mortality. Fourteen were fully developed but not appropriately scaled up across the country, hence denying neonates proper access to these interventions.

Conclusion: Nigeria may already have the required game-changing ideas to strategically scale up across the nation to accelerate neonatal survival. Therefore, LMIC healthcare systems may have to look inward to strengthen what they already possess.

Systematic Review Registration: https://inplasy.com/, identifier (INPLASY202380096).

KEYWORDS

Nigerian neonate, neonatal mortality, preterm neonate, low birth weight, first 7 days of life

Introduction

Medical academia in low- and middle-income countries (LMICs) possess the advantage of a better knowledge of the challenges that affect healthcare in their settings. These challenges could be sociocultural, infrastructural, and political factors that could easily be hidden from international agencies that support policy implementations in their countries. Therefore, the duties of LMIC medical academia, such as conducting research and creating solutions for local scientific needs, must never be neglected, irrespective of the volume of imported ideas into their countries. A lack of an active forefront role for LMIC academia could be a major limiting factor in creating sustainable solutions to reduce neonatal mortality rates (NMRs) in LMICs.

Since the 1990s, there have been concerted efforts in LMICs, such as Nigeria, to seek and implement pathways for reducing NMR. Generations of hardworking Nigerian academics have used whatever was available to them to make improvements. However, recent demographic reports—especially following the verdicts of Millennium Development Goal 4 (MDG4)—still suggest that Nigeria has made no significant progress towards NMR reduction. With an estimated population of 223 million people, Nigeria experiences a daily newborn death rate of 846 (1)—the highest in the world. It is widely agreed that many Nigerian neonates still die of preventable causes, with neonatal interventions still largely reserved for the few in major cities where most hospitals with neonatal care units are located (2). Neonates remain the most vulnerable population with limited advocacy for their right to life and access to potential game-changing applications for "neonatal death prevention" in the Nigerian context. The continuing failure of the Nigerian system to protect neonates seems to have become a norm, a huge source of nursing fatigue, and an unwelcome situation for which no one is held accountable. However, it is yet to be understood whether the lack of decisive solutions for this neonatal failure is due to a lack of understanding, poor research techniques, or academic weakness on the part of the Nigerian medical academia, whose duty it is to synthesise the required solutions, or whether the fault lies in the failures of the Federal Ministry of Health (FMOH) of Nigeria to support and inspire indigenous medical research. It is necessary to assess what mitigants the medical academics have provided—has the research strategy towards under-five (U5) mortality reduction been wrong, or the academia been misfiring at the wrong target? Has the medical academia been poor in tactics, neglecting to target the most vulnerable aspects of the U5 lifespan, where it mattered most? Have donor/funding agencies and the FMOH been funding/supporting the wrong research collaborations, leading to 30 years of "insignificant progress"? The questions about this failure and the probable restoration of neonatal hope may only be achieved by identifying the wrong steps of the custodians of Nigeria's neonatal health and proffering suggestions that could reposition the drive for effectively eliminating preventable neonatal deaths in Nigeria. The Nigerian neonate may have been treated unfairly, and there is an urgent need to test the case of the "Nigerian neonate (plaintiff) vs. Nigerian medical academia (defendants) along with FMOH and their leadership appointees at the tertiary hospitals" to verify why academic efforts have not done enough to significantly lower the neonatal mortality rate since the 1990s (3). Nigeria, in this context, is an example case study, as similar situations are faced by many other LMICs who are currently struggling to reduce the high mortality and morbidity rates.

What is already known

Clue A: Various publications by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) during the last 10 years of the UN's MDG4 indicated that nearly 50% of under-5 years mortality in Nigeria were neonatal deaths (4), which highlighted the neonatal age as the most devastated population group to focus on to achieve a reduction in under-5 mortality (4, 5). Clue B: Within the first 28 days of neonatal life, the literature identifies the first 7 days (F7D) as the period during which four out of five neonatal mortalities in Nigeria occur (5, 6). Hence, there might be no interventions that could significantly reduce neonatal mortality without, first, successfully addressing and eliminating preventable deaths during F7D. Clue C: The literature further identified that perinatal asphyxia, infection, and prematurity were collectively responsible for nearly 83% of the neonatal deaths in Nigeria (7). However, prematurity was an important risk factor, with 75%–80% of these neonatal deaths occurring among preterm and low-birth-weight neonates, irrespective of the dominant cause of death (8). These three clues are diagrammatically demonstrated in Figure 1, clearly showing that the weakest points with the higher concentration of deaths in the U5 lifespan are fully identifiable—here referred to as the "sinkhole" (in red). This suggests that the target for any game change should be solving the sinkhole inadequacies of the F7D period. The sinkhole casualties are widened by the high incidence rate of "intrauterine growth-retarded" neonates, resulting in abnormally low birth weight for gestational age. In addition, sinkhole casualties are more prevalent in rural poorer communities (9). Hence, targeted low-cost applications for treating such tiny neonates are required to be developed to prevent a high death rate. Deaths at sinkhole points, which are common in many LMICs, could be prevented

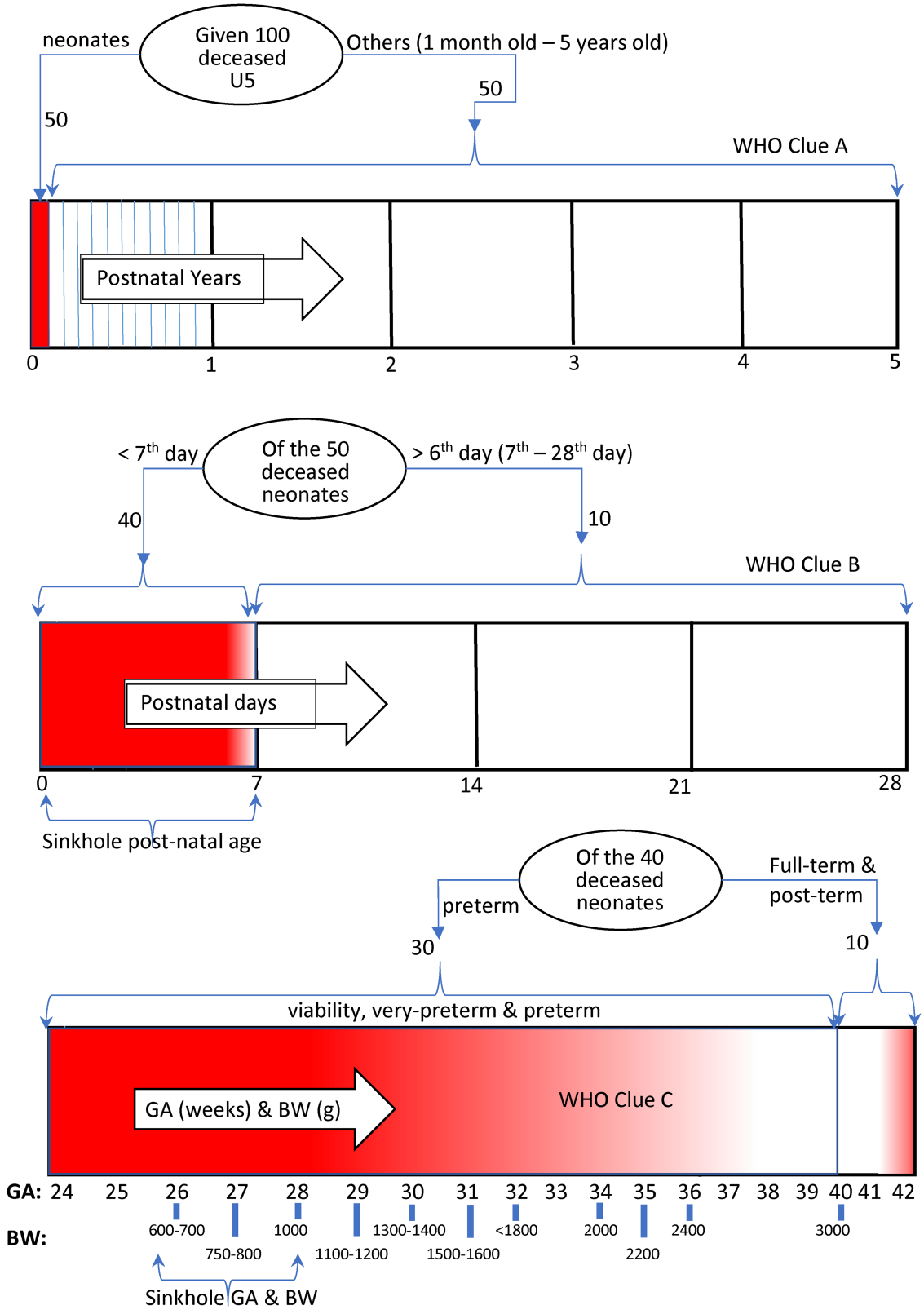

FIGURE 1
Depiction of mortality burden concentration in U5 lifespan—higher (red) and lower (white). GA, gestational age in weeks; BW, birth weight in grams.

by providing temperature stability, respiratory support, and treatments for infections, neonatal jaundice, and hypoglycaemia (10). However, most conventional technologies for achieving these tasks are designed for high-income countries (HICs) and are either unaffordable or unsuitable in LMIC settings (10). It is expected that LMIC-specific solutions must have been researched over the years by the LMIC academia, targeting these sinkholes to consequently pave the way for a drastic reduction in U5 mortality. However, if such deliberate efforts have not been actualised, this may hold answers for Nigeria's never-ending high NMR, for which there is a need to identify the liable wrongdoers and proffer recommendations for effective neonatal care strategies.

