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What is new on the horizon in neonatology? Recent advances in monitoring, diagnostics, and therapeutics in neonatal care

Edited by
Minesh Khashu and Karel Allegaert

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What is new on the horizon in neonatology? Recent advances in monitoring, diagnostics, and therapeutics in neonatal care

Topic editors

Minesh Khashu — University Hospitals Dorset NHS Foundation Trust, United Kingdom

Karel Allegaert — KU Leuven, Belgium

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David Warburton,
Children's Hospital Los Angeles, United States

*CORRESPONDENCE
Karel Allegaert
karel.allegaert@kuleuven.be

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Editorial: What is new on the horizon in neonatology? Recent advances in monitoring, diagnostics, and therapeutics in neonatal care

Minesh Khashu[1] and Karel Allegaert[2,3,4]*

[1]Department of Neonatology, University Hospitals Dorset NHS Foundation Trust, Dorset, United Kingdom, [2]Department of Development and Regeneration, KU Leuven, Leuven, Belgium, [3]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [4]Department of Hospital Pharmacy, Erasmus MC, Rotterdam, Netherlands

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Editorial on the Research Topic
What is new on the horizon in neonatology? Recent advances in monitoring, diagnostics, and therapeutics in neonatal care

Introduction

Neonates and infants are commonly referred to as "therapeutic orphans" due to the overall scarcity of therapeutic interventions that have been developed and tailored to their needs and specific characteristics (1, 2). This is well known by care providers and researchers active in this field, but is perhaps less on the radar of authorities, funding bodies or the broader public. There is significant health inequity when comparing newborns to other age populations in terms of specific drug and device development and therapeutics (1, 2). In addition there are health inequities in the provision of neonatal care globally which require special attention in terms of improvement (3).

Bronchopulmonary dysplasia, neonatal seizures, poor growth, necrotizing enterocolitis (NEC) and short bowel, hypoxic-ischemic encephalopathy, retinopathy of prematurity (ROP), neonatal infections and sepsis hereby serve as a non-exhaustive list of "orphan conditions" in need of more equity, through adequately and urgently funded research and improvement.

The good news is that there have been increased efforts, in recent years, by researchers and regulatory bodies to focus on the provision of drugs, devices, and treatment modalities tailored for neonatal use, while further advocacy remains an obvious need (2, 4, 5). This brings perspective and explains the initiative taken to organize a focused research topic on what is on the horizon as well as recent advances.

Overview of the topics covered

We targeted emerging or new aspects related to monitoring, diagnostics and therapeutics in neonatal care for the current research topic. Fortunately, this research topic was perceived as very relevant by the research community, as 135 authors expressed their interest as contributors, resulting in 20 accepted papers. This serves as a signal of the importance to continue to work on this topic.

Post-hoc, and in a somewhat arbitrary way (because of overlap in these subcategories) these papers were subdivided by the editors into different subcategories, with focus on (*1*, 5 papers) perinatal biomarkers in blood and urine and how these relate to or predict outcomes, (*2*, 6 papers) adaptations of existing and newly emerging equipment in neonatal units, (*3*, 3 papers) needed advances in pharmacotherapy, (*4*, 3 papers) machine learning or deep learning applications in neonatal care, and finally, (*5*, 3 papers) underreported aspects of contemporary NICU care, with a focus on the holistic nature of care for the infant and the family.

Perinatal biomarkers in blood and urine and how these relate to or predict outcomes

Two papers focused on biomarkers related to gestational diabetes, with reflections and data on maternal and neonatal outcomes. Postnatal maternal levels of glycated albumin and hemoglobin A1c in mothers of large-for-gestational-age (LGA) informed us of the relevance of accurate diagnosis during pregnancy. This is because postpartum women without diagnosis during pregnancy had higher glycated albumin values, associated with LGA and associated complications (Železnik et al.). Interestingly and related to this paper, Yin et al. reported on a untargeted metabolomics study in women with gestational diabetes, with the recommendation of a maternal serum metabolite panel to forecast neonatal adverse outcomes (hypoglycemia and macrosomia) (Yin et al.).

Other papers focused on the use of vitamin D, acid-base and biomarkers associated with fetal growth restriction with impaired neurodevelopmental outcome. In a cohort of 217 preterm neonates, a multivariate regression analysis identified antenatal steroids as protective, and lower birth weight, duration of ventilation, sepsis and the serum 25-(OH)D vitamin as risk factors to develop ROP (Yin et al.). Musco et al. reported on a systematic review on blood biomarkers indicating risks of adverse neurodevelopmental outcome in fetal growth restricted infants (Musco et al.). While the authors retrieved some data on neuron specific enolase and S100B, the overall conclusions reflect a call for further research. Finally, an association between lactate levels in umbilical cord blood and cerebral oxygenation in preterm neonates was studied as a secondary outcome analysis (Dusleag et al.). In non-asphyxiated preterm neonates with respiratory support, lactate levels were negatively associated with cerebral and arterial oxygenation. In term neonates without respiratory support, no associations were observed.

Adaptations of existing and newly emerging equipment in our units

In a review on emerging innovations in neonatal monitoring, Krbec et al. concluded that there is an urgent, still unmet need to develop wireless, non- or minimal-contact, non-adhesive technology, capable to integrate multiple signals in a single platform, tailored to neonates (Krbec et al.). Related to this call of action, Svoboda et al. reported on their pilot experience with contactless assessment of heart rate, applying imaging photoplethysmography (Svoboda et al.). Rectal and axillary temperature monitoring on admission were compared in a cohort of preterm ($n = 80$, <32 weeks gestational age) by Halabi et al., reporting that rectal measurement was likely more reliable in the event of hypothermia (Halabi et al.). Ultrasound-guided measurement of anterior cerebral artery resistive index in the first week of life in 739 preterm neonates (<35 weeks) was not associated with subsequent co-morbidities on admission or during neonatal stay (asphyxia, sepsis, NEC) (Singh Gill et al.). A case series of neurally adjusted ventilatory assist to rescue pulmonary interstitial emphysema in 5 extremely low birth weight infants illustrated the potential value of this ventilatory equipment and strategy and need for further study (Chen et al.). Finally, van Rens et al. compared a conventional to a modified Seldinger technique (a dedicated micro-insertion kit) for peripherally inserted central catheter (PICC) placement, illustrating the relevance of developing "low risk, high benefit" type of medical devices, adapted to the specific needs of neonates (van Rens et al.).

Advances needed in pharmacotherapy

The currently available medicines and dosing regimens in neonatal care are limited and there is an urgent need for improvement in this domain. This was illustrated by articles on sepsis, septic shock and steroids. Inequity in provision of neonatal care across the globe ought to be a major focus of improvement. Gezahegn et al. described the outcome in neonates admitted with sepsis in Harar (Ethiopia). Low white blood cell count, desaturation, preterm birth, absence of prenatal maternal care, and chorioamnionitis were important risk factors for sepsis-related mortality (Gezahegn et al.). Addressing these prognostic factors hold the promise to act as levelers to improve outcomes. A pilot study compared noradrenaline and adrenaline as first line vasopressor for fluid-refractory sepsis shock (Garegrat et al.). Both interventions were comparable to resolve the septic shock, while the overall mortality (13/42, 30%) remained significant, highlighting the need for better diagnostic and therapeutic options. Finally, in a systematic review, outcome of postnatal systemic corticosteroids (hydrocortisone to dexamethasone) were compared as reported in randomized controlled trials (Boscarino et al.). The authors concluded that dexamethasone appeared to be somewhat more effective than hydrocortisone in improving respiratory outcomes, but with inconclusive but relevant concerns

on the uncertainties on long-term neurodevelopmental outcome, again highlighting the need for better therapies for prevention and management of chronic lung disease of prematurity.

Machine learning or deep learning applications in neonatal care

Artificial intelligence is a rapidly advancing area with fast evolving clinical applications in healthcare, including in the NICU (6). It is no surprise that the current research topic also contains papers illustrating its relevance to improve our practices and outcomes. Two papers hereby focused on NEC, and a 3rd paper on prediction of significant patent ductus arteriosus (PDA). In a mini-review, Cuna et al. reports on the various pathophysiological processes underlying NEC endotypes, and how artificial intelligence holds the promise to influence further understanding and management (Cuna et al.). An approach to enhance surgical decision making in NEC is illustrated by Wu et al. Based on x-rays from 263 neonates diagnosed with NEC (94 surgical cases), a binary diagnostic tool was trained and validated, with Resnet18 as approach applied (Wu et al.). For PDA, an ultrasound-based assessment of ductus arteriosus intimal thickness in the first 24 h after birth was applied in 105 preterm neonates. A prediction model for closure on day 7 included birth weight, mechanical ventilation, left ventricular end-diastolic diameter, and PDA intimal thickness (Hu et al.). Such models can be considered to better target future study, integrated in a precision medicine approach. Use of AI and big data have the potential to significantly improve our understanding of neonatal conditions and also support neonatal researchers in asking better research questions.

Underreported aspects of contemporary NICU care, holistic care

As part of this research topic, we also accepted papers reporting on the use of music on pain management, on multisensory stimulation to improve maternal milk volume production, and parents' experiences related to congenital cardiac surgery. All these 3 papers reflect the need for holistic care and to further integrate the perspectives of (former) patients and parents into neonatal practice.

In a systematic review, Ou et al. demonstrated that music is an effective intervention to relief procedural pain (e.g., Premature Infant Pain Profile score) in preterm neonates, as it reduced some markers of stress, and improved blood oxygen saturation (Ou et al.). Multisensory stimulation (audiovisual, or audiovisual + olfactory) compared to a control setting improved maternal milk volume production, with evidence of positive effects of both interventions, even more pronounced if both interventions are combined (Cuya et al.). Finally, a quantitative analysis of parent's experiences with neonates admitted to NICU with a congenital heart disease reinformed us on the importance of actively focusing on parental experiences of care (Catapano et al.).

From advances in neonatal care to implementation

In our opinion, this research topic nicely illustrates the diversity in ongoing clinical research activities, that all hold the promise to improve our clinical management practices, with the overarching aim to improve neonatal outcomes. There is an urgent need to focus on the current health inequities in the provision of care to neonates (3). The trend towards a "neuro" dedicated NICU care is an illustration on how relevant progress may occur. This progress is based on improved neuromonitoring techniques (7), improved management and precision medicine in the field of anti-epileptic drugs (8), and integrating families as partners in neonatal neuro-critical care and similar improvement programs (9). The good news is that we are already experiencing a shift in the right direction. The neonatal community and all other relevant stakeholders need to work better together to improve the pace and scale of this improvement.

Author contributions

MK: Writing – original draft, Writing – review & editing. KA: Writing – original draft, 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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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Paolo Biban,
Integrated University Hospital Verona, Italy
Julie Lefever,
University Hospital Brussels, Belgium

*CORRESPONDENCE
Chung-Ting Hsu
✉ longtye014@gmail.com

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Case Report: Neurally adjusted ventilatory assist as an effective rescue treatment for pulmonary interstitial emphysema in extremely low birth weight infants

Chien-Ming Chen[1], Mei-Yung Chung[1,2,3], Hong-Ya Kang[2], Mei-Chen Ou-Yang[1], Teh-Ming Wang[4] and Chung-Ting Hsu[4,5,6]*

[1]Section of Neonatology, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, [2]Department of Respiratory Care, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [3]Chang Gung University of Science and Technology, Chiayi Campus, Chiayi, Taiwan, [4]Children's Medical Center, Taichung Veterans General Hospital, Taichung, Taiwan, [5]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan, [6]Department of Biomedical Engineering & Environmental Sciences, National Tsing Hua University, Hsinchu, Taiwan

Pulmonary interstitial emphysema (PIE) is a complication observed in extremely low birth weight (ELBW) infants on mechanical ventilation. Despite various proposed therapeutic interventions, the success rates have shown inconsistency. Neurally adjusted ventilatory assist (NAVA) stands out as a novel respiratory support mode, offering lower pressure and tidal volume in comparison to conventional ventilation methods. In this case report, we present five ELBW infants with refractory PIE who were transitioned to NAVA ventilation. Following the switch to NAVA, all cases of PIE gradually resolved. In contrast to traditional modes, NAVA provided respiratory support with significantly lower fraction of inspired oxygen, reduced peak inspiratory pressure, diminished mean airway pressure, and decreased tidal volume within 7 days of NAVA utilization ($p = 0.042$, 0.043, 0.043, and 0.042, respectively). Consequently, we propose that NAVA could serve as a valuable rescue treatment for ELBW infants with PIE.

KEYWORDS

neurally adjusted ventilatory assist, pulmonary interstitial emphysema, extremely low birth weight infants, non-invasive neurally adjusted ventilatory assist, case report

1 Introduction

Despite the advances in neonatology, such as the administration of prenatal steroids, postnatal surfactant, and the implementation of gentle ventilation, the increased survival of premature infants is still accompanied by pulmonary morbidities, including bronchopulmonary dysplasia (BPD), pulmonary hypertension, and pulmonary interstitial emphysema (PIE), especially in extremely low birth weight (ELBW) infants (1, 2). PIE is characterized by the presence of air leaks in interstitial or perivascular lung tissue entrapped along bronchovascular bundles, leading to hypoxemia and respiratory acidosis (3). Ventilator settings are frequently increased due to impaired gas exchange, potentially aggravating air trapping and resulting in further deterioration of ventilation and oxygenation (4, 5). The management of PIE can be challenging, and

previous studies have proposed various treatment modalities with varying degrees of success, such as the lateral decubitus position, gentle ventilation with reduced inspiratory time, decreased peak inspiratory pressure (PIP), adjusted positive end-expiratory pressure (PEEP), high-frequency oscillatory ventilation (HFOV), selective main bronchial intubation or occlusion, lung puncture, and even lobectomy (6–8).

In recent years, neurally adjusted ventilatory assist (NAVA) has been increasingly used in neonatal intensive care units (NICUs) (9). Theoretically, NAVA holds the potential to improve PIE by delivering lower PIP and lower work of breathing compared to synchronized intermittent mandatory ventilation (SIMV) (10, 11). However, there are limited studies on the use of NAVA for premature infants with PIE (12, 13). In this report, we present five extremely low birth weight premature infants with PIE who were unresponsive to conventional treatments but demonstrated significant improvement after being ventilated with NAVA.

2 Case description

Five ELBW infants were included in this case report. Out of these cases, three were diagnosed with localized PIE, while the remaining two had diffuse PIE. The conventional PIE management, including lateral decubitus position, gentle ventilation by reducing inspiratory time, decreasing PIP, adjusting PEEP, and transitioning to HFOV or non-invasive ventilation mode, was applied initially. Unfortunately, these traditional treatment methods for PIE proved ineffective in all cases, leading to the implementation of NAVA.

2.1 NAVA initial settings

The decision to switch to NAVA is based on the following specific criteria: First, the absence of improvement or worsening in PIE on chest x-ray after at least 48 h of attempting traditional ventilation adjustments. Second, clinical observation of increased episodes of bradycardia and cyanosis.

After transitioning to NAVA mode, the initial step involved determining the Breakpoint, which refers to the appropriate NAVA level for the initial setting (14, 15). This process commenced at a NAVA level of 0.5 cmH2O/μV and involved gradually increasing the level by 0.5 cmH2O/μV every 30–60 s of continuous monitoring. The adjustment persisted until the PIP reached a plateau, and the electrical activity of the diaphragm (Edi) peak level displayed a consistent downward trend, indicating the establishment of the Breakpoint. Notably, previous studies have not suggested a NAVA level exceeding 4 cmH2O/μV in neonates (16, 17).

The Edi trigger was recommended to be set at 0.5 μV. Additionally, the alarm pressure limit was set to be 5 cmH2O above the PIP reached during the patient's spontaneous breathing (9). To maintain oxygen saturation (SpO2) within the target range of 90%–95%, the fraction of inspired oxygen (FiO2) was adjusted accordingly. Given the high risk of apnea in ELBW infants, a short apnea time from 2 s was suggested. Furthermore, the backup ventilation settings were mirrored from the previous mode before transitioning to NAVA.

2.2 Strategy of NAVA adjustment

The patient was evaluated twice per day. If the patient's Edi peak level was consistently below 10 μV and vital signs remained stable, we would gradually taper the NAVA level by 0.1–0.2 cmH2O/μV. Additionally, we would gradually increase apnea time and decrease backup mode settings during episodes of fewer bradycardia and cyanosis clinically observed. Extubation would be considered if the NAVA level was maintained below 0.8–1.0 cmH2O/μV, and apnea time could be safely increased to 5 s.

After the extubation process, the patient transitioned to non-invasive NAVA (NIV NAVA). We increased the NAVA level by 0.5–1.0 cmH2O/μV post-extubation. Simultaneously, the apnea duration was adjusted back to 2 s. Using the same approach, we gradually reduced the NAVA level by 0.1–0.2 cmH2O/μV. Subsequently, the patient would be shifted to nasal continuous positive airway pressure (NCPAP) as soon as the NAVA level reached 0 cmH2O/μV, ensuring the patient achieves a clinically stable condition.

2.3 Clinical course in five cases

2.3.1 Case 1

A female premature neonate weighing 0.80 kg was delivered spontaneously at a gestational age (GA) of 24 + 6 weeks. Two doses of betamethasone were administered prenatally at a GA of 23 + 5 weeks. Following delivery, the neonate was subjected to nasal intermittent positive pressure ventilation (NIPPV). Due to an increasing FiO2, the neonate required intubation, and early rescue surfactant was administered twice. However, despite these interventions, the neonate experienced difficulty weaning from conventional synchronized ventilation. The patient was switched to HFOV with the aim of decreasing mean airway pressure (MAP) and reducing the risk of barotrauma after frequent apnea episode and an early type of bronchopulmonary dysplasia. However, we observed localized PIE in the right lower lobe on day 41, and the patient was subsequently positioned on the right lateral decubitus. On day 43, NAVA was initiated due to poor response to the right lateral decubitus position, along with the occurrence of bradycardia and cyanosis under HFOV at a reduced MAP setting. After 4 days of follow-up, we still noticed slight progression of PIE in the same area, accompanied by increased tidal volume. Nevertheless, the PIE situation significantly improved and stabilized after 7 days of NAVA usage, as evident from the chest x-ray, which showed complete resolution of PIE (shown in Figure 1A). Gradual weaning off NAVA was successful, and the neonate was extubated on day 91. After receiving NIV NAVA and NCPAP support, the patient did not require ventilator assistance until reaching a corrected age of 1.5 months.

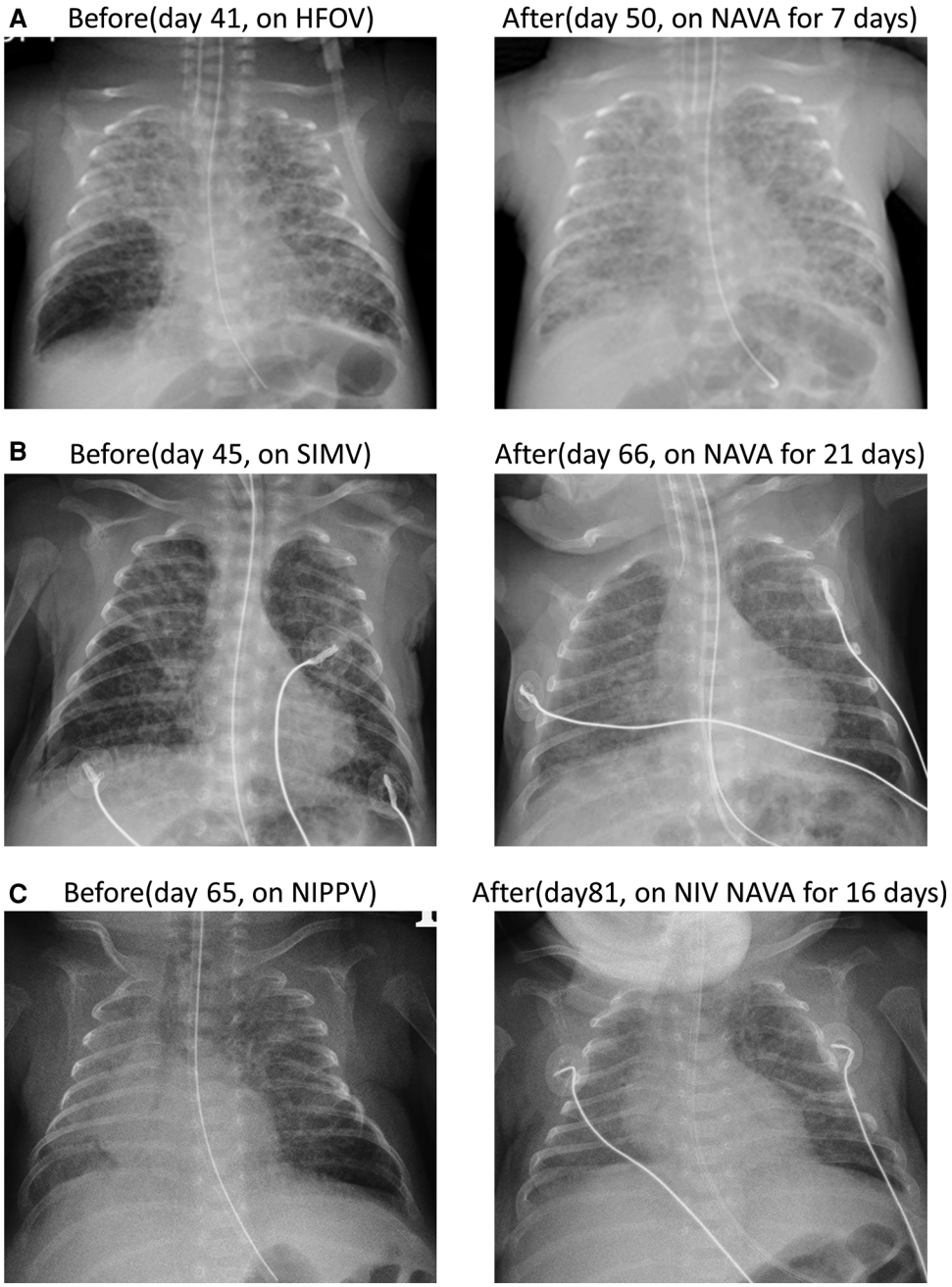

FIGURE 1
Three cases of localized PIE presented by anterior–posterior chest x-ray before and after NAVA. (**A**) In case 1, localized PIE over the right lower lobe was observed on day 43 and resolved on day 50 after 7 days of NAVA treatment. (**B**) In case 2, localized PIE over the right lower lobe presented on day 45 and resolved on day 66 after NAVA treatment for 21 days. (**C**) In case 5, localized PIE over left lower lobe on day 65 and completely resolved on day 81 after 16 days of NIV NAVA treatment.

2.3.2 Case 2

A male premature infant with a GA of 25 + 5 weeks and a birth weight of 975 g was delivered via emergency cesarean section due to placental abruption. Prenatal steroids with 2 doses of betamethasone were administered at a GA of 24 weeks. Immediately after delivery, intubation was performed, and early rescue surfactant was administered once. Ventilator support was provided with the synchronized intermittent mandatory ventilation (SIMV) mode. The infant suffered from patent ductus arteriosus (PDA) ligation and recurrent pneumonia resulting in the collapse of multiple lobes. On day 42, PIE manifested in the right lower lobe. In response, we implemented the right lateral decubitus position. Additionally, we reduced PIP and shortened inspiratory time in SIMV mode. Despite these adjustments, frequent desaturation persisted. Consequently, NAVA was introduced on day 45 to address the evolving condition. After

the switch to NAVA mode, the FiO2 could be gradually decreased. On day 66, the chest x-ray revealed complete resolution of the localized PIE (shown in Figure 1B). The infant was successfully extubated on day 67, but NIV NAVA and NCPAP were applied for an extended period due to BPD. At a corrected age of 3 months, the infant no longer required ventilator support.

2.3.3 Case 3

A female premature infant was delivered spontaneously at a GA of 24 + 1 weeks with a birth weight of 630 g. The mother received two doses of betamethasone as prenatal steroids 48 h before delivery. The infant was intubated and received surfactant administration due to respiratory distress syndrome (RDS), grade III. The PDA closed spontaneously on day 4. However, septic shock and bilateral intraventricular hemorrhage were noted on day 6, with both blood culture and placenta culture yielding E. coli. The infant developed obstructive hydrocephalus with increased intracranial pressure, requiring external ventricular drainage inserted by a neurosurgeon. On day 26, the infant developed diffuse PIE, and attempts were made to decrease PIP and shorten inspiratory time under SIMV mode to mitigate barotrauma. However, recurrent lung collapse with unstable saturation occurred frequently. On day 45, NAVA was initiated, leading to an improvement in PIE one day after the start of treatment. Additionally, the FiO2 was gradually decreased after using NAVA. The infant was extubated and shifted to NIV NAVA on day 68. PIE completely resolved after starting NAVA for four weeks (shown in Figure 2A). NCPAP was applied since day 85 due to BPD and periventricular leukomalacia, requiring ventilator support for a prolonged period. Weaning from NCPAP and discontinuing oxygen support were achieved at a corrected age of 6 months.

2.3.4 Case 4

A female infant was delivered via cesarean section due to malpresentation at a GA of 26 + 5 weeks with a birth weight of 920 g. Preterm premature rupture of membranes with oligohydramnios was noted for 2 weeks prior to delivery. Prenatal steroids with 2 doses of betamethasone were administered 10 days before delivery. The infant was intubated immediately after birth and received ventilator support with SIMV mode after admission to the NICU. However, diffuse PIE occurred early on day 2, which may be attributed to hypoplastic lungs, induced by oligohydramnios during the prenatal stage.

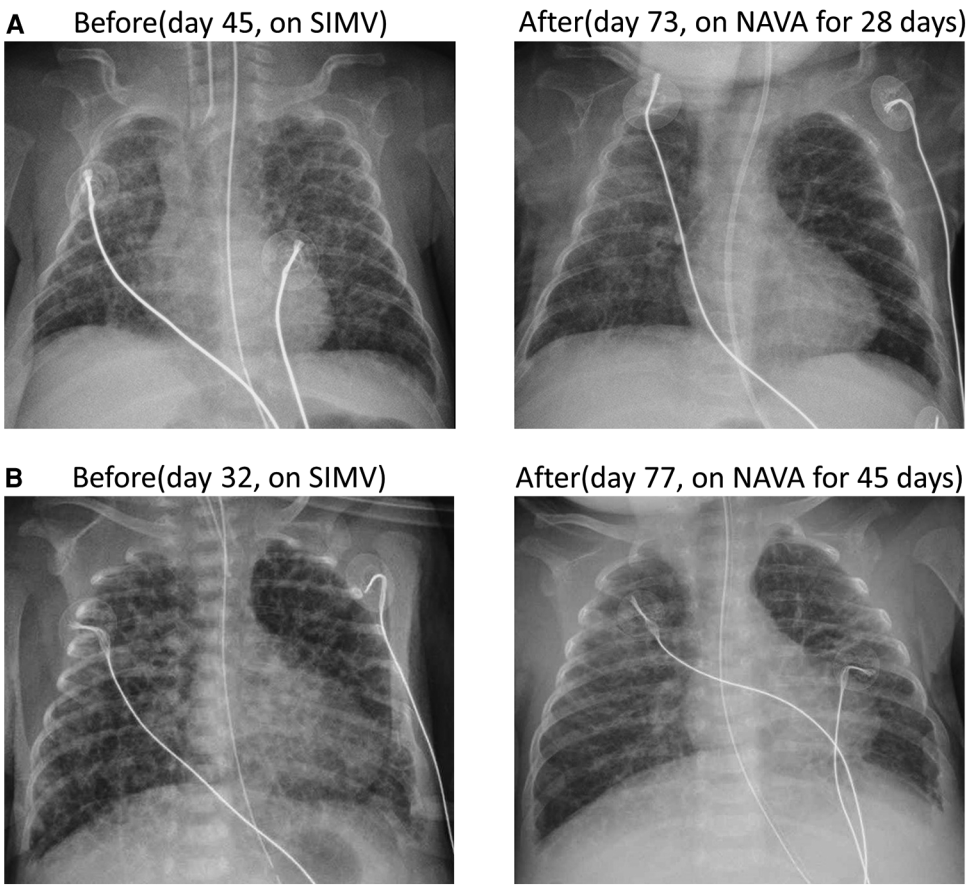

FIGURE 2
Two cases of diffuse PIE were observed through anterior-posterior chest x-ray before and after NAVA. (**A**) In case 3, diffuse PIE was observed on day 45 and resolved on day 73 after 28 days of NAVA and NIV NAVA treatment. (**B**) In case 4, diffuse PIE was detected on day 32 and resolved on day 77 after 45 days of NAVA and NIV NAVA treatment.

Based on the principles of lung protection and reducing barotrauma, the patient was extubated and shifted to NIPPV support. The PDA closed spontaneously on day 3. In the following days, progressive abdominal distension and frequent desaturation developed as a result of continuous positive airway pressure belly syndrome. Consequently, re-intubation was performed on day 24 due to severe cyanosis and bradycardia. PIE deteriorated severely after intubation even under decreasing PIP and shortening Ti in SIMV mode. The ventilator was shifted to NAVA mode on day 32. The level of saturation became more stable after NAVA ventilation, and the FiO2 level could be gradually tapered. The infant was extubated and then placed on NIV NAVA on day 65. PIE resolved completely on day 77 (shown in Figure 2B). Due to BPD, the infant needed NCPAP support until corrected age of 3 months.