We seek to verify whether this is a case of academia's misjudgement of the real targets—challenges of the sinkhole casualties during the F7D period—which ought to have been discovered and rendered impotent. Therefore, the objectives of this investigation were to (1) systematically search the literature and ascertain if there had been substantial Nigerian studies that proffered some viable solutions specifically targeting preterm neonates in the F7D of life, whether Nigeria captured such messages and ideas, and perhaps, why such ideas were not scaled up; and (2) promote a mixed methods approach designed to evaluate game-changing technologies or solutions targeting the most vulnerable neonates at age F7D.

Materials and methods

A systematic review protocol structure following the PRISMA 2020 checklist was designed and registered at INPLASY (registration number: INPLASY202380096, doi: 10.37766/inplasy2023.8.0096) as a standard for this investigation. Hence, the unconventional jury panel technique was deployed to investigate why Nigerian neonates still die in huge numbers. At conceptualisation, the inquest was themed "The Case of the Nigerian Neonate vs. The Nigerian Medical Academia (NMA) & Ors" within the jurisdiction of the Nigerian intelligentsia, made up of young Nigerian paediatricians. The Nigerian neonate was identified as the ultimate victim of the 32 years in question, but the intelligentsia was to determine who was at fault for this. The main perpetrator could be the NMA, but other influencing bodies were to be investigated as well—such as the FMOH, hospital management, WHO, and UNICEF, as these are alleged wrongdoers who may have wittingly or unwittingly contributed to the plight of the Nigerian neonate by failing to warn the FMOH against their wrong directions and strategies. If found liable, the intelligentsia would determine to what extent each party is responsible.

In a typical jury setting, a set number of randomly picked citizens (jurors) are selected to assist in deciding a case. The presiding judge—chief arbiter—explains the case to the jurors, provides evidence and clues, guides them, and specifies the dilemmas of the case that the jurors would investigate as a team using the provided evidence. It is the duty of the judge to ensure that the jurors understand the case being tried and what constitutes an offence; hence, the judge could summon the jurors for briefing until there is a conviction that the jurors have understood the essentials of the wrongdoing. The judge may extend deliberation to enable the jury to reach the required unanimity or supermajority in their verdict to avoid a deadlock. The jurors would discuss, argue, and vote on the case to return a "liable" or "not liable" verdict. Inspired by the jury system in the present inquest, four passionate young Nigerian paediatricians were recruited to form the jury panel as jurors. A benchmark of experience requirements was set as a guide for the recruitment of the jurors, which, amongst others, included the following criteria: (1) must have >5 and <15 years of post-qualification experience as a doctor, (2) must have continuously practiced in neonatology for a minimum of 3 years within this period, (3) must be a qualified consultant, or in the part-2 (final) stage of consultant qualification training, or >5 years working as a senior medical officer in newborn care, and (4) must have achieved research co-authorship in >3 published journal articles. A relatively more senior and well-experienced researcher served as the arbiter, assisted by another senior researcher who chaired the hearing sessions during discussions of issues of conflicting interest with the primary arbiter. A guest arbiter, a senior nursing fellow, was recruited to stand in during the unlikely event of the absence of the assistant arbiter in any session. The arbiters were chosen from a wider medical spectrum of highly experienced scientific researchers with >10 years of research leadership experience, holding ranks from associate to full professors, or senior professional qualifications such as "RN" with over 15 years of experience. The third group in the setup was the observers. This group comprised two practicing lawyers of judicial competence who were able to attend the jury sittings to observe the fairness of the debates and decisions.

Considerations of conflicts of interest

As a necessity, all the constituent parties in the investigation panel—arbiters, jurors (paediatricians), and observers—were screened to minimise the possibilities of conflicts of interest. All confirmed the independence of their opinions and declared their ability to maintain unbiased opinions. The arbiters interviewed and selected the jurors from early-career practicing paediatricians in Nigeria, who do not have any baggage of personal guilt towards the neonatal failure on trial.

Systematic review

A possibility might exist where previous publications have provided answers to the current neonatal dilemmas but have been swallowed up in piles of unutilised findings in the last 32 years. It would be unfair to assume that the hardworking Nigeria academia and research community did not provide answers. Typically, a systematic review meticulously delivers a summary of all available primary research relating to a specific research question. Therefore, the systematic review technique, albeit modified, was used to carefully assess the existing literature

for the country and provide unbiased recommendations for the LMIC context.

Search strategy

In our modified adjudication panel style, the literature was assessed on titles addressing Nigerian U5, infant, and neonatal mortality and morbidity from 1990 to 2022. The local research efficiency of NMA was investigated, essentially for the challenges during the F7D period of neonatal life. Therefore, the search specifically looked for studies highlighting new solutions to existing Nigerian problems—research conducted within Nigeria, rather than global initiatives. The arbiters scoped the literature on titles that addressed "Nigeria and under-five," "Nigeria and infant or infants," and "Nigeria and neonate or neonates" from 1990 across three Internet search engines—PubMed, Google Scholar, and the Web of Science.

Inclusion and exclusion criteria

Old and recent publications about novel U5 devices, improved protocols, and modified procedures aimed at improving outcomes, which could have been capable of national scale-up across Nigeria, were identified. All the extracted titles and abstracts of these publications were imported into Rayyan Systematic Review software (11). In brief, Rayyan is an Internet-based systematic review platform that enables team members of a study to independently access the same workspace to assess, exclude, or include extracted titles. In Rayyan, the team leader uploads all publications for assessment and turns-on a "blindfold" key to ensure that each team member conducts their assessments privately without seeing others decisions until every member has finished their review. The leader schedules an online meeting for assessment reconciliation when the "blindfold" key is turned off to reveal how the team members judged the publications and to possibly debate "conflicting" judgements, which are those publications that failed unanimous "inclusion" or "exclusion" by all team members. We designed six stages of the rigorous technique to eliminate non-qualifying articles per stage (Figure 2). A fresh Rayyan environment was initiated and blinded for the jurors' independent assessments and judgements in each stage. Article rejection criteria for the stages were the following:

(1) non-paediatrics publications;
(2) not strictly related to U5 patients or research;
(3) not neonate-specific, not Nigeria-specific, not published by academics in Nigeria, or anchored by a Nigerian researcher for cases of authorship involving non-Nigerians;
(4) not primarily about new or modified devices, improvement protocols, or procedures for better outcomes—jurors were required to choose the reasons for exclusion from a dropdown menu;
(5) final elimination stage—the portable document format (PDF) of accepted publications were uploaded to the Rayyan stage 5 portal to aid full understanding of its contents and to re-assess paper's eligibility as strictly "novel" or "modified"—"novel" refers to previously non-existent devices for solving existing problems, while "modified" pertains to existing techniques systematically improved for better outcomes.

The "included" publications were re-grouped based on topical issues they addressed.

(6) Jurors extracted information relating to the technique's subsequent success rate, national coverage, or impacts, awarding assessment scores, as given in Table 1. Jurors carried out this function through independent wider literature search and direct contact and interviews with available co-authors of the technique.

Impacts and outcomes assessed

Jurors were to take notice of the beneficiary population—whether the technology was used in one facility or across multiple centres, spanning one or more climatic regions (southern, middlebelt, and northern), and whether its usage extended across one or more of the states of Nigeria. The success rate of a technology was evaluated based on its effectiveness in addressing the weakest point of the neonatal life spectrum—the sinkhole region—represented by birthweights of 600–900 g during the F7D period (Figure 1). Scores were graded as follows: 0–2 for no impacts, 3–6 for low impacts, and 7–10 for high impacts. The measurement criterion was strictly based on published, referenceable data demonstrating successful treatment outcomes for a fraction of n >9 "sinkhole neonates" or referenceable quantitative data from any of the Nigerian tertiary hospitals. Sinkhole neonates were adjudged "successful" with the applied piece of technology or life-support protocol if the application was proven to have delivered the expected positive outcome towards neonates' eventual survival. The nationwide usage score was determined as the fraction of the total referral special care baby units (SCBUs) in Nigeria adopting the technology. Assuming an average of two tertiary SCBUs per Nigerian state, full nationwide coverage was assumed at 74.