2.3.5 Case 5

A male premature infant was spontaneously delivered at a GA of 24 + 2 weeks, weighing 640 g. Prenatal steroids, including two doses of Dexamethasone, were administered 24 h before delivery. Due to bradycardia and cyanosis, immediate intubation was performed after birth. Upon admission to the NICU, the infant was supported with a ventilator using SIMV mode. On day 8, the infant's right lung collapsed, and pneumonia was diagnosed, prompting a switch to HFOV ventilation mode. The infant underwent ligation of a hemodynamically significant PDA and received peritoneal drainage and broad-spectrum antibiotics for necrotizing enterocolitis with gastrointestinal perforation. The infant's respiratory condition gradually improved, leading to extubation on day 51 and use of NIPPV. However, on day 60, PIE was noted over the left lower lobe due to the high settings of NIPPV for abdominal distention. Despite our attempts to address the situation by placing the infant in the left lateral decubitus position and decreasing PIP and PEEP levels of NIPPV, frequent episodes of bradycardia and cyanosis persisted. Consequently, NIV NAVA was initiated on day 65. Following this intervention, oxygen saturation became notably more stable, and abdominal distention also improved. A series of chest x-rays revealed gradual improvement of PIE, which completely resolved on day 81 (shown in Figure 1C). At postmenstrual age of 41 + 2 weeks, the infant was able to tolerate room air without ventilator support.

2.4 NAVA effectiveness in PIE resolution

The clinical characteristics of these five ELBW infants were summarized in Table 1. All of them had received prenatal steroids before delivery and were diagnosed with RDS after birth. Among these cases, only three infants received early rescue surfactant treatment due to an increasing demand for oxygen during ventilation. The criterion for surfactant administration was that the patient required an FiO2 above 0.4 to maintain SpO2 above 90%. We all use traditional method for surfactant administration via endotracheal tube in ELBW infants. In the fifth case, PIE developed while the patient was undergoing non-invasive ventilation after extubation. Consequently, we utilized NIV NAVA directly.

Chest x-rays were performed daily in the first 3 days after transitioning to NAVA, with the frequency subsequently decreasing to once every 2–3 days based on clinical decision until PIE resolution. The complete resolution of PIE is determined through radiological imaging and assessed by two or more clinical physicians. Based on our experience, we observed successful resolution of PIE in all five cases following NAVA treatment. The initial settings of NAVA level are around 1.5–2.5 cmH2O/μV after switching to NAVA mode. The localized PIE typically resolved within one to three weeks after NAVA treatment, whereas diffuse PIE required a longer period of time, often exceeding four weeks. Throughout the duration of NAVA treatment, no complications were observed. Although NAVA was

TABLE 1 Demographic data of 5 cases.

	Case 1	Case 2	Case 3	Case 4	Case 5
Gestational age (weeks)	24	25	24	26	24
Birth weight (grams)	800	975	630	920	640
Gender	Female	Male	Female	Female	Male
Prenatal steroid	Twice	Twice	Twice	Twice	Twice
Surfactant use	Twice	Once	Once	None	None
Onset of PIE	41th day	42th day	26th day	2nd day	60th day
Type of PIE	Localized	Localized	Diffuse	Diffuse	Localized
Ventilator mode before NAVA	HFOV	PC-SIMV	PC-SIMV	PC-SIMV	NIPPV
Treatments before NAVA	Lateral decubitus MAP↓in HFOV	Lateral decubitus PIP↓, Ti↓in SIMV	PIP↓, Ti↓in SIMV	Non-invasive mode PIP↓, Ti↓in SIMV	Lateral decubitus PIP/PEEP↓in NIPPV
Timing of switching to NAVA	43th day	45th day	45th day	32th day	65th day
Initial NAVA level (cmH2O/μV)	1.5	1.5	2.5	2.5	2.5
Total duration of NAVA (Days)	59	38	40	60	26
NAVA	45	22	23	33	-
NIV NAVA	14	16	17	27	26
Duration of PIE resolution after NAVA (Days)	7	21	28	45	16

HFOV, high frequency oscillatory ventilation; MAP, mean airway pressure; NAVA, neurally adjusted ventilatory assist; NIPPV, nasal intermittent positive pressure ventilation; NIV NAVA, non-invasive neurally adjusted ventilatory assist; PC, pressure control; PEEP, positive end-expiratory pressure; PIE, pulmonary interstitial emphysema; PIP, peak inspiratory pressure; SIMV, synchronized intermittent mandatory ventilation; Ti, inspiratory time.

effective in resolving PIE, all cases still developed BPD due to severe lung trauma. However, eventually all five of these cases were weaned off the ventilator and were able to tolerate room air without requiring oxygen support later in life.

2.5 Ventilator setting reduction following NAVA

Figure 3 illustrates the daily ventilator settings and measurements before and one week after the transition to NAVA in all five cases. Following the switch to NAVA mode, a significant downward trend was observed in several parameters, including FiO2, PIP, MAP, and tidal volume, within the initial 7 days. The corresponding *p*-values for these changes were calculated by the Wilcoxon signed-rank test as 0.042, 0.043, 0.043, and 0.042, respectively. Clinically, it was confirmed that all five cases achieved respiratory stability following the shift to NAVA. Moreover, the frequency of bradycardia and cyanosis episodes was lower compared to the traditional ventilator modes.

3 Discussion

In our study, the intractable PIE in ELBW infants was successfully resolved following treatment with NAVA ventilation. NAVA has demonstrated substantial potential in reducing oxygen demand, peak inspiratory pressure, mean airway pressure, and tidal volume in ELBW infants compared to conventional ventilation methods. NAVA utilizes the patient's Edi to trigger and deliver synchronized and proportional assisted ventilation. The good synchronization achieved by NAVA also diminishes the necessity for sedation with narcotics (18, 19). Previous studies have indicated that both NAVA and NIV NAVA provide superior patient-ventilator interaction and gas exchange, resulting in reduced oxygen requirements, decreased peak inspiratory pressure, and diminished respiratory muscle load when compared to conventional ventilation methods (9, 20). These factors are believed to be the key reasons why NAVA shows promise in alleviating PIE.

In terms of determining the breakpoint in NAVA initial settings, two earlier studies advocate a gradual increase of 0.5 cmH2O/μV every 3 min (14, 15). However, an alternative recommendation was proposed in another review article, suggesting an increase every 30 s (9). Based on our clinical experience, we have found that a 30- to 60-second interval is adequate for observing a typical plateau, particularly when the patient is calm. We used a cutoff level of 10 μV for Edi peak to assess NAVA level adjustments. This choice was informed by previous observational studies, which indicated that the normal range of Edi peak in premature babies is approximately 10.8 ± 3.7 μV (21). Lee et al. (12) has also shown a downward trend in FiO2, PIP, and tidal volume after switching to NAVA mode for PIE management, mirroring the results of our study. This consistency suggests that the mechanism of PIE treatment with NAVA involves gentle ventilation and synchronization. However,

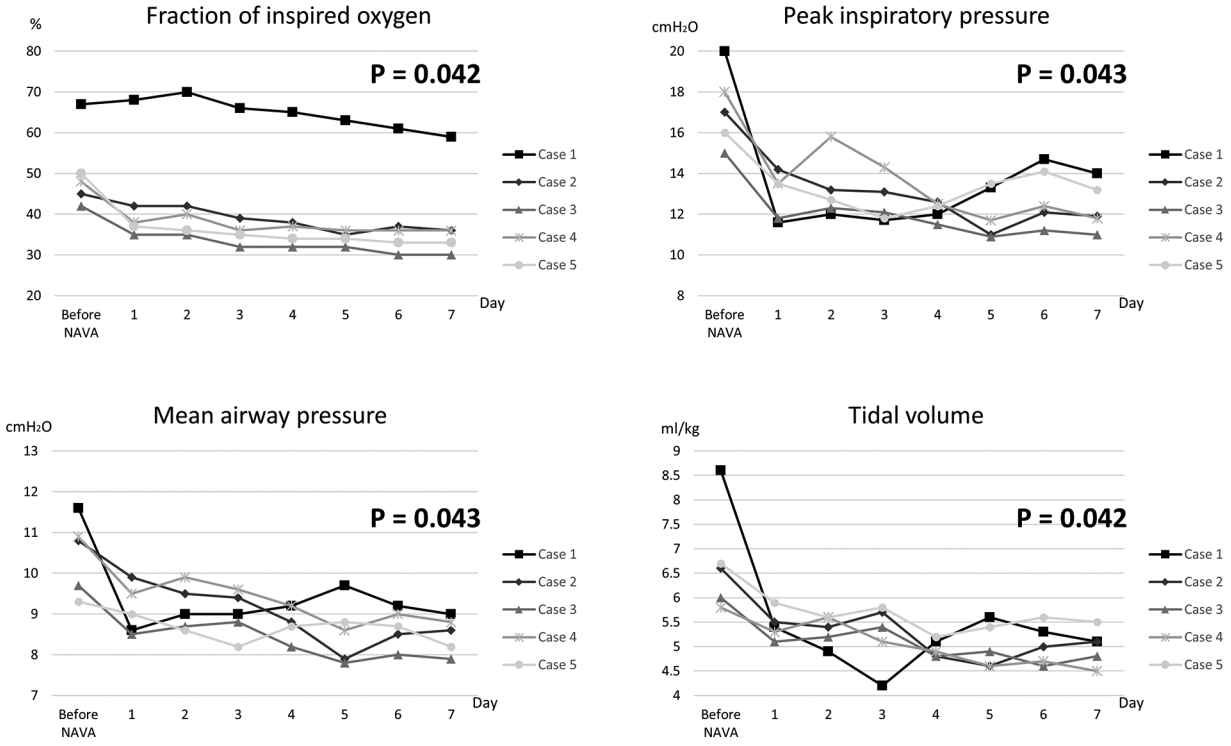

FIGURE 3
The daily ventilator settings and measurements for all five cases before and after the transition to NAVA over a duration of 1 week.

in this previous case report (12), the initial NAVA level was set at 3 cmH2O/μV, which is higher than in our study. A letter to the editor (22) highlighted the concern about setting the NAVA level above 2.5 cmH2O/μV, suggesting it might provide excessive assistance to premature infants and lead to lower Edi peak levels, as observed in the aforementioned case report.

Traditionally, the radiological manifestation of PIE has been observed in ELBW infants with RDS who were ventilated with a mechanical ventilator (23). The mechanism of PIE is characterized by the hyperdistention of alveoli and terminal airways, ultimately leading to tissue rupture. Air leaks and alveolar rupture may occur due to various factors, such as mechanical ventilation, positive pressure ventilation, uneven ventilation, and reduced lung compliance, especially in cases of premature lungs that are highly sensitive to stretch. The increased transpulmonary pressure that exceeds the tensile strength of the alveoli and airways damages the respiratory epithelium, resulting in the entry of air into the interstitial tissue of the lung due to elevated intra-alveolar pressure (5, 6, 24, 25). Currently identified etiologies of PIE comprise prematurity, extremely low birth weight, RDS, positive pressure or mechanical ventilation employing high peak pressure, high tidal volume or prolonged inspiratory time, meconium aspiration syndrome, amniotic fluid aspiration, pulmonary infection, pulmonary hypoplasia, and improper positioning of the endotracheal tube (3, 6, 26, 27). All five of our ELBW premature infants were diagnosed with RDS and underwent intubation with mechanical ventilation. Pulmonary infection episodes were also noted prior to the development of PIE in cases 2 and 5. The cause of PIE in our study is readily apparent.

The fundamental treatment approach for PIE involves utilizing gentle ventilation techniques to decrease barotrauma and volutrauma (28). This includes non-invasive ventilation, volume control, or high-frequency ventilation, all of which have been found effective in minimizing the development of PIE (8, 29). Other treatment methods that have been reported to successfully resolve PIE include lateral decubitus position, selective main bronchial intubation or occlusion, lung puncture, and lobectomy (7, 30–36). In our case report, we attempted conventional strategies such as the lateral decubitus position, gentle ventilation with shortened inspiratory time, reduced PIP, adjusted PEEP, HFOV with decreased MAP, and non-invasive ventilation. Unfortunately, these measures were unsuccessful in resolving PIE. The interval between the onset of PIE and the initiation of NAVA varied among our five patients, ranging from 2 days–30 days. This considerable variability is attributed to parental hesitation regarding the substantial expense of NAVA treatment and individual differences in the clinical course.

Previous studies have shown that NAVA can provide the benefits of delivering optimal volume and precise cycling-off based on the patient's own Edi (37). This is advantageous in treating patients with PIE, particularly in addressing discrepancies between both lungs and preventing further overdistension of PIE or under-ventilation of the contralateral lung (13, 37). These advantages are not possible with traditional synchronized ventilation methods, as achieving a balanced tidal volume and accurate inspiratory time for both lungs without Edi is difficult for physicians. Compared to conventional synchronized ventilation, HFOV and non-invasive ventilation, NAVA appears to be a more effective treatment for patients with PIE. Additionally, NAVA is safer and less invasive than other treatments such as selective main bronchial intubation or occlusion, lung puncture, and lobectomy, and does not require sedation (13).

Before introducing NAVA for the treatment of PIE in our units, we were limited to traditional methods involving ventilator adjustments. This approach often resulted in lung collapse or the progression of PIE, complicating matters with severe BPD later. Such complications led to patient mortality or the necessity for home ventilator support after discharge.

Our study has certain limitations. NAVA is a relatively novel ventilation mode, and our clinical experience in manipulating NAVA is limited compared to traditional modes in ELBW infants. This comparative lack of experience could result in conservative management during the weaning process of NAVA, potentially prolonging the resolution period of PIE. Additionally, our study suffered from a small sample size, attributed to a data collection period of only two years across two medical centers. It is worth noting that NAVA is a self-pay treatment in Taiwan, and the high cost of the Edi catheter makes it unaffordable for many parents, contributing to the limitations in our sample size during collection. Consequently, further research with a larger sample size is imperative to validate our findings.

4 Conclusion

Based on our limited experience, we suggest that NAVA may be an effective rescue treatment option for patients with PIE. However, further larger studies are necessary to evaluate its effectiveness.

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 Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital and Taichung Veterans General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by participants' legal guardians. Written informed consent was obtained from the minors' legal guardians, for the publication of any potentially identifiable images or data included in this article.

Author contributions

C-MC: Formal Analysis, Writing – original draft. M-YC: Conceptualization, Writing – review & editing. H-YK: Data curation, Methodology, Writing – review & editing. M-CO: Investigation, Writing – review & editing. T-MW: Investigation, Writing – review & editing. C-TH: Formal Analysis, 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.2024.1332332/full#supplementary-material

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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Natália Damiani,
Federal University of Rio Grande do Sul, Brazil
Christ-jan Van Ganzewinkel,
Máxima Medical Center, Netherlands

*CORRESPONDENCE
Zhenghao Wang
✉ wangzh202105@163.com

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

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The effect of music on pain management in preterm infants during daily painful procedures: a systematic review and meta-analysis

Yiran Ou[1†], Ling Chen[2†], Xinyue Zhu[1], Tianci Zhang[1], Ye Zhou[1], Lu Zou[1], Yun Gao[1], Zhenghao Wang[1*] and Xiaofeng Zheng[1]

[1]Department of Endocrinology and Metabolism, Center for Diabetes and Metabolism Research, West China Hospital, Sichuan University, Chengdu, China, [2]Institute of Taoism and Religious Culture, Sichuan University, Chengdu, China

Background: The present systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to investigate the effects of music on pain management in preterm neonates during painful procedures.
Methods: The PubMed, Embase, Web of Science, EBSCO and Cochrane Library databases were searched to identify relevant articles published from their inception to September 2023. The study search strategy and all other processes were implemented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.
Results: Four RCTs that satisfied the inclusion criteria were included in this meta-analysis. The music group had significantly lower Premature Infant Pain Profile (PIPP) scores during (RR = –1.21; 95% CI = –2.02––0.40, $p = 0.0032$) and after painful procedures (RR = –0.65; 95% CI = –1.06––0.23, $p = 0.002$). The music group showed fewer changes in PIPP scores after invasive operations than did the control group (RR = –2.06; 95% CI –3.16––0.96; $p = 0.0002$). Moreover, our results showed that music improved oxygen saturation during (RR = 3.04, 95% CI = 1.64–4.44, $p < 0.0001$) and after painful procedures (RR = 3.50, 95% CI = 2.11–4.90, $p < 0.00001$). However, the change in peak heart rate during and after painful procedures was not statistically significant (RR = –12.14; 95% CI = –29.70–5.41 $p = 0.18$; RR = –10.41; 95% CI = –22.72–1.90 $p = 0.10$).
Conclusion: In conclusion, this systematic review demonstrated that music interventions are effective for relieving procedural pain in preterm infants. Our results indicate that music can reduce stress levels and improve blood oxygen saturation. Due to the current limitations, large-scale, prospective RCTs should be performed to validate the present results.

KEYWORDS

premature infant, music, procedural pain, PIPP, meta-analysis

Abbreviations
RCTs, randomized controlled trials; PIPP, Premature Infant Pain Profile; NICU, Neonatal intensive care unit; PICC, peripherally inserted central venous catheter; NCPAP, nasal continuous positive airway pressure; ROP, retinopathy of prematurity; HDU, high dependency unit; NNS, nonnutritive sucking.

1 Introduction

The World Health Organization defines preterm birth as a birth before 37 completed weeks of gestation or fewer than 259 days after the first day of the woman's last menstrual period. In 2020, an estimated 13.4 million babies were born preterm, accounting for 10% of all live births worldwide. In 2020, the preterm birth rate varied widely, from 4%–16% among different countries (1). In 2019, 5.30 million children younger than 5 years died—17% of whom died due to preterm birth complications (2)—and most survivors were hospitalized in the neonatal intensive care unit (NICU), with a length of hospitalization ranging from a few days to months. Hospitalized neonates experience acute episodic pain every day, including pain caused by heel lancing, naso- and endotracheal suctioning, venipuncture, arterial puncture, tracheal intubation, tracheal extubation, peripherally inserted central venous catheter (PICC) placement, retinopathy of prematurity (ROP) examination and other special invasive operations according to their individual clinical requirements (3). Most preterm infants require hospitalization in the NICU, where pain exposure is even more prevalent. According to a European multicenter study, many painful and stressful procedures were performed in the NICU, and the majority of them were performed without analgesic measures (4). According to the traditional definition, pain is an unpleasant sensory and emotional experience that leads to systemic physiological changes. However, this definition strongly relies on patients to describe their pain, establishing the primacy of self-reports as the "gold standard" for newborns (who are nonverbal) and proposing that pain in newborns be classified as acute episodic, acute recurrent, prolonged, persistent or chronic pain (5). Based on a global, four-stage consensus and validation, acute episodic pain is described as a painful response to a procedure or an event. An episode is defined as a single event or a sequence of events related to a procedure (6). Although newborns are unable to describe their pain, physiological and behavioral responses are difficult to ignore. The physiological changes include increased heart rate and blood pressure, decreased blood oxygen saturation, fluctuating cortisol levels, and tissue damage (7). The physiological changes include increased heart rate and blood pressure, decreased blood oxygen saturation, fluctuating cortisol levels, and tissue damage (5). In addition to erratic fluctuations in vital signs caused by painful stimuli, the long-term adverse effects of painful experiences are of concern. Recent studies have shown that exposure to persistent or recurrent pain or stress in the infancy period has long-term consequences that not only affect brain and behavioral development but also affect all organs, leading to serious morbidity and potential mortality (6, 7). Moreover, preterm infants who survive are more susceptible to prolonged negative effects throughout their lives, such as permanent changes in the endocrine and immune systems and impaired reactivity toward stressful events (8–10). According to the evidence-based clinical practice guidelines for the management of newborn pain, pain management in newborns requires a multidimensional approach that includes environmental, pharmacological and non-pharmacological measures (3). Although pharmacological treatments for neonates are established early and have relatively certain effects, the immature drug metabolism and related negative side effects, such as respiratory depression, apnea, bradycardia and hypotension, are difficult to overlook, especially for premature infants (11). Therefore, there has been growing interest in nonpharmacological analgesic options such as oral sucrose administration, nonnutritive sucking (NNS), kangaroo care, breastfeeding, and massage (11, 12).

Among all nonpharmacological analgesic options, music has long been used to enhance well-being and reduce pain and suffering. According to the definition put forward by the American Music Therapy Association, music therapy refers to the clinical and evidence-based use of music as a therapeutic intervention to accomplish individualized goals facilitated by a credentialed professional who has completed an approved music therapy program (13). Music therapy has been utilized as a strategy to ameliorate pain in various healthcare settings due to its noninvasiveness, cost effectiveness, reduction in anesthetic dosage and promising analgesic effects. However, the effects of music on pain management in preterm infants during painful procedures from the aspect of pain assessment have not been determined. For newborn patients, especially preterm infants, self-expression is not possible. Therefore, valid and reliable tools for assessing the degree of pain in newborns are needed (14). There are approximately 40 pain assessment instruments available to date, with various evaluation dimensions (15). The different assessments include different items and have been validated for patients with various kinds of pain and ages (16). The Premature Infant Pain Profile (PIPP) was developed by Stevens, Johnston, Petryshen, and Taddio to evaluate preterm infants' pain responses. This scoring system includes seven items: two items that describe baseline characteristics (gestational age and behavioral state); two items that are physiological indicators (heart rate and oxygen saturation); and three items that describe the neonate's facial expression (brow bulge, eye squeeze, and nasolabial furrow); the score for each item ranges from 0 to 3. A PIPP score of 0–6 points indicates mild pain, 7–12 points indicates moderate pain, and 13–21 points indicates severe pain (17). The PIPP is used to evaluate acute procedural pain in preterm and term infants (18). As the instrument takes contextual factors such as gestational age into account, the PIPP is recommended for its ability to judge pain in preterm and even extremely preterm neonates (16).

In addition, new studies with more detailed data and higher evidence levels have been published (19–22). Thus, we performed the present systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effects of music on pain management in premature newborns. The results of this investigation may guide future decision-making regarding the use of music for managing pain in premature newborns.

2 Materials and methods

This systematic review and meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions. Ethical approval and patient consent were not required because all analyses were based on previously published studies.

2.1 Literature search and selection criteria

We systematically searched several databases, including PubMed, Embase, the Web of Science, EBSCO and the Cochrane Library, from inception to September 2023. The research strategy was as follows: ((((((((((((((((((((“Music”[Mesh]) OR (Song)) OR (Melody, Vocal)) OR (Vocal Melody)) OR (Vocal Melodies)) OR (Melodies, Vocal)) OR (Songs)) AND (“Infant, Premature”[Mesh])) OR (Infants, Premature)) OR (Premature Infant)) OR (Preterm Infants)) OR (Infant, Preterm)) OR (Infants, Preterm)) OR (Preterm Infant)) OR (Premature Infants)) OR (Neonatal Prematurity)) OR (Prematurity, Neonatal)) AND (premature infant pain profile)) OR (PIPP)) AND (painful procedures)) AND (randomized controlled trial). The reference lists of retrieved studies and relevant reviews were hand-searched, and the process mentioned above was repeatedly performed to ensure the inclusion of all eligible studies. The inclusion criteria were as follows: (1) RCTs, (2) studies in which the patients were preterm infants, (3) studies in which a music intervention was used to relieve pain and discomfort for participants, (4) studies in which a music intervention group was compared with a control group, and (5) full-text studies with sufficient data for extraction for further analysis. Studies written in all languages were included.

2.2 Data extraction and outcome measures

The data were independently and separately extracted by two investigators. The following baseline information was extracted from the original studies: first author, publication year, number of patients, gestational age and sex distributions, evidence level, detailed intervention method and duration. Any discrepancies were resolved by consensus. The primary outcomes were the PIPP score during the procedure (absolute change in the PIPP during the procedure, PIPP score during the procedure) and PIPP after the procedure (absolute change in the PIPP score after the procedure, PIPP score after the procedure). The secondary outcomes were the mean SaO_2, peak heart rate and blood cortisol concentration.

3 Results

3.1 Literature searches, study characteristics, and quality assessment

In total, 108 articles were initially identified from the databases. After removing duplicates, 108 articles were retained. A total of 98 studies were excluded from our study due to unrelated abstracts and titles. We also excluded two studies that were not RCTs, one study that presented insufficient data, two studies that reported an improper methodology, and one study that presented a nonconformity at baseline. Ultimately, four RCTs satisfied the inclusion criteria and were included in this meta-analysis. The article selection process was performed in accordance with the PRISMA statement (Figure 1). The baseline characteristics of the 4 included studies (23–26) are shown in Table 1. Four studies compared a music intervention to no special intervention. Lullaby music was used in three groups (23, 24, 26), and classical music was used in one group (25). The involved painful clinical procedures included PICC placement (24), nasal continuous positive airway pressure (NCPAP) (23), venipuncture (26) and ROP screening (25). There were no statistically significant differences in patient baseline characteristics. The music duration varied according to the specific procedure. All the studies in our meta-analysis were published between 2018 and 2022, and the total sample size was 252. Two reviewers independently assessed the methodological quality of each study based on the revised Cochrane Risk of Bias tool for RCTs (27). The quality assessment considered seven aspects (random sequence generation, allocation concealment, blinding of participants or personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other bias), with each aspect rated as low, high, or unclear in terms of risk of bias. We used Review Manager (RevMan) software 5.3 to construct a risk of bias graph and summary (Figure 2).

4 Primary outcomes

4.1 PIPP score during the procedure

4.1.1 Absolute change in the PIPP score during the procedure

All the studies examined the PIPP scores before and during painful procedures. Our results revealed that music did not significantly change the score in the intervention group compared to the control group (RR = −1.41; 95% CI = −2.95 −0.12, $p = 0.07$), and there was significant heterogeneity [$I^2 = 89\%$, $p < 0.00001$; Figure 3A].

4.1.2 PIPP score during the procedure

The PIPP scores significantly differed between the music intervention group and the control group (RR = −1.70; 95% CI = −2.24–−1.16, $p < 0.00001$), and there was significant heterogeneity [$I^2 = 86\%$, $p < 0.0001$; Figure 3B]. After removing the Tang et al. study, the heterogeneity became nonsignificant [$I^2 = 0\%$, $p = 0.57$; Figure 3C], and the overall effect of music remained significant (RR = −0.79; 95% CI = −1.46–−0.12, $p = 0.02$).

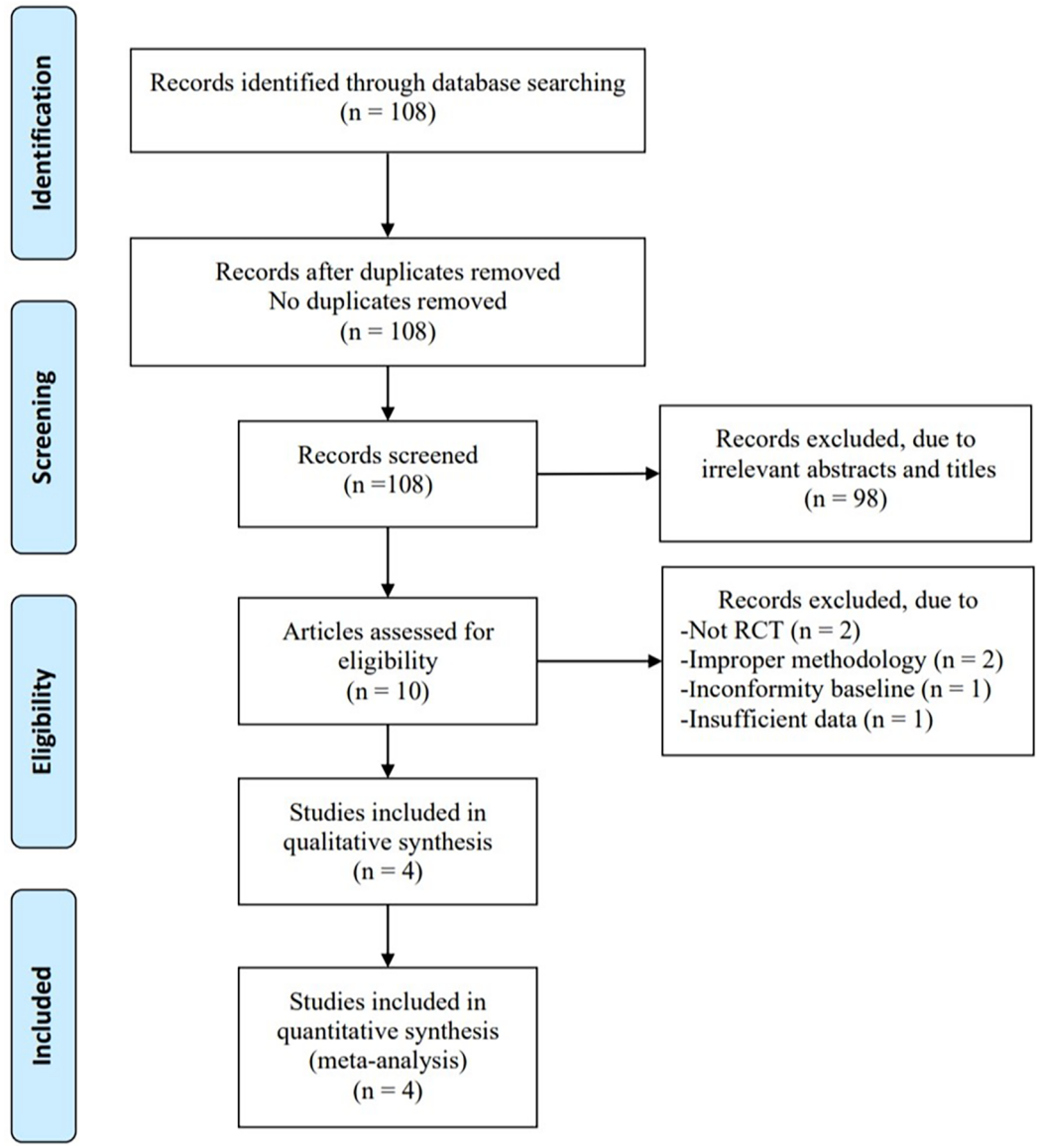

FIGURE 1
Flow diagram of the study search and selection process.