Jury sittings

The jurors, the arbiters, and the observers assembled virtually, all logging into the Rayyan environment stage being discussed. The chief arbiter initiated the meeting and disabled the "blindfold" key, allowing each juror to see how others judged the elimination criterion. All the publications that were unanimously included or excluded by all four jurors (paediatricians) automatically moved into the Rayyan "include" or "exclude" file lists, respectively. All the remaining articles automatically moved into the Rayyan "conflicted" judgement list. The "conflicted list" tool identified all articles selected by three of the four jurors, which were then also moved to the "include" file. All the publications accepted by only one juror were moved to the "exclude" file. Publications accepted

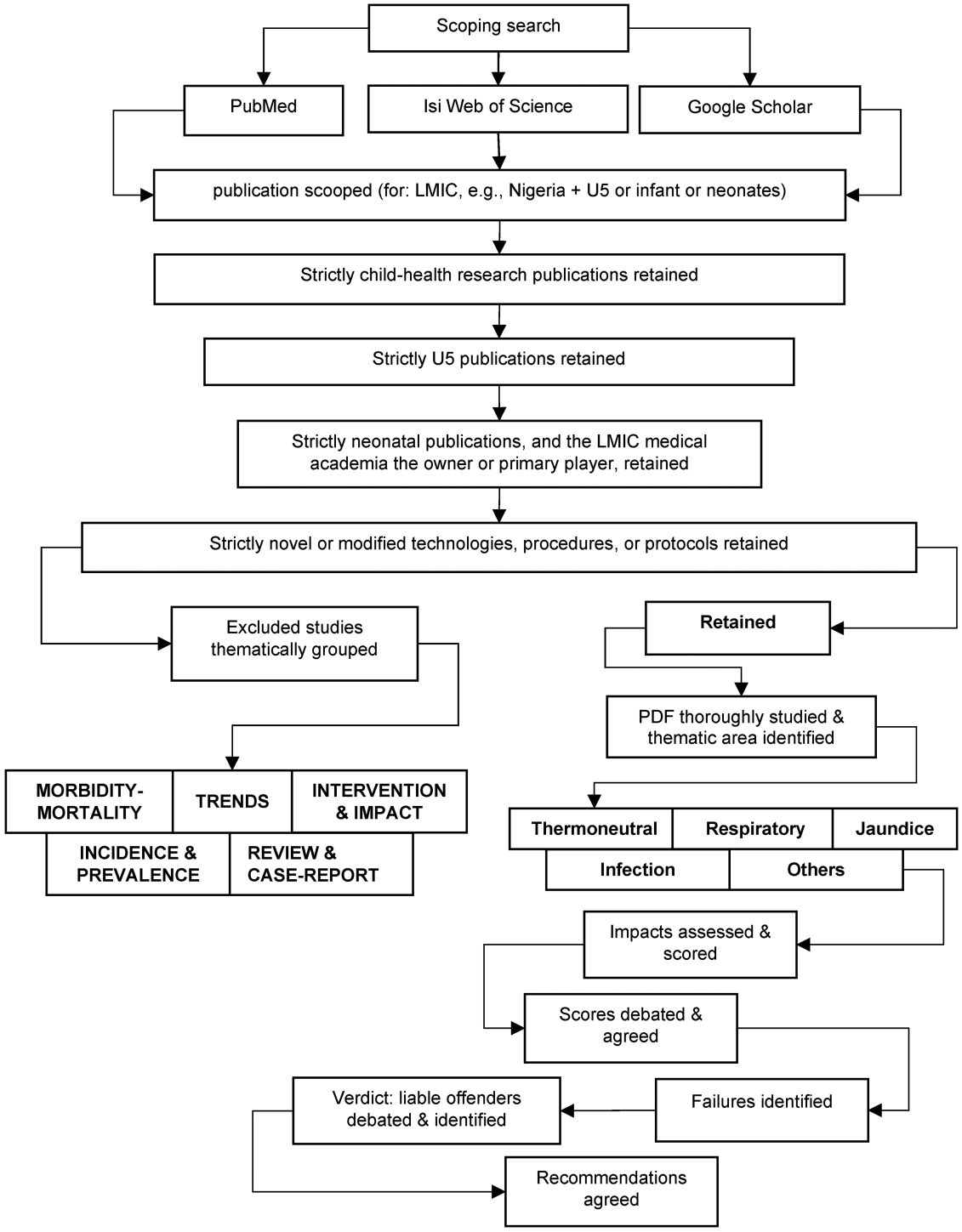

FIGURE 2
Modified PRISMA for article elimination.

by only two jurors were brought forward for joint reassessment by the jurors, presided over by the chief arbiter. After dialogue on the article in question, the four jurors voted on its inclusion or exclusion. In the event of a tie, the assistant arbiter cast the deciding vote. All jury sittings were conducted via Zoom.com Online Conferencing (Zoom Video Communications, Inc., San Jose, CA, United States) and WhatsApp conference calls, simultaneously. The combined use of these two communication platforms enabled us to combat the limitations posed by poor Internet connectivity for jurors joining from Nigeria. Any conflict of interest relating to any jury member resulted in their recusal until a decision was reached in their absence.

The assessment outcome guided the jurors to deliberate and agree on verdicts on the failures of the NMA, if any, and their

TABLE 1 Potentially game-changing intervention ideas.

Group	S No.	Article id	Idea presented with its describing article(s)	Current development status (fully developed and available Y/N)	Known user coverage (Y/N)			Reported success rate on 600—900 g and sinkhole neonates (score: 0–10)	Nationwide user coverage	Why poor coverage or whose failing? (1 – 6)
					>1 SCBU? If "Y," how many are known?	>1 Nigeria region? If "Y," how many are known?	>1 State? If "Y," how many are known?			
(A) Neonatal thermoneutral support ideas	1.	Amadi et al. 2014, EFS	A weatherproof nursery design (12)	Y	13	3	7	8	14/74	3, 4, 5
	2.	Amadi et al. 2007, RIT	Digitally recycled incubators (13)	Y	24	3	21	9.5	24/74	3, 4, 5
	3.	Ige et al. 2021, Incubator hood	Suitability of hood geometry (14)	N	N	N	N	N/A	N/A	1, 3
	4.	Amadi 2012, Handy approach (HHA)	Neonatal thermoneutrality in a tropical climate (15)	Y	>24	3	21	9.7	24/74	3, 4, 5
	5.	Amadi et al. 2017, HISA	A novel technique that minimises early neonatal mortality (16)	Y	>8	3	>9	9.8	9/74	3, 4, 5
(B) Neonatal respiratory support ideas	1.	Obu et al. 2020, PoliteO_2 blend	Air-oxygen blender for respiratory support (17, 18)	Y	2	1	2	8.5	2/74	1, 3, 4, 5, 6
	2.	Onwe et al. 2020, The PSS	A novel oxygen-splitter system (19, 20)	Y	4	2	4	10	4/74	1, 3, 4, 5
	3.	Amadi et al. 2019, Polite-heart CPAP	A low-cost commercial bubble CPAP machine (21)	Y	10	3	6	9.3	10/74	1, 3, 4, 5
	4.	Audu et al. 2013, ibCPAP	Customised bubble CPAP device (22, 23)	Y	47	3	37	0	47/74	1, 3, 4, 5
(C) Neonatal jaundice intervention ideas	1.	Powell et al. 2020, Irradiance meter	A smartphone-enabled phototherapy meter (24)	Y	N	N	N	N/A	N/A	1, 5, 6
	2.	Olusanya et al. 2017, Nomogram	Transcutaneous bilirubin nomograms in African neonates (25)	Y	3	2	3	8	3/74	1, 3
	3.	Slusher et al. 2013, Filtered sunlight	Treatment of neonatal jaundice with filtered sunlight (26)	Y	N/A	2	2	N/A	N/A	1, 4, 5, 6
	4.	Abdulkadir et al., Phototherapy	Nigerian-fabricated phototherapy devices (27)	Y	10	3	6	5	10/74	1, 4, 5, 6
(D) Other topical issues	1.	Amadi et al. 2022, NRS	A community-integrated concept (2)	Y	4	3	4	8	4/74	3, 4, 5
	2.	Modekwe et al. 2021, Oral ketamine	Trial on the efficacy and safety of oral ketamine in circumcision (28)	Y	N	N	N	N/A	1/74	1, 3, 4, 5
	3.	Sobowale et al. 2020, Fuzzy system	A clinical decision support system-based neonatal monitor (29)	Y	2	N	N	N/A	2/74	1, 3
	4.	Emuoyibofarhe et al. 2019, Fuzzy logic	A fuzzy rule-based model for remote monitoring of preterms (30)	N	N	N	N	N/A	0/74	1

(*Continued*)

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TABLE 1 Continued

Group	S No.	Article id	Idea presented with its describing article(s)	Current development status (fully developed and available Y/N)	Known user coverage (Y/N)			Reported success rate on 600—900 g and sinkhole neonates (score: 0–10)	Nationwide user coverage	Why poor coverage or whose failing? (1 – 6)
					>1 SCBU? If "Y," how many are known?	>1 Nigeria region? If "Y," how many are known?	>1 State? If "Y," how many are known?			
	5.	Eregie et al. 1991, GA estimation	A simplified method of estimating gestational age (31)	Y	3	2	3	6	3/74	1, 3, 4, 5
	6.	Amadi and Abubakar 2023, Polite-Light-Bank	LMIC facility-lighting technology (32)	Y	4	2	3	9	4/74	4, 5

Nationwide user coverage (in fraction): It is based on an assumed total of 74 tertiary SCBUs in Nigeria, justified via literature evidence or by referenceable observation and facility contacts. Why poor coverage or who is to blame—(1) tool, (2) neonate, (3) medical academia, (4) hospital management, (5) federal and state ministries of health, and (6) foreign partners.