4.2 PIPP score after the procedure

4.2.1 Absolute change in the PIPP score after the procedure

Four studies examined the PIPP scores before and after painful procedures. The score change significantly differed between the music intervention group and the control group (RR = −2.06; 95% CI = −3.16–−0.96, $p = 0.0002$), and there was significant heterogeneity [$I^2 = 79\%$, $p = 0.0007$; Figure 4A].

4.2.2 PIPP score after the procedure

Our results revealed a significant difference in the scores of the music intervention group compared with those of the control group (RR = −1.99; 95% CI −3.27–−0.71; $p = 0.002$), and there was significant heterogeneity [$I^2 = 88\%$, $p < 0.00001$; Figure 4B]. After removing the study by Barandouzi et al. in which data was collected 10 min after the procedure, the heterogeneity decreased ($I^2 = 49\%$, $p = 0.12$), and the overall effect of music remained significant [RR = −2.60; CI = −3.31–−1.88, $p < 0.00001$; Figure 4C].

5 Secondary outcomes

5.1 Mean SaO_2 during/after the procedure

Two studies examined data relating to the mean SaO_2 (23, 25). For the mean SaO_2, our meta-analysis indicated that there were significant differences in the duration of music during [RR =

TABLE 1 Characteristics of included studies.

				Music treatment group					Control group				
No	Author	Year	Procedure	Number (n)	Sex (male/ female)	(Mean ± SD)	Birth weight (Mean ± SD)	Intervention	Number (n)	Sex (male/ female)	Gestational (Mean ± SD)	Birth weight (Mean ± SD)	Intervention
1	Tang	2018	PICC	30	16/14	32.57 ± 1.76	2,185 ± 165	Lullaby and nursery rhymes with50–60 dB was played 10 min before PICC puncture until 10 min after the procedure by an MP4-player with small mobile speaker which placed 30 cm from the infants' ears.	30	16/14	32.57 ± 1.83	2,212 ± 172	Bed rest
2	Tekgündüz	2019	NCPAP nursing	35	19/16	31.57 ± 3.18	1,774.14 ± 647.74	Lullaby with 50–60 dB was played from the reinsertion of the tracheal tube until the intervention finished by an CD speaker located around 30 cm away from the infants' heads.	37	19/18	30.26 ± 3.54	1,460.67 ± 684.91	Routine application
3	Barandouzi	2020	venipuncture	30	14/16	34 ± 1.41	1,987 ± 367.86	Lullaby music with 40–50 dB was played 2 min before the venipuncture for 10 min via headphone; received 0.5 ml sterile water via syringe on the anterior portion of infants' tongue	30	17/13	33.86 ± 1.35	2,012 ± 352.83	Had headphones without music, received 0.5 ml sterile water via syringe on the anterior portion of infants' tongue
4	Dur	2022	ROP examination	30	13/17	29.43 ± 2.88	1,312.30 ± 404.07	Classic music with 55 dB was played 1 min before PICC puncture until 1 min after the examination via loudspeaker.	30	14/16	29.03 ± 2.63	1,311.33 ± 378.37	swaddled and laid onthe examination table

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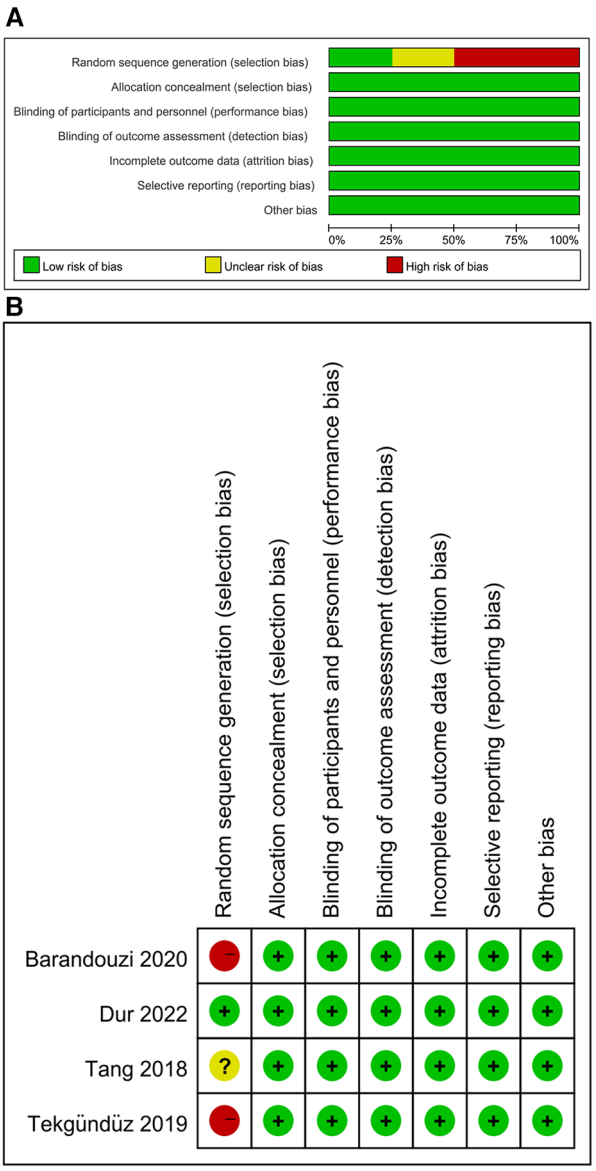

FIGURE 2
Review author's judgement about each risk of bias item as percentages across all included studies.

3.04, 95% CI = 1.64–4.44, $p < 0.0001$; Figure 5A] and after the procedure [RR = 3.50, 95% CI = 2.11–4.90, $p < 0.00001$; Figure 5B]. There was also nonsignificant heterogeneity ($I^2 = 0\%$, $p = 0.83$; $I^2 = 0\%$, $p = 0.82$). Overall, music improved the blood oxygen saturation of preterm infants not only during but also after painful procedures.

5.2 Peak heart rate during/after the procedure

Two studies examined changes in the peak heart rate (23, 25). Our results demonstrated that the music intervention group did not show a significant decrease in the peak heart rate during the procedure compared to the control group [RR = −12.14; 95% CI = −29.70–5.41 $p = 0.18$; Figure 6A], and there was significant heterogeneity ($I^2 = 84\%$, $p = 0.01$). Additionally, a comparison of the statistical data after the procedure showed a negative correlation [RR = −10.41; 95% CI = −22.72–1.90 $p = 0.10$; Figure 6B], with significant heterogeneity ($I^2 = 73\%$, $p = 0.10$).

5.3 Blood cortisol concentration

One study (24) analyzed the blood cortisol concentration as a stress level index. The results showed that the cortisol concentration was significantly increased in the control group, but no obvious increase was observed in the music intervention group.

6 Discussion

Increasing evidence has shown that nonpharmacological analgesic methods are essential components of all effective interventions designed for managing procedural pain in preterm infants. However, there is no comprehensive understanding of the effect of music interventions on pain control and its physiological parameters. Considering that the PIPP has been validated to be a reliable assessment of pain in premature infants (28, 29), we performed this PIPP-centered meta-analysis to evaluate the analgesic effects of music and obtain higher-level evidence.

Our results showed that music had a nonsignificant effect on reducing the absolute change in the PIPP score during invasive procedures. However, due to the high heterogeneity ($I^2 = 89\%$) and the lack of clarity regarding the specific duration of the intervention may have led to unreliable conclusions. Furthermore, music can significantly reduce pain during painful procedures, and the heterogeneity decreased precipitously from 86% to 0% after removing the study by Tang et al. (24) due to its use of a different methodology. In their study, compared to other studies, music was played for a longer duration (10 min) before the start of the invasive procedure. Moreover, music had a significant effect on pain reduction at the end of the invasive procedure according to the PIPP score after the painful procedure. By comparing the results obtained during and after the operation, the importance of the duration of music before the start of the procedure was reemphasized. Thus, future studies are needed to verify the analgesic effect of playing music for a long period before painful procedures and explore a related standard scheme. According to our results and the findings of previous studies, the analgesic effect of music is understood, and music interventions have great potential for application in clinical practice to ease the pain of preterm infants, reduce the duration of invasive procedures, decrease the use of narcotic and analgesic drugs, and avoid the long-term effects of repetitive, acute episodic pain. Questions for future research remain. The optimal duration and amplitude of music therapy for pain relief still have yet to be determined. There are no studies that aimed to define the best choice of music for music therapy. To our knowledge, the aspect of overstimulation has not been studied. If possible, we strongly recommend that more experts in the field of music therapy focus on

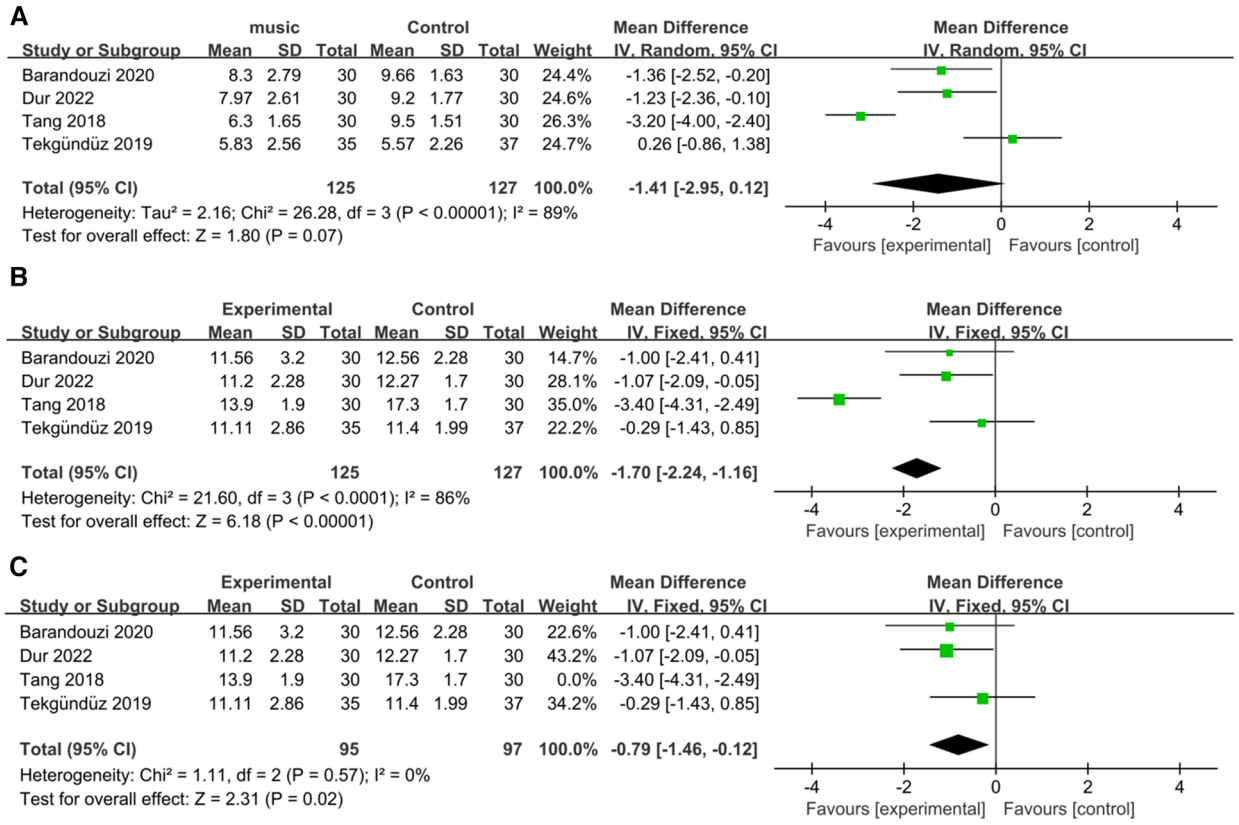

FIGURE 3
Forest plot for the meta-analysis of PIPP during procedure. (A) PIPP absolute change. (B) PIPP scores and (C) after PIPP scores sensitivity analysis.

and participate in preterm infant acute episodic pain alleviation projects, assisting clinicians and nurses in clinical decision making. Admittedly, we should emphasize that as a supplementary measure, the pain-relieving effect of music is limited because the pain category was unchanged.

Our results also indicated that music could significantly reduce pain levels during daily painful procedures. First, as an auditory stimulus, music not only provides a distraction but also has a potential effect on modulating perception by reducing delta-band activity in the cingulate gyrus and increasing gamma-band activity in somatosensory brain structures at different pain processing stages (30), thereby helping relieve painful responses. Moreover, studies have suggested that the analgesic effects of music can be partly explained by the endorphin release-induced reduction in the sympathetic nervous system response (31). Second, hearing music can physically reduce disturbing noises from the armamentarium and protect neonates against experiencing negative feelings (32, 33). Third, music can block pain pathways by facilitating sensorial saturation (34).

Improvement in physiological parameters is another indication of stress levels that reflect pain management outcomes. Several studies have demonstrated that music leads to an increase in oxygen saturation levels, as it reduces stress and has positive effects on both the heart rate and rhythm as well as on the respiratory rate (20, 35). Our results further validated this result, as music can increase the blood oxygen saturation of neonates during and after painful procedures. According to a recent systematic review, music/vocal interventions could reduce the heart rate in preterm infants during procedures, and the effect was greater after the procedures (36). Nevertheless, music did not have an obvious advantage in decreasing the peak heart rate in the present study. Blood oxygen saturation is affected by multiple factors, such as the whole respiratory and circulatory system. Therefore, the improvement in blood oxygen saturation may be more meaningful than the decrease in the peak heart rate.

As a recognized stress hormone, cortisol has always been a widely used indicator of stress levels (37). Studies have shown that music exposure can decrease stress hormone levels in preterm neonates in the NICU environment (38). Previous studies have confirmed that music decreases the levels of stress hormones before, during, and after surgery (39–41). However, only one of the four studies measured cortisol levels, and the cortisol concentration in the music intervention group was significantly lower than that in the control group, which further confirmed the stress-relieving effect of music. Therefore, additional studies are needed to further analyze cortisol levels to obtain a more visual representation of the influence of music on the degree of stress alleviation.