EFS, evening fever syndrome; RIT, recycled incubator technology; HHA, handy approach; HISA, initial setpoint algorithm; PSS, politeO_2 splitter system; CPAP, continuous positive airway pressure; ibCPAP, improvised bubble CPAP.

co-defendants. The jurors agreed on recommendations on how the co-defendants might encourage, inspire, or influence researchers to dwell more on game-changing studies that could have eliminated the high "sinkhole" NMR.

Results

The search engine scoping pooled 194 publications from PubMed, 673 from Google Scholar, and 3,418 from Web of Science, producing a total of 4,286 articles. The removal of duplicates left 4,015 articles for assessment. The stage-wise elimination process left only 19 pieces of intervention techniques, as shown in Figure 3 (2, 12–17, 19, 21–31). The stage 1 filtration exercise was completed after a cumulative of 39 individual juror working sessions and a total of 1,162 h. Stage 2 lasted 45 sessions and totalled 1,254 h, stage 3 lasted 38 sessions and totalled 1,149 h, stage 4 lasted 29 sessions and totalled 796 h, and stages 5 and 6 involved tens of sessions and thousands of hours, excluding jury sitting hours.

Some of the 19 ideas produced impressive results during their trials and subsequent usage at a few tertiary hospitals. However, none of these applications gained full national coverage, hence failing to scale up nationally. The academia and solution creators were unable to ensure wider usage of their successful ideas. Most reviewed papers demonstrated no evidence of agency funding or other support from the FMOH or hospital management. There was no evidence of adoption or encouragement by the FMOH for these potential game changers. The full assessment of the 19 potentially game-changing ideas is presented in Table 1—thematic areas as identified included the following: (1) five papers regarding thermoneutral support, (2) four focused on respiratory support, (3) four on the diagnosis and management of jaundice, and (4) six additional interventions. Notable amongst them were "Treatment of neonatal jaundice with filtered sunlight" (26), "A novel oxygen-splitter system that expands the utility of oxygen cylinder by up to 700%" (19, 20), "A new low-cost commercial bubble CPAP machine" (21), and "A novel air-oxygen blender for neonatal respiratory support," which was fully described in a more recent publication (18).

Discussion

Critical concerns, such as the trend of persistent high neonatal mortality rate in LMICs, are resolved by the intervention of indigenous local scientists, amongst other players, who understand the health situation and possess a personal patriotic passion for ending the suffering of their people. Frugal usage of available time and resources for making a significant impact must, therefore, target identified research questions and gaps, focusing on those with the highest likelihood of contributing to overall mortality reduction. Any other strategy that ignores the weightier gaps could be described as "misfiring," and could go on for many years without changing the overall situation. Game-changing solutions must necessarily be created around bridging

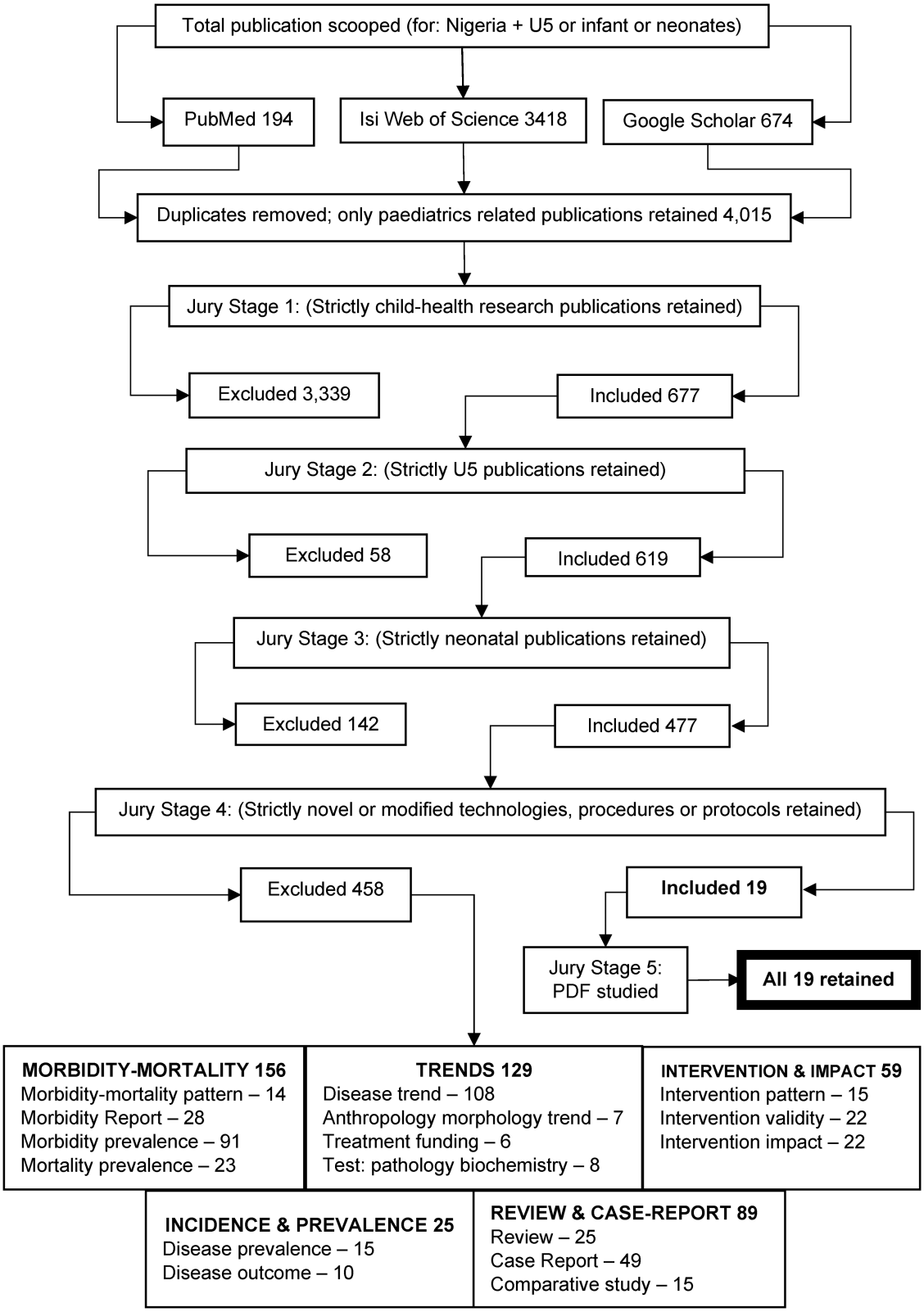

FIGURE 3
Inclusion and exclusion summary chart.

the weightier gaps, without which the overall situation remains unsolved. It could therefore be concluded that the unacceptably high neonatal mortality that has lasted for more than 32 years in Nigeria is an issue for which its weightier gaps are either undiscovered or left without a deliberate synthesis of problem-specific interventions.

We aimed to investigate whether the NMA and associated agencies (the co-defendants) have contributed to the age-long high death rate of the Nigerian neonate (the plaintiff) by failing to identify the weightier gaps and develop effective problem-specific interventions for these. It is understood that importing foreign-developed devices and ideas is a quicker option for LMICs to bridge these gaps. There is nothing wrong with this approach, as research is, by definition, international. However, LMIC researchers are certainly responsible for conducting high-quality intervention science/operational research studies to assess effectiveness, labouring to tweak ideas or creating their own culturally compliant versions. However, they often fail to appreciate that technology importation alone may not sustainably solve the problem without knowledgeable tweaking of associated issues of operational infrastructure, culture, and climate. Therefore, there may be no shortcut to avoiding "getting dirty on the research bench" for LMIC medical academia.