In this systematic review and meta-analysis, we first investigated the impact of music on pain management in preterm infants during acute episodic pain. This study has several limitations. First, the

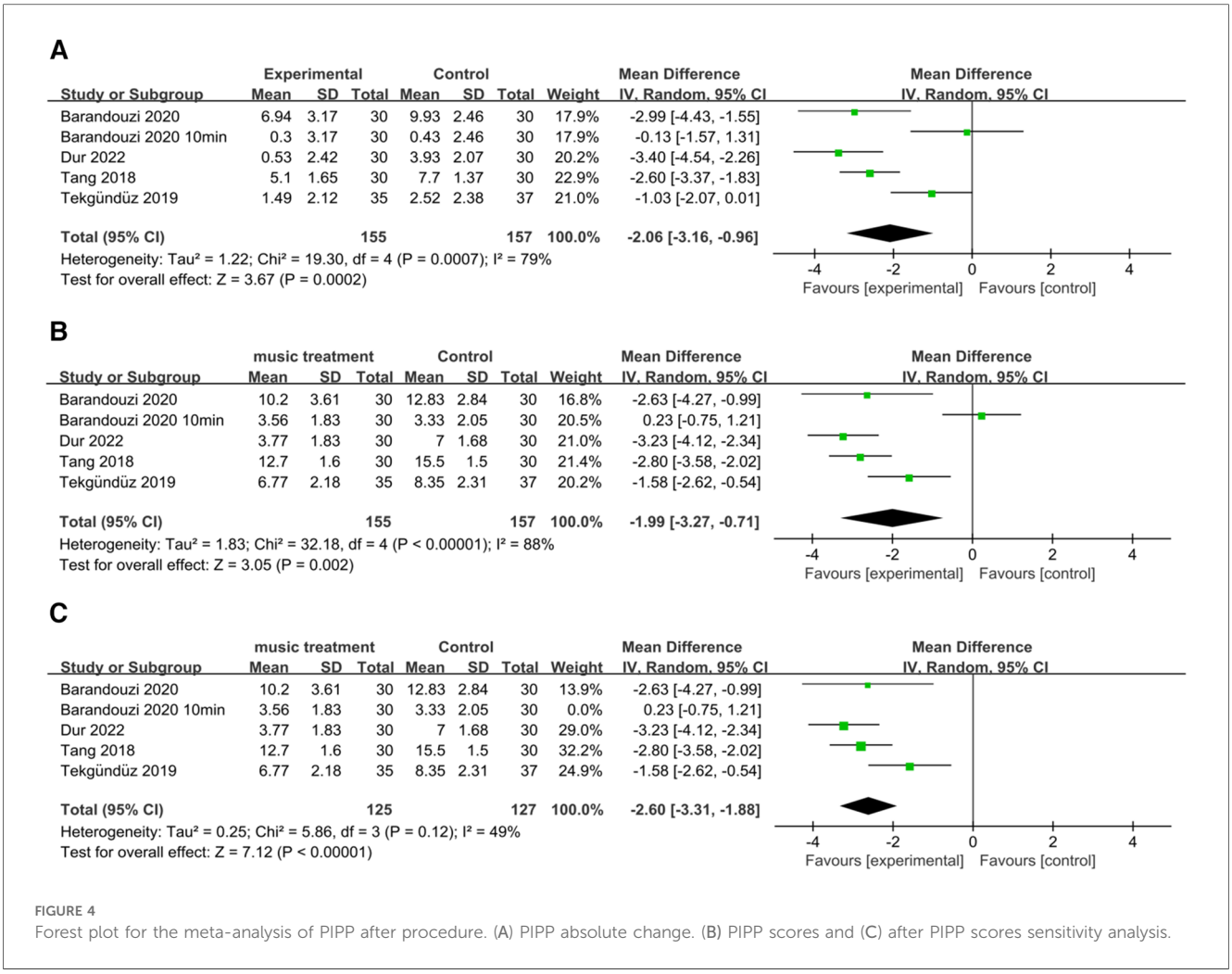

FIGURE 4
Forest plot for the meta-analysis of PIPP after procedure. (A) PIPP absolute change. (B) PIPP scores and (C) after PIPP scores sensitivity analysis.

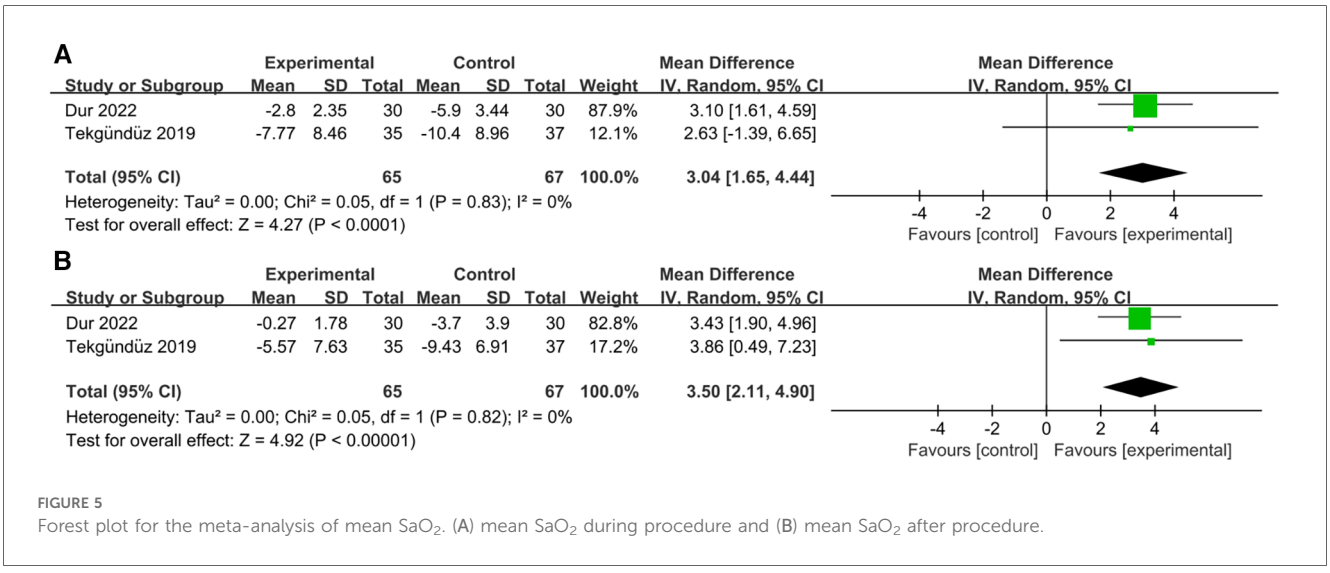

FIGURE 5
Forest plot for the meta-analysis of mean SaO_2. (A) mean SaO_2 during procedure and (B) mean SaO_2 after procedure.

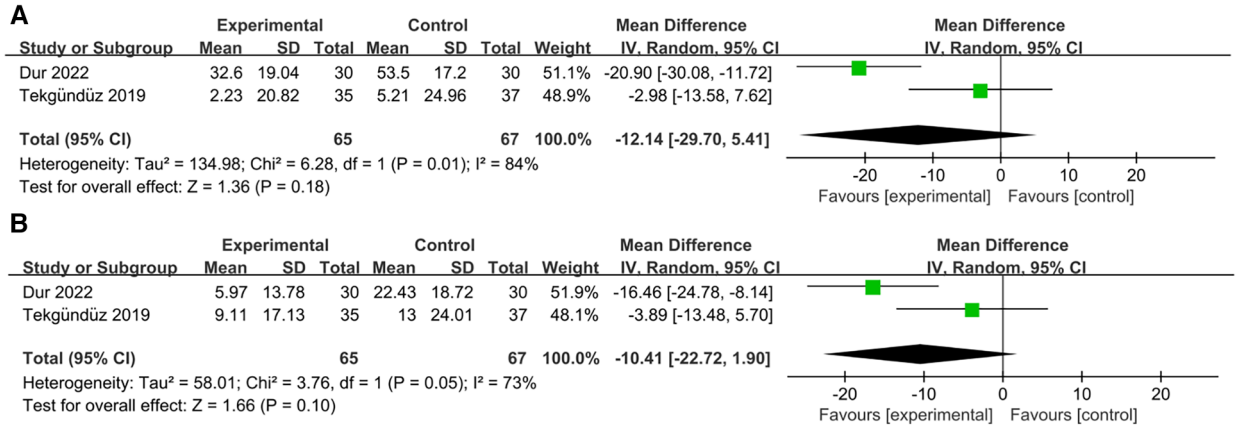

FIGURE 6
Forest plot for the meta-analysis of peak heart rate. (A) peak heart rate during procedure and (B) peak heart rate after procedure.

sample size in each study was relatively small. Second, the included studies involved diverse invasive operations and different evaluation time points, which contributed to a major part of the heterogeneity. Third, the duration and genre of the music and the approach of the music intervention largely varied in this study, and the related standard is worth investigating in future studies. Additionally, the selected studies involved various durations. Finally, missing and unpublished data also led to bias in the true impact of the music intervention. Thus, robust RCTs with large sample sizes and a standard protocol should be conducted in the future to obtain more accurate data and to verify our results.

7 Conclusion

In conclusion, this systematic review demonstrated that music is an effective intervention for relieving procedural pain in preterm infants. Our results indicated that music can reduce stress levels

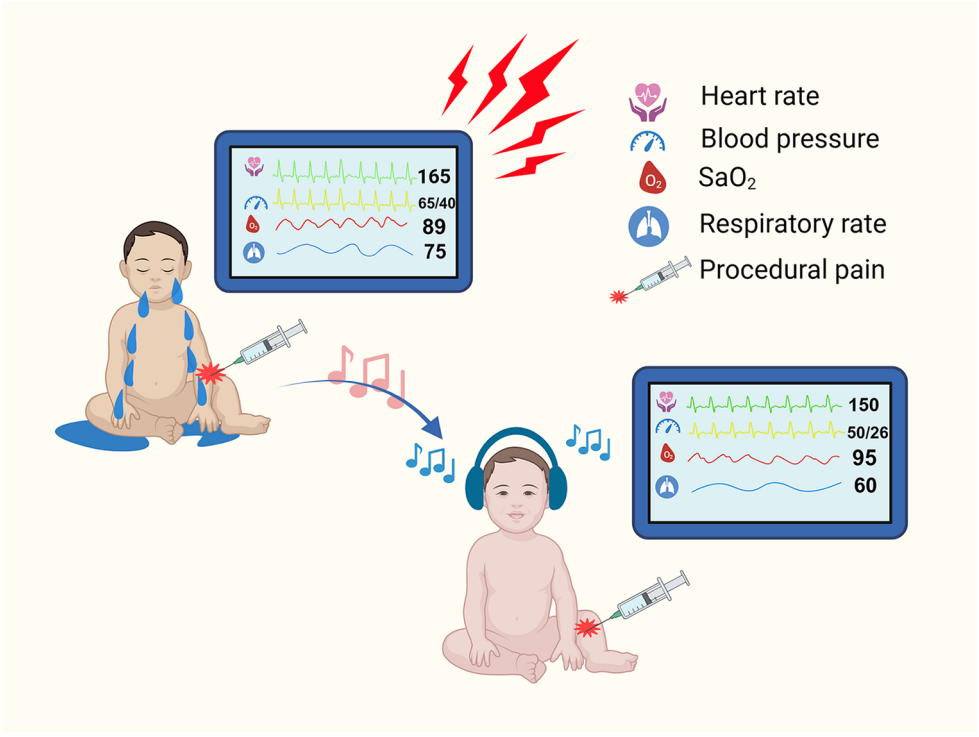

FIGURE 7
Illustration for the ideal outcome of music intervention of procedural pain management in preterm infants. (Created with BioRender.com.).

and improve blood oxygen saturation. Figure 7 shows the ideal outcome of music for procedural pain management in preterm infants. As a noninvasive, nonpharmaceutical, relatively low-cost intervention that can be applied at the bedside, music has an extremely impressive application in the NICU daily nursing routine. Due to the limitations of the present study, large-scale, prospective RCTs should be performed to validate these results.

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.

Author contributions

YO: Writing – original draft. LC: Writing – original draft. XZ: Writing – review & editing. TZ: Writing – review & editing. YZ: Writing – review & editing. LZ: Writing – review & editing. YG: Writing – review & editing. ZW: Writing – review & editing. XZ: 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

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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Anne Greenough,
King's College London, United Kingdom
Noah H. Hillman,
Saint Louis University, United States
Shalin Parikh,
Ganpat University, India

*CORRESPONDENCE
Gianluca Terrin
gianluca.terrin@uniroma1.it

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Outcomes of postnatal systemic corticosteroids administration in ventilated preterm newborns: a systematic review of randomized controlled trials

Giovanni Boscarino[1], Viviana Cardilli[1], Maria Giulia Conti[1], Federica Liguori[1], Paola Repole[1], Pasquale Parisi[2] and Gianluca Terrin[1]*

[1]Department of Maternal and Child Health, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy, [2]Pediatrics Unit, Department of Neuroscience, Mental Health and Sense Organs (NESMOS), Faculty of Medicine and Psychology, Sant' Andrea Hospital, Sapienza University of Rome, Rome, Italy

Introduction: Prolonged mechanical ventilation, commonly used to assist preterm newborns, increases the risk of developing bronchopulmonary dysplasia (BPD). In recent decades, studies have demonstrated that systemic corticosteroids play a significant role in the prevention and management of BPD. In this systematic review of randomized controlled trials (RCTs), we evaluated the association between the administration of systemic corticosteroids in preterm infants and its long-term outcomes, such as neurodevelopment, growth, extubation rate, and related adverse effects.

Methods: We conducted an electronic search in Medline, Scopus, and PubMed using the following terms: "premature infants" and "corticosteroids." We considered all RCTs published up to June 2023 as eligible. We included all studies involving preterm newborns treated with systemic corticosteroids and excluded studies on inhaled corticosteroids.

Results: A total of 39 RCTs were evaluated. The influence of steroids administered systemically during the neonatal period on long-term neurological outcomes remains unknown, with no influence observed for long-term growth. The postnatal administration of systemic corticosteroids has been found to reduce the timing of extubation and improve respiratory outcomes. Dexamethasone appears to be more effective than hydrocortisone, despite causing a higher rate of systemic hypertension and hyperglycemia. However, in the majority of RCTs analyzed, there were no differences in the adverse effects related to postnatal corticosteroid administration.

Abbreviations

BPD, bronchopulmonary dysplasia; ELGAN, extremely low gestational age newborns; GA, gestational age; HG, hyperglycemia; IV, intravenous; IVH, intraventricular hemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NDV, neurodevelopment; PO, orally; PDA, patent ductus arteriosus; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCTs, randomized controlled trials; ROP, retinopathy of prematurity.

Conclusion: Dexamethasone administered during the neonatal period appears to be more effective than hydrocortisone in terms of respiratory outcomes; however, caution should be taken when administering dexamethasone. Data derived from current evidence, including meta-analyses, are inconclusive on the long-term effects of the administration of systemic steroids in preterm infants or the possibility of neurodevelopmental consequences.