Previous publications by the WHO provided insights into the real gaps fuelling the high U5 mortality rate in Nigeria. By carefully piecing together these publications, it was possible to unravel where research efforts should have been channelled to enhance overall reduction in U5 deaths in Nigeria (Figure 1). Hence, the FMOH and NMA needed to (1) identify successful research that has implemented solutions that are likely to be successful in the Nigerian context of healthcare provision, particularly targeting F7D preterm and low-birth-weight neonates—the so-called "sinkhole" stage of the neonatal life spectrum, (2) promote and strategically scale up these solutions to reach neonates even in most remote areas of Nigeria, and (3) encourage more locally driven research to improve the existing solutions by ensuring that deployable research funds for U5 interventions, whether from the Nigerian Government or any partners, are allocated based on the fraction of the total mortality burden represented by neonatal deaths. The first clue from the WHO implies that noticeable progress could be achieved by allocating 50% of the available funding to neonatal care (4). The second clue suggests that 80% of neonatal deaths occurred during F7D (5). Therefore, to make noticeable progress, 80% of neonatal funding and energies should focus on research targeting the first quarter of neonatal life. From the third clue, we found that >75% of deceased F7D neonates had low birth weight and/or were born prematurely (8). Therefore, good progress could have made by channelling 75% of deployable funding towards research activities targeting the weaker neonates of age F7D. However, these resource-allocation strategies were never implemented.

However, after a total of 141 individual juror assessment sessions covering 4,361 h and numerous gruelling jury sittings, jurors found only 19 out of 4,015 publications from the NMA containing potentially game-changing innovations. Jurors considered this outcome of only 19 potentially game-changing ideas over 32 years to be insufficient; hence, they agreed that, despite their hard work, the NMA did not demonstrate enough leadership or play a sufficient role in synthesising adequate solutions for the aching problems. Furthermore, there was no evidence that these few innovations were encouraged, patronised, or scaled up by the co-defendants in this case. It is noteworthy that in high-income countries, discoveries often do not lead to rapid implementation, as the process may take numerous years. However, none of the assessed innovations in this inquest received any specific funding or assistance to support indigenous developers in reaching neonates in remote areas of Nigeria. Hence, the victims suffered considerably through preventable deaths from the time these innovations were discovered. We consider this failure as a negation of responsibilities by the NMA, FMOH, and hospital management. Some blame also falls apportioned on all support agencies, which for many years have not insisted on proportionately allocating funds to weightier gaps. The jury identified weaknesses and culpabilities across many sides, including the failure of the academia to raise concerns on problem areas for research, failures by implementers despite knowing what has been discovered to work, and the failure of the government to fund/support these efforts. Global research funders could have made exclusive calls for research to address this specific problem (neonatal sinkhole) in LMICs but failed to do so.

Verdict

With no prejudice prior to this investigation, the jurors have carefully examined all evidence from extracted publications and unanimously agreed to uphold that the Nigerian neonate has not been given a fair chance of survival in the last 32 years by the defendants and co-defendants and, hence, wish to state the following:

The jury unanimously agreed to hold that the so-called sinkhole of neonatal life is the most devastating but unchallenged healthcare gap that has kept NMR high in Nigeria. The jury primarily faults the Nigerian healthcare system, represented by the FMOH and the NMA, which has failed to apply and disseminate information on available novel technologies and innovations within the country. The implementers of global health policies in Nigeria also failed the LMIC neonates—and every group is held responsible for their failure to act or ask the right questions when it became obvious that the anticipated results were not being realised. The actions of the FMOH and the academia in the last 32 years did not demonstrate a full knowledge of the devastating "sinkhole" as explained in this inquest. Therefore, the devastating F7D was left unchallenged till date. Funding grants were not made available by the Nigerian Government or indicative research advocacy policy by the FMOH, who should be responsible for developing innovative policies, monitoring the adherence to the policies, and ensuring that the right researchers received the right amount of support and inspiration. Foreign partners should not

be held responsible very much because Nigeria needed to have gotten her acts right and insisted on the best course of action for her problems. The jury apportions part of the fault on the tool developers who could have done better in marketing the developed ideas by striking a fair balance between "money making" and "life saving." Nigeria is always mentioned internationally as an important country, and there are Nigerian representatives in all the UN bodies—they should have worked harder, made more noise for the Nigerian neonates, and requested more information and data from the home academia to be able to correctly represent Nigeria and what it needs. They all failed the neonates.

Recommendations

Novel medical devices that have been created and adapted for the Nigerian climate for premature and/or low-birth-weight neonates, which have undergone clinical trialling with published significant success rates but with low nationwide usage coverage, such as those mentioned in this report, should all be brought to the attention of policymakers and stakeholders as ideas deserving of promotion and adoption to enhance neonatal interventions in remote and rural hinterlands across Nigeria.

The concept of a community-integrated neonatal rescue scheme (NRS) in resource-poor environments is brilliant and embraces intervention at three key levels of neonatal care (2). Upon its introductory publication in 2022, its third level of care (the hub centre) already demonstrated huge success in Minna metropolis (Niger State), reducing neonatal mortality from 90% to 4% in 6 years; this is one scheme that could be launched nationwide as soon as possible and serve as a good lesson for the other LMICs (33). Algorithms such as the handy approach (HA), as described in the IntechOpen publication (15), and the initial set-point algorithm (ISA) (16) are validated tools that have demonstrated evidence-based success rates (34) and should be scaled up in caregiving.

Research aimed at diagnosing and managing preventable life-threatening complications in neonates and improving neonatal outcomes of "sinkhole"-classified neonates should be at the forefront of efforts by the LMIC academia. Strategic ideas, concepts, designs, and proposals proven effective by research should be fast-tracked or adapted where needed and scaled up by the appropriate committees and bodies assigned to these roles.

Data availability statement

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

Author contributions

HA: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. IA: Data curation, Formal Analysis, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. UU: Data curation, Formal Analysis, Methodology, Supervision, Visualization, Writing – review & editing. R-DE: Data curation, Formal Analysis, Investigation, Validation, Visualization, Writing – review & editing. NE: Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. ON: Formal Analysis, Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. CD: Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

Author NE was employed by Frederick & Co., Barristers and Associates.

The remaining 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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Safe delivery kits and newborn infection in rural Ethiopian communities

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Objectives: Our goal in this study to investigate the impacts of using safe delivery kits, along with education on their appropriate use, has on preventing newborn and maternal infection.

Design: A cross-sectional study.

Setting: Participants, and Interventions: we conducted the study on 23 sites across a rural district in Oromia Region, Ethiopia. Safe delivery kits were distributed by health extension workers. Participants comprised 534 mothers between the ages of 17 and 45 years, who were given a safe delivery kit at 7 months' pregnancy for use during their subsequent delivery. Data collection was performed by the trained interviewers in rural Ethiopian communities.

Results: Multiple logistic regression analyses showed an independent association between using the cord tie provided in the kits and decreased newborn infection. Specifically, newborns whose mothers used the cord tie were 30 times less likely to develop cord infection than those not using the cord tie in the kits. Further, mothers who received education regarding safe delivery kit use had lower rates of puerperal infection.

Conclusion: Single-use delivery kits, when combined with education regarding the appropriate means of using the kit, can decrease the likelihood of maternal infection.

Implications for nursing: Nurses and health extension workers in low and middle-income countries should educate mothers on safe delivery kits by providing information regarding their usefulness and the importance of correct and consistent use. Implications for Health Policy: our findings emphasize the need for further interventions in vulnerable countries designed to increase the rate of hygienic birthing practices for deliveries outside health-care facilities.

KEYWORDS

cross-sectional observational research, Ethiopia, infection, newborn, safe delivery kit, supply kits

1 Introduction

Globally, 2.3 million children died in the first 20 days of life in 2022. There are approximately 6,500 newborn deaths every day, amounting to 47% of all child deaths under the age of 5 years (1).

Newborns have a higher mortality rate than children of older ages (2). The leading causes of newborn death include infection, suffocation during delivery, and complications related to premature birth. In particular, over half of all newborn mortalities are related to delivery

environments (3, 4). Meanwhile, over 90% of maternal mortalities that occur in low and middle-income countries (LMIC) are caused by hemorrhage, infection, unsafe abortion, and eclampsia, and over 20% of such mortalities can be prevented by providing safe delivery environments (5).