KEYWORDS

hydrocortisone, dexamethasone, neurodevelopment, growth, extubation, pulmonary outcome, systemic hypertension, hyperglycemia

Introduction

The survival rate of preterm newborns has improved over the last 20 years due to advances in neonatal care (1). However, the improvement in survival has been associated with an increased morbidity rate and reduced long-term neurodevelopmental (NDV) outcomes (2, 3). Two of the most important innovations in neonatal care are the introduction of surfactant therapy and the improvement in mechanical ventilation (MV). However, prolonged MV (PMV) is harmful and increases the risk of developing bronchopulmonary dysplasia (BPD) (4, 5). BPD is a chronic inflammatory lung disease of premature neonates characterized by impaired lung development (4, 6). It has a multifactorial pathogenesis, wherein prolonged oxygen exposure induces a destructive local inflammatory response in the lung alveoli, associated with a simultaneous impaired repair response (6). In addition, it has been demonstrated that BPD is associated with impaired long-term NDV and pulmonary function outcomes (7, 8). Thus, neonatologists aim to extubate preterms as soon as possible, albeit not always possible, especially for extremely low gestational age newborns (ELGAN). Corticosteroids (e.g., dexamethasone and hydrocortisone) are currently administered intravenously (IV) or orally (PO) for the treatment and prevention of BPD. Studies have related their beneficial effects to their anti-inflammatory activity (9–11). The authors researched inhaled corticosteroids (12); however, no beneficial effects were found on the risk of neurological disability although the mortality rate was higher in the treated group, thus not allowing the routine administration (13, 14). However, whether the use of dexamethasone or hydrocortisone IV or PO improves or reduces long-term neurological outcomes is still debated. In addition, there are concerns regarding the prophylactic use of systemic corticosteroid therapy for possible adverse effects (i.e., sepsis, infection, and metabolic side effects).

In this systematic review of randomized controlled trials (RCTs), we studied the association between the administration of systemic corticosteroids during the neonatal period and its long-term outcomes, in terms of NDV and growth. Additionally, we evaluated the respiratory outcomes and possible adverse effects.

Material and methods

Studies, population, and intervention

We considered all RCTs published up to June 2023 as eligible. We included all studies involving preterm newborns treated with systemic (IV or PO) corticosteroids and excluded studies on inhaled corticosteroids.

Outcomes

Our primary outcome was the long-term effects such as NDV and growth. Our secondary outcomes were as follows: the rate of extubation, reintubation, BPD, other respiratory outcomes (considering the duration of invasive or non-invasive MV, supplemental oxygen therapy, FiO2, or other specific ventilatory/respiratory data), and steroid-related adverse effects. We considered the following as adverse effects: systemic hypertension, hyperglycemia (HG), sepsis or other infections, patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP).

Research methods and study selection

We performed a systematic review of the published RCTs, in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (15). We conducted an electronic search in Medline, Scopus, and PubMed using the following medical subject headings and terms: “premature infants” and “corticosteroids.” Only English manuscripts and RCTs were considered. Two authors (G.B. and F.L.) independently assessed the study eligibility according to the pre-established criteria and performed an accurate check to exclude duplicates. A discussion with a third part researcher (G.T.) resolved different in opinion, to achieve consensus. We performed a manual search of the reference list of the systematic reviews and meta-analyses published and excluded them from this review.

Data extraction, management, and risk of bias

Two authors (G.B. and F.L.) independently extracted the data from the selected articles using specifically designed data forms. For each selected RCT, the form summarized data on authorship, year of publication, population, inclusion and exclusion criteria,

doses of steroids, days to extubation, duration of therapy, more than one cycle of steroids, and administration of other steroids. Another specific data form summarized the outcomes (e.g., extubation, reintubation, BPD, other respiratory outcomes, systemic hypertension, HG, sepsis/infection, PDA, IVH, NEC, ROP, and long-term outcomes). These data were checked for missing information, errors, and inconsistencies with published reports. If evidenced, differences were resolved by discussion and consensus between the researchers. The corresponding authors were contacted when the eligibility criteria of their papers were unclear.

The risk of bias was assessed independently by two researchers (G.B. and G.T.) using a specific form. We considered bias as selection bias (random sequence generation and allocation concealment), performance bias (blinding of the study personnel as to which intervention a neonate had received), detection bias (blinding of personnel evaluating outcomes), attrition bias (completeness of reporting data, reason, and balance across groups of missing data), reporting bias (reporting of the study's prespecified or expected outcomes of interest to the review), and other sources of bias (early interruption of the trial due to data-dependent process or bias related to the specific study design). We categorized the risks of bias as high, low, or unclear for each study, using standard methods (15). The selection bias was judged as unclear when these aspects were not available. The differences in opinion were resolved by discussion and consensus.

Results

Study description

During the research process using the mesh term described in the Materials and methods section, we found 1,011 articles, and 11 RCTs were selected in the first qualitative synthesis after the screening process (Figure 1). After a manual search of the reference list of the systematic reviews and meta-analyses analyzed in the previous stages, we added 28 RCTs, and 39 RCTs were analyzed in the final step of this systematic review (Figure 1). Data extracted are summarized in Tables 1–6 (16–54).

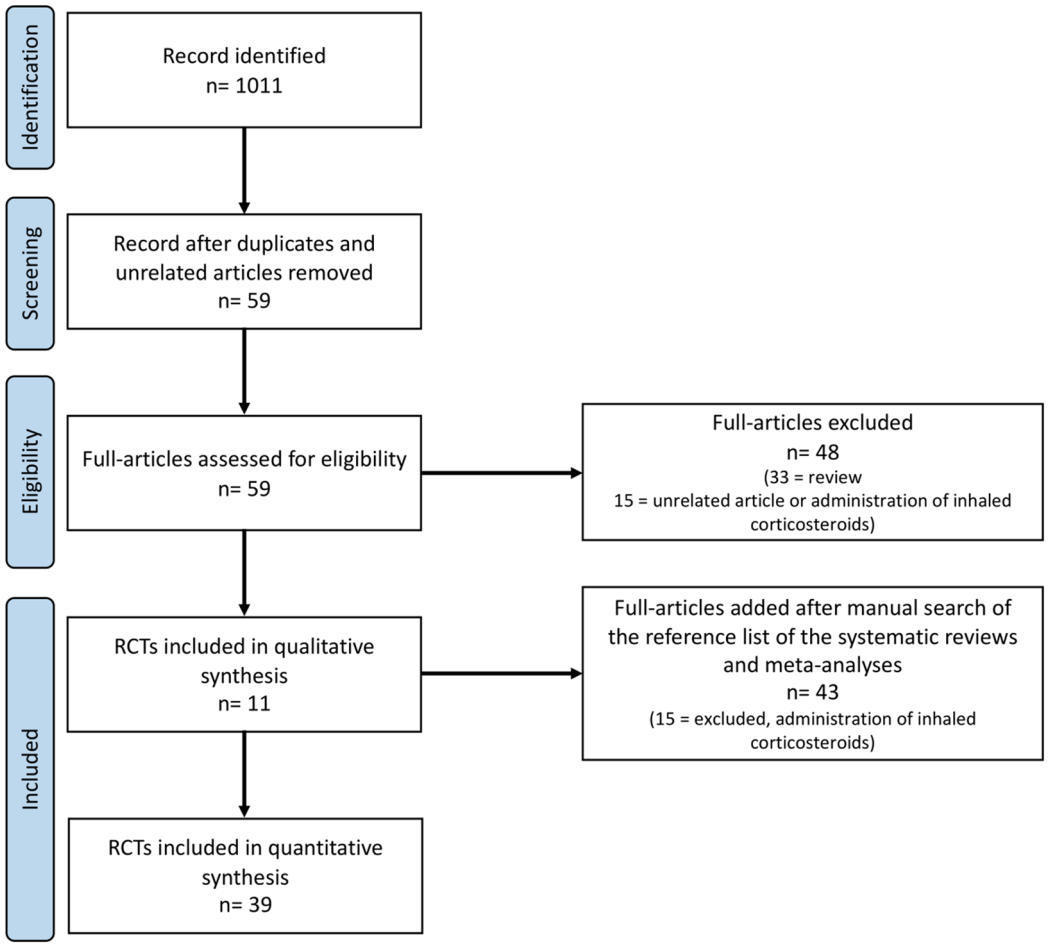

FIGURE 1
PRISMA flow-chart. RCTs, randomized controlled trials.

TABLE 1 Randomized controlled trials comparing hydrocortisone vs. placebo.

Reference (authors, year)	Population (*n*)	Inclusion criteria	Exclusion criteria	Doses of steroids	Start at	Extubation (days of life)	Duration of therapy by protocol (days)	More than one cycle of steroids	Administration of other steroids
Halbmeijer (16)	Intervention: 182 Control: 190	GA <30 weeks and/or BW <1,250 g, ventilator dependent in the II week of life	No consent	Tapered dosing scheme of 22 days with a cumulative dose of 72.5 mg/kg	7–14 days after birth	Intervention: 9 Control: 15	22	ND	Placebo group (56.8%) treated with open-label hydrocortisone (excluded for sensitivity analyses)
Watterberg (17)	Intervention: 398 Control: 402	GA <30 weeks intubated for at least 7 days at 14–28 days	Congenital anomalies, indomethacin or ibuprofen treatment within 48 h before trial entry, and previous systemic glucocorticoid treatment	4 mg/kg/day tapered over a period of 10 days (4 mg/kg/day for 2 days, 2 mg/kg/day for 3 days, 1 mg/kg/day for 3 days, and 0.5 mg/kg/day for 2 days)	14–28 postnatal days	ND	10	ND	Open-label dexamethasone was administered to the hydrocortisone group (39.7%) and placebo group (42.1%)
Onland (18)	Intervention: 181 Control: 90	GA <30 weeks and/or BW 1,250 g, ventilator dependent between 7 and 14 days of life and at high risk of BPD	Chromosomal defects, congenital malformations, previous corticosteroids for improving lung function in the I week of life	5 mg/kg/day in 4 doses for 7 days, followed by 3.75 mg/kg/day in 3 doses for 5 days, subsequently lowering the frequency by 1 dose every 5 days (cumulative dose of 72.5 mg/kg for 22 days)	7–14 days after birth	ND	22	ND	The rate of open-label glucocorticoid use in the hydrocortisone group was 28.2% and 56.8% in the placebo
Baud (19)	Intervention: 194 Control: 185	GA <27 weeks	PROM before 22 weeks of GA, SGA, perinatal asphyxia, congenital malformations, or chromosomal aberrations	1 mg/kg/day into two doses for 7 days, followed by 0.5 mg/kg/day for 3 days	First 10 days of life	ND	10	ND	ND
Baud (20)	Intervention: 255 Control: 266	GA <27 weeks	PROM before 22 weeks of GA, SGA, perinatal asphyxia, congenital malformations, or chromosomal aberrations	1 mg/kg/day into two doses for 7 days, followed by 0.5 mg/kg/day for 3 days	First 10 days of life	ND	10	ND	ND
Parikh (21)	Intervention: 29 Control: 29	BW <1,000 g 10-days of life ventilated	<23 weeks, previously treated with corticosteroids, or indomethacin, presumed sepsis or NEC, congenital malformation	3 mg/kg/day for the first 4 days, 2 mg/kg/day for 2 days, 1 mg/kg/day for 1 day; total of 17 mg/kg over 7 days	10 and 21 postnatal days	ND	7	ND	ND
Parikh (22)	Intervention: 31 Control: 33	BW <1,000 g 10-days of life ventilated	<23 weeks, previously treated with corticosteroids, or indomethacin, presumed sepsis or NEC, congenital malformation	3 mg/kg/day for the first 4 days, 2 mg/kg/day for 2 days, 1 mg/kg/day for 1 day; total of 17 mg/kg over 7 days	10 and 21 postnatal days	ND	7	ND	Six infants in the hydrocortisone (19%) and seven in the placebo (21%) received postnatal corticosteroids after study drug completion ($P = 0.85$). Six infants (2 in the hydrocortisone group and 4 in the placebo group) received dexamethasone for ventilator-dependent BPD and five infants (3 in the hydrocortisone group and 2 in the placebo group) received hydrocortisone for suspected adrenal insufficiency
Peltoniemi (23)	Intervention: 21 Control: 19	GA <30 and BW <1,250 g and the requirement for mechanical ventilation	Malformations or early death	2.0 mg/kg for 2 days, 1.5 mg/kg for 2 days, and 0.75 mg/kg for 6 days, started before 36 h of life	Before the age of 36 h	ND	10	ND	ND

(*Continued*)

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TABLE 1 Continued

Reference (authors, year)	Population (*n*)	Inclusion criteria	Exclusion criteria	Doses of steroids	Start at	Extubation (days of life)	Duration of therapy by protocol (days)	More than one cycle of steroids	Administration of other steroids
Watterberg (24)	Intervention: 126 Control: 126	BW <1,000 g and intubated	Congenital anomaly, congenital sepsis, postnatal glucocorticoid treatment other than hydrocortisone, triplet or higher-order multiple gestation	1 mg/kg/day divided twice daily for 12 days, followed by 0.5 mg/kg/day for 3 days	12 and 48 h of life	ND	15	ND	ND
Bonsante (25)	Intervention: 25 Control: 25	BW <1,500 g, GA <30 weeks, need of mechanical ventilation after surfactant administration	Malformations, perinatal asphyxia, death within 12 h after recruitment, and use of steroids for any clinical reason before and during the 12 days of treatment	0.5 mg/kg/12 h for 9 days, 0.5 mg/kg/day for 3 days	Before 48 h of life	ND	12	ND	ND
Ng (26)	Intervention: 24 Control: 24	GA <32 weeks, BW <1,500 g, hypotension medically treated	Congenital or chromosomal abnormalities, postnatal systemic or inhaled corticosteroids treatment of severe lung disease before receiving the trial drug, proven systemic infection or NEC, or underwent major surgery	1 mg/kg per dose every 8 h for 5 days	Within the first 7 days of life	ND	5	ND	ND
Peltoniemi (27)	Intervention: 25 Control: 26	GA <30 and BW <1,250 g and the requirement for mechanical ventilation	Malformations or suspected chromosomal abnormalities	2.0 mg/kg for 2 days, 1.5 mg/kg for 2 days and 0.75 mg/kg for 6 days, started before 36 h of life	Before the age of 36 h	ND	10	ND	ND
Efird (28)	Intervention: 16 Control: 18	GA <29 weeks and BW <1,000 g	Malformations and chromosomal abnormalities	1 mg/kg every 12 h for 2 days, followed by 0.3 mg/kg every 12 h for 3 days	First days of life	ND	5	ND	ND
Watterberg (29)	Intervention: 179 Control: 178	BW <1,000 g and intubated	Congenital anomaly, congenital sepsis, postnatal glucocorticoid treatment other than hydrocortisone, triplet or higher-order multiple gestation	1 mg/kg/day divided twice daily for 12 days, followed by 0.5 mg/kg/day for 3 days	12 and 48 h of life	ND	15	ND	ND
Watterberg (30)	Intervention: 20 Control: 20	Appropriate for GA, BW <1,000 g and ventilated mechanically	Maternal diabetes, congenital sepsis, and SGA	1.0 mg/kg/day every 12 h, for 12 days: 9 days at 1.0 mg/kg/day, and a 3-day taper at a reduced dose of 0.5 mg/kg/day	Before 48 h of life	ND	12	ND	ND

ND, not declared; GA, gestational age; SGA, small of gestational age; BW, birth weight; PROM, premature rupture of membranes.