In other words, the deaths of many newborns and mothers could be prevented by providing a hygienic delivery environment and trained assistants; unfortunately, the international community does not prioritize maternal-newborn health. Nevertheless, in countries in Sub-Saharan Africa, including Ethiopia, the mortality rate of children under 5 years of age has steadily decreased over the last two decades, and this has been attributed to international involvement; however, the mortality rate in this region remains higher than that in other countries. Despite the overall decrease in mortality among children younger than 5 years, the proportion of deaths that occur in the neonatal period is increasing (5, 6).

Furthermore, Ethiopia has made significant progress in reducing childhood mortality rates, but it still faces challenges. Ethiopia is among the top 10 countries with the highest neonatal mortality rate in 2020. Approximately, 97,000 babies die every year in their first 4 weeks of life in Ethiopia. Subnational neonatal morality and hospital-level neonatal mortalities are variable, particularly in developing or pastoralist regions; data are not readily available (7).

In Ethiopia, 94% of children are birthed at home unattended by trained persons. The government introduced an innovative strategy, the Health Services Extension Program, in 2003. Safe delivery service is a component of the program's maternal and child health care package. However, little is known about the status of the service uptake. This study thus aimed to assess the utilization of clean and safe delivery service and associated factors in rural Ethiopia (7). Further, as of 2008, less than half of the Millennium Development Goals (MDGs) (8), which were targets for 2015 agreed by all United Nations member states, had been accomplished (5, 9). In particular, studies have reported that countries in Africa and Southeast Asia have not shown any improvement. Thus, health-care-related aid should focus on the Maternal and Child Health Project, which is one of the priority projects of the MDGs and SDG (10, 11). Safe delivery improves the health of both the mother and the newborn and, therefore, the health of the family, which is the fundamental element of economic development; thus, creating a safe delivery environment is important.

Infection is the main cause of infant and maternal mortality in low and middle-income countries (11). Infection in the first week of life is associated with maternal infection (12). While family planning interventions, high-quality delivery, and postpartum care, delivering in facilities are research-proven strategies to prevent maternal and neonatal mortality, many women in low and middle-income countries lack access to these interventions, even though such measures have been recommended as effective strategies by which governments can enhance maternal and child health-care services (13, 14). In low and middle-income countries such as Ethiopia, newborn infection is a primary cause of newborn death. However, prematurity and perinatal events (asphyxia) are also leading causes (14, 15). In general, newborn infection is caused by using contaminated delivery instruments in unhygienic delivery environments. Therefore, the most direct and fundamental solution is to control bacterial infection by providing a clean delivery environment.

There are only a few studies on water, sanitation, and hygiene (WASH) looking at this. We believe instruments and environmental containments play a large role in maternal and newborn infection, however, this is complicated. There are several issues to consider such as, mothers may not deliver in a facility which increases risk, they may have prolonged rupture of membranes. Prematurity and perinatal events (asphyxia) are also leading causes of newborn and maternal death (15).

The World Health Organization (WHO) has emphasized the need for six "clean" elements (clean hands, clean vagina, clean umbilical-cord-cutting instruments, clean cord-tying instruments, clean delivery surface, and clean cutting surface) to ensure a hygienic delivery environment (16). To help achieve such an environment, delivery kits, typically reusable, are given to community-based women and traditional birth attendants (TBAs) after training. The items in a safe delivery kit (SDK) include a plastic sheet for cleaning the delivery space, soap for the delivery helper, a surgical blade for cutting the umbilical cord, a clean cord tie, and a clamp for tying the umbilical cord with cotton. SDKs are also cost-effective (17, 18). Thus, the WHO states that this delivery kit is the most simple and useful tool for a clean delivery. The WHO has also begun to provide countries with a manual to enable them to customize the kit to suit the respective situations in their countries. A feasibility study reported that by distributing SDKs to rural regions with poor medical care facilities and high infant mortality rates, this project can decrease the risk of infection for newborns by nearly 80% (19). Also, it can contribute to the development of local communities, as residents can continue to operate the project by themselves. However, the meta-analysis has controversial outcomes (12).

We expand on previous research and conclusions about safe home delivery kits, including in Ethiopia and regionally. As TBAs are not part of the health system in Ethiopia formally, and health extension workers (HEWs) are, this study does not consider TBAs. HEWs provide prenatal/postnatal care and refer to skilled attendants. The family planning intervention service program is being implemented by deploying female HEWs who received training. Each Kebele will have a health post, the operational center for the HEWs (20). Antenatal care and clean and safe delivery services are among the elements of the maternal and child health services package (21). Implementing these elements focuses on empowering women, their families, and communities to recognize pregnancy-related risks and take responsibility for developing and implementing appropriate responses.

In order to solve infant and maternal mortality-related problems in low and middle-income countries, international organizations and many other non-government organizations (NGOs) are actively promoting the SDK as a cost-effective measure (5). For example, the United Nations Development Programme has successfully promoted "mama kits" in rural regions of Uganda (3); as a result, medical-specialist-supported deliveries have increased nine-fold, and cases of bacterial infection in the vagina, eye infection in newborns, diarrhea, tetanus, and sepsis, all of which could occur during delivery in an unhygienic environment, have fallen remarkably. In Pakistan, SDKs were distributed after providing TBAs with basic knowledge regarding delivery (21). Examinations consequently found that rates of maternal mortality and stillbirth decreased by almost 30%, and infection in newborns decreased by nearly 80% (22, 23). Thus, it is clear that the

SDK project can create conditions for pregnant women to deliver their babies safely, mainly because most of the female residents in the targeted regions deliver babies at home or in an unhygienic environment (24).

1.1 Aim of the study

The purpose of the present study is to investigate the impacts of using SDK that is provided with education training on how to use the kit to prevent newborn and maternal infection.

2 Methods

2.1 Research design

This study utilizes data from community-based interventions designed to reduce maternal and newborn mortality conducted in 23 sites across a rural district of the Oromia region, which is situated in eastern Ethiopia. SDKs were distributed by health extension workers (HEWs) who received training in SDK use.

2.2 Sample and setting

In total, 599 female respondents to a pre-survey on a family planning intervention project. Of those, 534 mothers received and used a SDK during delivery. The women between 17 and 45 years of age were given SDKs by the trained personnel at 7 months of pregnancy. 89% of those who received SDK used them for subsequent deliveries. Data collection was performed by the trained interviewers in Woreda, Ethiopia, from October 22 to November 21, 2011.

2.3 Contents of the safe delivery kit

Local health-care providers were consulted to determine the items that would be necessary for inclusion in an SDK for their respective communities (Figure 1). Consequently, the items selected for the kits were a surgical blade, soap, a cord tie, a plastic sheet, a fabric cover, a flashlight, a pair of sterilized gloves, and a user manual according to the need assessment.

2.4 Preparation, production, and promotion of SDK

The SDK project comprised four phases (Figure 2). Phase 1 was the preparation phase. Each community's opinions were collected by performing a needs assessment on the requirements of the community; then, after deciding on the items that should be included in the SDKs, such as soap, cord tie, and lantern, market research was conducted, the seven items included and a user's manual was developed.

In order to collect opinions on means of producing and distributing SDKs in the community, a meeting with local residents was held, and meetings with parties related to the community were held on nine occasions across the 23 sites. Previously, to collect opinions on the means of producing and distributing SDKs in the community, one meeting with local residents was held in each community, and nine meetings with parties related to the community.

Phase 2 was the production phase. A production manual for the SDKs was developed, and local residents were educated and trained. Then, SDKs were produced by employing local female laborers. By November 2010, 11 local laborers had produced 15,000 SDKs over 59 days. The average daily production was 254 kits, and average production per person was 23 kits.

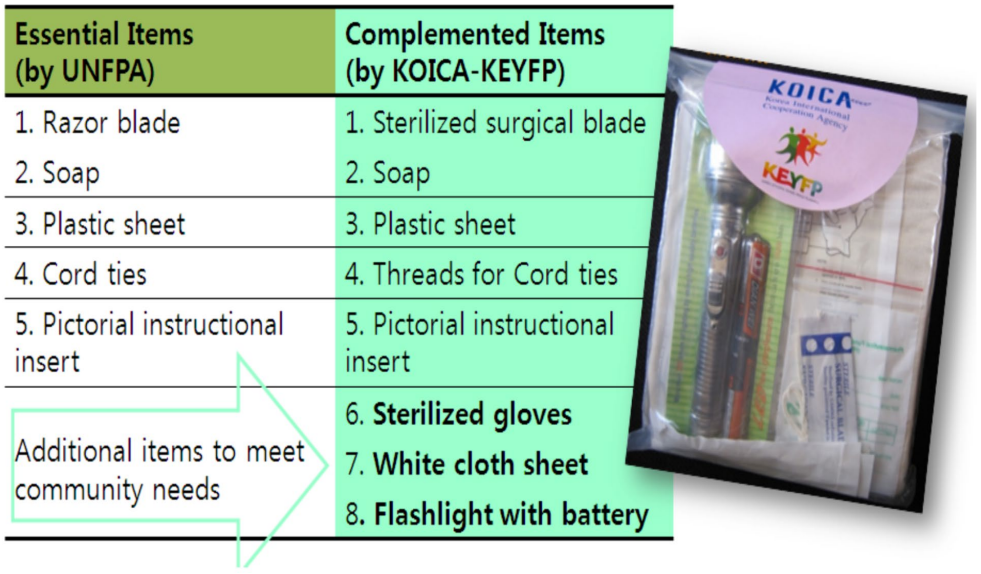

FIGURE 1
Safety delivery kit items.

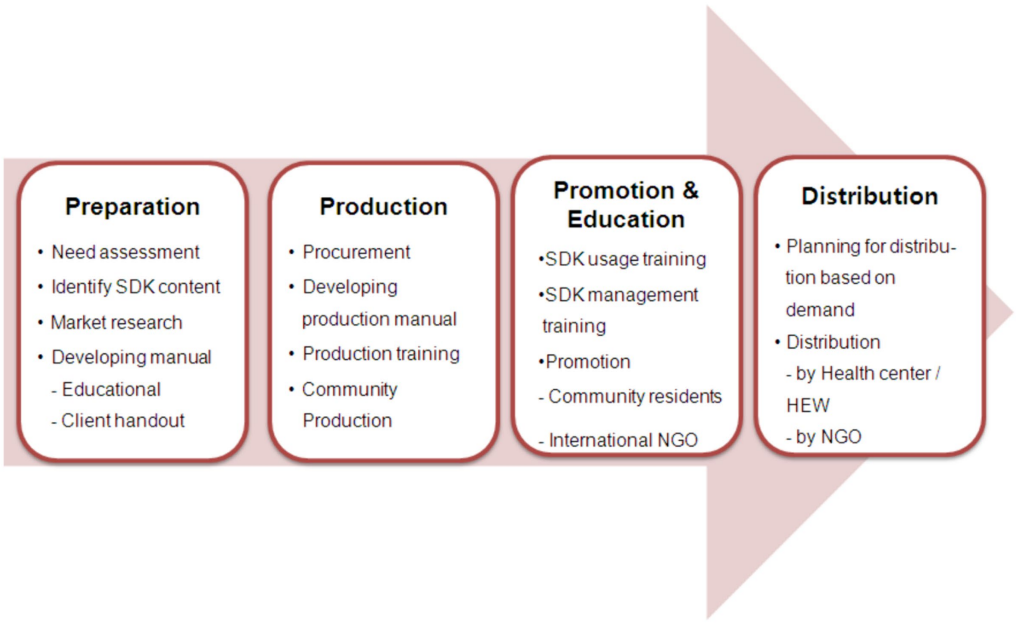

FIGURE 2
Safety delivery kit project procedure.

Phase 3 was promotion and education. Before distributing the SDKs, the residents of each community were given education regarding safe delivery and how the kits should be used. In order to distribute the SDKs efficiently, operation, management, and promotion training was provided. In the distribution phase, a distribution plan was established and implemented through need assessment. This included research such as the need assessment of pregnant women in the community. In order to increase local residents' awareness of SDKs and to encourage them to effectively distribute and manage SDKs, various promotions were conducted for local leaders, medical specialists, and community leaders. Specifically, during the project period, a total of 57 SDK promotions were provided to a total of 19,662 community people. These promotions were performed at the Public Health Training Center which is located in or in communities in Oromia State. SDK promotions were held, with a total of 1,911 people in attendance. The promotion team collaborated with the local health center to hold over 22 program events for residents in the community, which had 4,098 attendees. Further, 16 promotions and campaigns were performed in collaboration with external centers. Additionally, 12 promotions were performed through outreach strategies, which 9,557 people attended.

2.5 Instruments

Survey instruments were developed by revising and supplementing a survey instrument for family planning and maternal-child health, a basic delivery kit guide, and a survey instrument testing satisfaction. This survey instrument was developed in English by the research team based on population survey and then revised after a review by a local adviser.

The questionnaire comprised six sections – the socioeconomic characteristics of the population, maternal-child health (delivery process, information regarding delivery helpers, etc.), use of SDKs, satisfaction with SDKs, distribution of SDKs, and infection rate of newborns and mothers.

2.6 Ethical approval

The study was conducted after obtaining approval from the Institutional Review Board (IRB) of the Yonsei University College of Nursing. For the face-to-face interviews, we employed well-trained survey interviewers with experience conducting national surveys with households in the community. Before the start of the survey, the interviewers were provided with a half-day training to familiarize them with the questionnaire, and a feedback meeting was held to assess how data should be collected. Comments were provided on aspects that needed improvement. The survey supervisor was responsible for the coordination and supervision of the overall data collection. Data quality control was performed by the supervisor who randomly cross-checked 10% of the questionnaires every day. Survey interviewers (one man and one woman working as a team).

A parent was required to sign a consent form for mothers under 19 years of age. All of the participants provided written informed consent to participate in this study, which the IRB also approved. In addition, all respondents provided written consent using paper consent forms, which were documented in the electronic data system. The relevant IRBs approved these consent processes.

2.7 Data collection

In locations where there were few female residents, surveys were performed through survey interviewers. The survey interviewer

verbally explained the study objectives to each female resident, and an informed consent statement was then signed by the women. Meanwhile, in regions with many female residents, surveys were conducted with the cooperation of health centers and people based in Woreda. For illiterate women, the information sheet was read aloud. For some questions, data from the mother's registration record was used to collect information on mothers before conducting the survey. Maternal and newborn puerperal infection was defined as the mother and newborn presenting with a fever.

2.8 Data analysis

Analysis of the data focused on measuring the impact SDK use had on puerperal infection in mothers and newborns (puerperal infection was defined as both the mother and newborn presenting with a fever). To measure this, multiple logistic regression analyses were performed This paper reports summary statistics on use of birth kits in the target population, and uses hierarchical logistic regression to analyze associations between baseline characteristics of respondents and use of birth kits, as well as associations between use of birth kits and outcomes (puerperal infection in mothers and newborns) during pregnancy and delivery.

3 Results

3.1 Characteristics of the study participants

The sociological characteristics of the mothers who reside in Hetosa Woreda are shown in Table 1. A total of 534 women participated in this survey, and their average age was 25.6 years. The respondents had been pregnant four times on average; almost 36.2% had more than five children, and most were married. Regarding religion, 396 (74.4%) were Muslim, 129 (24.2%) were Ethiopian Catholic, and seven (1.4%) were atheists or believers of other religions. Their education levels were very low: 230 (43.1%) were uneducated, 284 (53.2%) had graduated from elementary school, and only 20 (3.7%) had graduated from middle/high school. Most participants were married (95%) and had elementary-school-level education or lower (96%). The mean age was 26.6 years. Most participants delivered at home (94%) without a skilled birth attendant present (89%). Cord tie used by 519(96.1%) mothers in SDK. Only 35% used the user's manual in the SDK (Table 2).

3.2 Factors influencing puerperal infection

Multiple logistic regression analyses showed an independent association between the use of the cord tie in the SDK and decreased newborn infection [OR = 0.03; 95% confidence interval (95%CI): 0.001–0.616; (Table 3)]. Mothers who received education regarding how to use the SDK had lower rates of puerperal infection (OR = 0.46, 95%CI: 0.24–0.88). Further, mothers who were assisted by HEWs and skilled birth attendants also had lower rates of infection (OR = 0.53, 95%CI: 0.28–1.02), although the statistical strength of this association was of borderline significance ($p = 0.058$).

4 Discussion

Safe delivery kits are not a new phenomenon, having been widely distributed and marketed for a number of decades. However, the evidence underpinning this 'commonsense' intervention is not as robust as might be expected. Increasing the uptake of interventions that are effective for improving maternal and perinatal outcomes is critical. Supplying SDKs has been suggested as a feasible strategy for ensuring the timely availability and effective follow-up of care (5, 24).

Distribution and use of SDKs varies considerably from country to country, however most reports indicated some degree of health system involvement. The experience in Ethiopia suggests that SDKs can be harnessed to improve care, such as attendance at antenatal care. In contrast it has been suggested that the availability of a trained attendant using a kit may be a factor in encouraging 'high-risk' mothers to give birth at home rather than travel to a health center (23, 24). More data are urgently needed before making recommendations to further scale up mother held birth kits or to expand kit contents.

The importance of context cannot be over-emphasized, and better descriptive methods are needed to capture contextual factors that may impact the implementation process. For example, by using local laborers for production, the capacity of the residents was strengthened, and new means of income generation were created for this community. To move this work forward, a multidisciplinary approach, the SDK, is essential.

TABLE 1 Items used in the safe delivery kit.

Type	Mothers (n = 534)	
	N	%
Soap	519	(97.2)
Cord tie	513	(96.1)
Plastic sheet	519	(97.2)
Clothes sheet	521	(97.6)
Flashlight	471	(88.2)
Gloves	513	(96.1)
Surgical blade	506	(94.8)
Illustrated instruction manual	187	(35.0)

TABLE 2 Sociodemographic and gynecological characteristics of the participants.

Type		Mother (n = 534)	
		N	%
Age*	Average†	25.6 ± 4.43	
	15–19	18	(3.4)
	20–29	407	(76.9)
	30–39	100	(18.9)
	40–49	4	(0.8)
Marital status	Married	507	(95.1)
	Single	26	(4.9)
Number of children	0	4	(0.8)
	1–2	185	(34.7)
	3–4	151	(28.3)
	5+	193	(36.2)
	Average†	3.7 ± 2.15	
Number of pregnancies	1–2	170	(31.9)
	3–4	136	(25.5)
	5+	227	(42.6)
	Average†	4.1 ± 2.39	
Education	None	230	(43.1)
	Elementary school	284	(53.2)
	Middle/High school	20	(3.7)
Religion	Orthodox	129	(24.2)
	Muslim	396	(74.4)
	No religion/other	7	(1.4)

†Value is mean ± standard deviation. * indicates results influenced by missing values.

TABLE 3 Results of multiple logistic regression on newborn infection.

Variables	*B*	Wald	df	*P*	Odds	95% CI	
						Lower	Upper
Age	0.036	0.036	1	0.38	1.04	0.96	1.12
Skilled birth attendant	−0.632	−0.632	1	0.06	0.53	0.53	1.02
Cord tie use	−0.907	−0.907	1	0.49	0.89	0.89	5.35
SDK training*	0.776	0.776	1	<0.05	0.46	0.46	0.88

*Only significant variables are shown. 95%CI: 95% confidence interval.

4.1 Findings

The present study aimed to measure whether promoting an SDK project can decrease infection in mothers and newborns and, ultimately, lower maternal and child mortality rates in rural areas of Ethiopia, where health-care service for mothers and newborns is poor. Through various promotional activities and education, community residents' awareness of safe delivery was improved, and community health-care providers were educated regarding how to use and manage SDKs. Additionally, a community capacity building program was created, which enabled local residents to continue to operate the project. By using local laborers for production, the competence of the local residents was strengthened and a new means of income generation was created for this community.

The key findings of the present study are that most births in Ethiopia occur at home and that the use of the SDK was not widespread. SDKs have been distributed in Ethiopia since about 2010. It may not have saturated this region, but multiple international NGOs have been involved with the kits donated by the United Nations Population Fund (UNFPA) (25). The study also found that education regarding the SDK was a significant determinant of puerperal infection in mothers. It is clear from the present results that when the SDK-provided cord tie is used during delivery, newborns are significantly less likely to have umbilical infections.

The result of the systematic review shows that the SDK can decrease the infection rate in newborns and mothers in rural areas of Ethiopia indicating a similar level of effectiveness as that reported in a previous meta-analysis of the effect of such kits (2), and can be tailored to suit the delivery environment and residents' needs in the region. A total of 15,000 SDKs were produced and distributed to almost 90% of the 16,000 pregnant women in the project region; also, an education benefit was provided to the pregnant women who received an SDK. Thus, most pregnant women in the project region received important benefits as a result of using the safe-delivery-related services.

Second, educational and promotional activities targeted toward local residents and medical-care providers improved awareness of safe delivery, demonstrated the importance of using SDKs, and increased the accessibility of safe delivery services for residents of rural areas. Promotions of the SDKs also strengthened community competence. As a result, this project, involving producing and distributing SDKs, successfully contributed to decreasing infection rates in newborns in rural areas of Ethiopia. Studies have shown that health-care providers, such as midwives and birth attendants, can prevent approximately two-thirds of the deaths among women and newborns, provided they are well-trained, well-equipped, well-supported, and authorized (24, 26). Considering the fact that few women in the study region deliver their babies at hospital facilities, instead delivering at home with the help of family members (because of local traditional delivery customs), it is necessary to expand infrastructure for health-care services and encourage women to deliver babies at hospitals with professional delivery assistants, which would ultimately decrease infant and maternal mortality (14, 27).

4.2 Study limitations

There are some limitations to this research. First, this was a cross-sectional study rather than a pre-post study, and we did not use an objective measure of puerperal infection; instead, we tested for infection by checking the infant for fever. Therefore, it is possible that some participants were missed. Second, other organizations also provided health education with SDK in the area. Data was collected by trained personnel, who were different from HEWs, who also educated the participants.

Finally, fever was the most experienced danger sign in our study and in most of the other studies reviewed, except in Africa, where fever was frequently represented as an infection sign (12, 25). This is because fever is more easily identified than other neonatal infection signs (28). However, we only have early studies on we only have early studies on water, sanitation, and hygiene (WASH) looking at this (28). We believe instruments and environmental containments play a large role in driving maternal and newborn sepsis, but it is complicated. Mothers may not deliver in a facility, which is an increased risk, may have prolonged rupture of membranes, etc.

5 Conclusion

These findings emphasize the need for further interventions for increasing the rate of hygienic birthing practices for deliveries occurring outside facilities (29). Several meta-analyses on SDKs, including this study (21), have been conducted. SDKs are well-proven in-home or unattended deliveries.

Notably, the present results support the existing theory that it is important to use the cord tie included in the SDKs (21) and also shows that mothers can and should be trained to use such kits properly (30, 31). It is reported that, in order to lower postpartum infections, it is not sufficient to merely train birth attendants (32–34); greater emphasis must be placed on the use of these kits by mothers, especially during home births (35). Further, it is important not only to distribute SDKs, but also to provide training regarding their usefulness and the importance of their correct and consistent use.

5.1 Implications for nursing

Nurses, midwives, and health extension workers in low and middle-income countries should educate mothers on SDKs by providing information regarding their usefulness and the importance of their correct and consistent use.

5.2 Implications for health policy

Our findings emphasize the need for further interventions for increasing the rate of hygienic birthing practices in vulnerable countries in regard to deliveries that occur outside health-care facilities.

5.3 Implications for practice and/or policy

1 What is already known about this topic? (include key points and/or knowledge gaps).
All newborns are exposed to a higher mortality risk compared to children of older ages. Many newborn deaths can be prevented by providing a hygienic delivery environment and trained helpers.

2 What this paper adds: (research findings/key new information).
Newborns whose mothers used the cord tie in the delivery kit were 30 times less likely to develop cord infection. When combined with education about Safe Delivery Kits, single-use delivery kits can decrease the likelihood of maternal infection.

3 The implications of this paper: (how findings influence or can be used to change policy/practice/research/education).
Medical professionals and health workers should educate mothers on the proper use of Safe Delivery Kits by providing information about their usefulness and the importance of their correct and consistent use. The findings emphasize the need for further interventions aimed at increasing the rate of hygienic birthing practices for deliveries occurring outside health care facilities.

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 humans were approved by Yonsei University institutional review board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WH: Conceptualization, Writing – original draft, Writing – review & editing. TL: Funding acquisition, Project administration, Supervision, Writing – original draft.

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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.

Publisher's note

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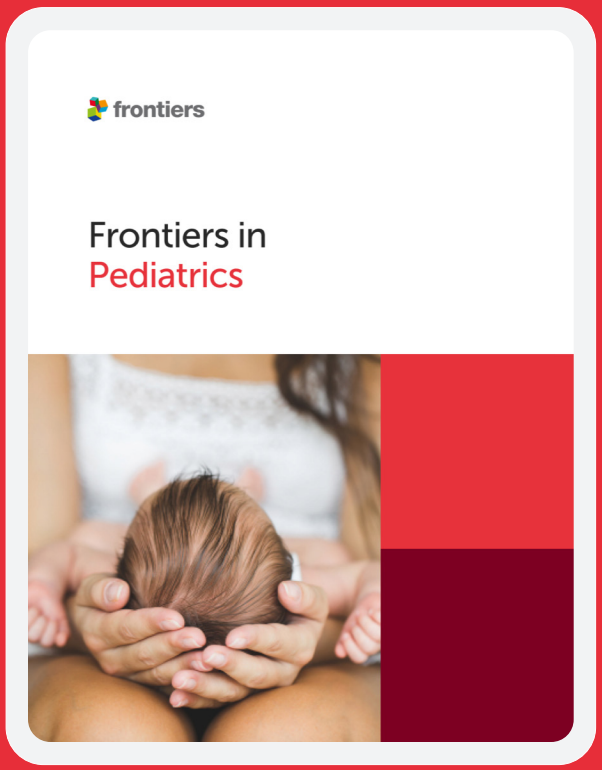

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