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TABLE 2 Randomized controlled trials comparing dexamethasone vs. placebo.

Reference (authors, year)	Population (*n*)	Inclusion criteria	Exclusion criteria	Doses of steroids	Start at	Extubation (days of life)	Duration of therapy by protocol (days)	More than one cycle of steroids	Administration of other steroids
Doyle (31)	Intervention: 29 Control: 26	GA <28 weeks or BW <1,000 g, ventilator dependent in the I week of life	Congenital defects, chromosomal anomalies	0.89 mg/kg over 10 days	After 7 days of life	ND	10	ND	ND
Doyle (32)	Intervention: 35 Control: 35	GA <28 weeks or BW <1,000 g, ventilator dependent in the I week of life	Congenital defects, chromosomal anomalies	0.89 mg/kg over 10 days	After 7 days of life	Intervention: 14 Control: 21	10	Treatment with second course intervention: 10 Control: 10	A small proportion of infants in each group had been exposed to short-course, low-dose corticosteroids before trial entry, for purposes of blood pressure control
Yeh (33)	Intervention: 72 Control: 74	BW <2,000g, severe radiographic respiratory distress syndrome requiring mechanical ventilation within in the first 6 h of life	Absence of prenatal infection, congenital anomalies, and lethal cardiopulmonary status	Two doses/day, days 1 through 7, 0.25 mg/kg/dose; days 8 through 14, 0.12 mg/kg/dose; days 15 through 21, 0.05 mg/kg/dose; and days 22 through 28, 0.02 mg/kg/dose	Within 12 h after birth	ND	28	ND	ND
Walther (34)	Intervention: 19 Control: 17	GA ≤32 weeks and RDS required mechanical ventilation	Sepsis or other infection, congenital heart disease, systemic hypertension, unstable clinical status, multiple congenital anomalies	At day 7–14. 14 days-treatment (0.2 mg/kg/day start, max 1.9 mg/kg cumulative)	7–14 after birth	ND	14	ND	ND
Romagnoli (35)	Intervention: 15 Control: 15	Oxygen and ventilator dependent on the 10th day of life and at high risk of chronic lung disease	No consent	0.5 mg/kg/day for the first 6 days, 0.25 mg/kg/day for the next 6 days, and 0.125 mg/kg/day for the last 2 days of treatment (total dose 4.75 mg/kg)	At 10 days of life	NE	14	ND	Five infants in each group received two doses of 0.5 mg/kg dexamethasone to facilitate weaning from mechanical ventilation after the first month of life
Romagnoli (36)	Intervention: 25 Control: 25	BW <1,250 g, GA <32 weeks, ventilator and oxygen-dependent at 72 h of life and at high risk of chronic lung disease	Prenatal infections, congenital malformations, and evidence of sepsis	From the 4th day of life for 7 days: 0.5 mg/kg/day for the first 3 days, 0.25 mg/kg/day for the next 3 days, and 0.125 mg/kg/day on day 7	At 4th days of life	ND	7	ND	ND
O'Shea (37)	Intervention: 50 Control: 45	BW <1,501 g, age between 15 and 25 days, <10% decrease in ventilator settings for previous 24 h and FiO2 >0.3, no signs of sepsis and echocardiogram indicating the absence of a patent ductus arteriosus	no consent	0.25 mg/kg twice a day for 3 days, then 0.15 mg/kg twice a day for 3 days, then a 10% reduction in the dose every 3 days until the dose of 0.1 mg/kg was reached on day 34. After 3 days on this dose, 0.1 mg/kg qod was given until 42 days after entry.	Between 15 and 25 days of life	NE	42	ND	ND

(*Continued*)

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TABLE 2 Continued

Reference (authors, year)	Population (*n*)	Inclusion criteria	Exclusion criteria	Doses of steroids	Start at	Extubation (days of life)	Duration of therapy by protocol (days)	More than one cycle of steroids	Administration of other steroids
Kothadia (38)	Intervention: 57 Control: 61	BW <1,501 g, age between 15 and 25 days, <10% decrease in ventilator settings for previous 24 h and FiO2 >0.3, no clinical signs of sepsis and echocardiogram indicating the absence of a patent ductus arteriosus	Congenital malformation, congenital viral infection, or mother with positive serologic testing for hepatitis B or HIV	0.25 mg/kg twice a day for 3 days, then 0.15 mg/kg twice a day for 3 days, then a 10% reduction in the dose every 3 days until the dose of 0.1 mg/kg was reached on day 34. After 3 days on this dose, 0.1 mg/kg qod was given until 42 days after entry	Between 15 and 25 days of life	NE	42	ND	ND
Lin (39)	Intervention: 20 Control: 20	BW <2,000g, radiography respiratory distress syndrome, ventilated at 6 h of life	Prenatal infection, congenital anomalies, and lethal cardiopulmonary status shortly after birth	Days 1–7: 0.25 mg/kg/dose; days 8–14: 0.12 mg/kg/dose; days 15–21: 0.05 mg/kg/dose; days 22–28: 0.02 mg/kg/dose	First days of life	NE	28	ND	ND
Yeh (40)	Intervention: 132 Control: 130	BW <2,000g, severe radiographic respiratory distress syndrome requiring mechanical ventilation within the first 6 h of life	Absence of prenatal infection, congenital anomalies, and lethal cardiopulmonary status	Two doses/day, days 1 through 7, 0.25 mg/kg/dose; days 8 through 14, 0.12 mg/kg/dose; days 15 through 21, 0.05 mg/kg/dose; and days 22 through 28, 0.02 mg/kg/dose	<12 h of life	ND	28	ND	Six infants in the dexamethasone group (8%) and seven in the control group (9%) who had severe BPD required glucocorticoid therapy after the completion of the initial study. Because of the relatively short duration of therapy, these were included in the analyses as members of their initially assigned groups
Suske (41)	Intervention: 14 Control: 12	GA <34 weeks with surfactant-treated respiratory distress syndrome	Septicaemia during the I week of life, relevant cardiac anomalies, except for patent ductus arteriosus, or malformations	0.5 mg/kg IV into two fractions, for 5 days, first doses <2 h after the first surfactant dose	<2 h of life	Intervention: 6 Control: 14	5	ND	ND
Brozanski (42)	Intervention: 39 Control: 39	BW 1,500 g, ventilator support at 7 days of postnatal age	Congenital anomalies, pulmonary hypoplasia, or hemodynamic instability	Beginning at 7 days of postnatal age pulse doses of 0.25 mg/kg/dose for 3 days, repeated every 10 days until the infant reached 36 weeks postmenstrual age, or the infant no longer required ventilator support or supplemental oxygen	After 7 days of life	ND	3 days, repeated every 10 days until the infant reached 36 weeks postmenstrual age, or the infant no longer required ventilator support or supplemental oxygen	ND	ND

(*Continued*)

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TABLE 2 Continued

Reference (authors, year)	Population (*n*)	Inclusion criteria	Exclusion criteria	Doses of steroids	Start at	Extubation (days of life)	Duration of therapy by protocol (days)	More than one cycle of steroids	Administration of other steroids
Durand (43)	Intervention: 23 Control: 20	BW of 501–1,500 g, GA 24–32 weeks, ventilator-dependent at 7–14 days of age despite weaning trials, ventilator rate more than 15 cydes/min, Fi02 requirement of 0.30 or more to maintain a pulse oximeter oxygen saturation of 90% or more	Documented sepsis, evidence of systemic hypertension, congenital heart disease, renal failure, grade IV intraventricular hemorrhage, and infants with multiple congenital anomalies	0.5 mg/kg/day in two divided doses for the first 3 days, 0.25 mg/kg/day for the next 3 days, and 0.1 mg/kg/day on the seventh day	7–14 days of life	ND	7	Six patients (26%) in the dexamethasone group required a second 7-day course of steroid therapy	After the study period, 13 patients in the control group were subsequently treated with dexamethasone at a later postnatal age if the clinical team felt the infant could benefit from dexamethasone therapy
Kari (44)	Intervention: 17 Control: 24	BW <1,500 g or less, GA >23 weeks, dependence on mechanical ventilation at 10 days of age, no signs of patent ductus arteriosus, sepsis, gastrointestinal bleeding, or major malformation at entry	No consent	0.5 mg/kg/day in two doses for 7 days	After 10 days of life	NE	7	ND	ND
Couser (45)	Intervention: 27 Control: 23	Required mechanical ventilation and had either traumatic or multiple intubations or if the duration of intubation was more than 14 days	Congenital anomalies, who either had previously been treated with dexamethasone for chronic lung disease or who had received pancuronium bromide therapy or other sedation 12 h before extubation	0.25 mg/kg per dose approximately 4 h before the scheduled extubation and then again, every 8 h for a total of three doses	More than 14 days of life	ND	ND	ND	ND
Cummings (46)	Intervention: 25 (42-days 13, 18-days 12) Control: 11	BW ≤1,250 g, GA ≤30 weeks, dependence on mechanical ventilation or oxygen at 2 weeks of life	Symptomatic patent ductus arteriosus, sepsis or renal failure at entry	42 days: 0.5 mg/kg/day for the first 3 days, 0.3 mg/kg/day for the next 3 days, then reduced by 10% every 3 days until a dose of 0.1 mg/kg was reached at day 34. After 3 days at this dose, the drug was given on alternate days for 1 week and discontinued 18 days: same initial dose of 0.5, but their dose then decreased more rapidly, dropping by 50% every 3 days until a dose of 0.06 mg/kg was reached at days 10. After 3 days of this dose, the drug was given on alternate days for 1 week and then discontinued. For the remaining 24 days saline placebo	After 2 weeks of life	ND	42 and 18	ND	ND

ND, not declared; GA, gestational age; BW, birth weight.

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TABLE 3 Randomized controlled trials comparing different doses of dexamethasone.

Reference (authors, year)	Population (*n*)	Inclusion criteria	Exclusion criteria	Doses of steroids (intervention)	Doses of steroids (control)	Start at	Extubation (days of life)	Duration of therapy by protocol (days)	More than one cycle of steroids	Administration of other steroids
Marr (47)	Intervention: 30 Control: 29	GA ≤28 weeks radiographic findings consistent with the diagnosis of evolving BPD and ventilator support	Preexisting conditions with known increased risk for neurodevelopmental impairment. Infants with sepsis or significant patent ductus arteriosus became study-eligible if treated before the end of the enrollment window	42-day group: 0.5 mg/kg/day for the first 3 days and 0.3 mg/kg/day for the next 3 days. The dose was reduced by 10% every 3 days until a dose of 0.1 mg/kg was reached on day 34. Thereafter, this dose was maintained for 3 days, alternated daily with a saline placebo for 1 week, and then discontinued	9-day group: dexamethasone: 0.5 mg/kg/day for the first 3 days, 0.25 mg/kg/day for the next 3 days, and then 0.125 mg/kg/day for 3 days, followed by saline placebo	10–21 days of life	Intervention: 23 Control: 35	Intervention: 42 Control: 9	66% in the 9-day group qualified for only 1 course of dexamethasone, 17% received 2 courses, and 17% received all 3 courses	Two infants in each group received hydrocortisone for the treatment of refractory hypotension prior to study enrollment. One infant in the 42-day group developed hypertension and required a single dexamethasone dose reduction
Odd (48)	Intervention: 16 Control: 17	BW ≤1,250 g, ventilated between 1 and 3 weeks of life	Anomalies and surgical problems	0.5 mg/kg/day for 3 days, 0.3 mg/kg/day for 3 days, then a dose decreasing by 10% every 3 days to 0.1 mg/kg/day over a further 30 days, then 0.1 mg/kg on alternate days for one further week	0.5 mg/kg/day for 3 days, 0.3 mg/kg/day for 3 days, 0.1 mg/kg/day for 3 days, then 0.1 mg/kg every 72 h until the infant was extubated and required a FiO2 <0.25 for three doses (9 days)	After 7 days of life	Intervention: 17 Control: 22	42	ND	ND
Malloy (49)	Intervention: 8 Control: 8	GA <34 weeks BW ≤1,500 g ventilator dependent	Congenital and chromosomal anomalies, necrotizing enterocolitis, or culture-proven sepsis, who had already received any corticosteroid treatment	0.5 mg/kg/day for 3 days followed by 0.3 mg/kg/day for 4 days, every 12 h	0.08 mg/kg/day for 7 days, every 12 h	<28 days of age	ND	Intervention: 16 Control: 13	ND	ND
McEvoy (50)	Intervention: 29 Control: 33	BW <1,500 g, GA <32 weeks, ventilator dependent at 7–21 days	Congenital anomalies, documented sepsis, systemic hypertension, renal failure, and grade IV intraventricular hemorrhage	0.5 mg/kg/day for 3 days, 0.25 mg/kg/day for 3 days, and 0.1 mg/kg/day on day 7 (total dose of 2.35 mg/kg). All daily doses administered every 12 h	0.2 mg/kg/day for 3 days and 0.1 mg/kg/day for 4 days (total dose of 1 mg/kg). All daily doses administered every 12 h	7–14 days of age	ND	7	ND	Three infants in the high dose and one in the low dose had one dose held: 2, secondary to bright red blood in the orogastric tube; 1, due to increased systolic blood pressure; 1, inadvertently not given
Durand (51)	Intervention: 23 Control: 24	BW <1,500 g, GA <32 weeks, ventilator dependent at 7–21 days	Documented sepsis, systemic hypertension, renal failure, grade IV intraventricular hemorrhage, and congenital anomalies or chromosomal abnormalities	0.5 mg/kg/day for 3 days, 0.25 mg/kg/day for 3 days, and 0.1 mg/kg/day on day 7 (total dose of 2.35 mg/kg). All daily doses administered every 12 h	0.2 mg/kg/day for 3 days and 0.1 mg/kg/day for 4 days (total dose of 1 mg/kg). All daily doses administered every 12 h	7–14 days of age	ND	7	ND	After the study period, 5 patients (22%) in the high dose and 7 (29%) in the low dose were treated with dexamethasone at a later postnatal age, at the discretion of the neonatologist

(*Continued*)

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TABLE 3 Continued

Reference (authors, year)	Population (*n*)	Inclusion criteria	Exclusion criteria	Doses of steroids (intervention)	Doses of steroids (control)	Start at	Extubation (days of life)	Duration of therapy by protocol (days)	More than one cycle of steroids	Administration of other steroids
Armstrong (52)	Intervention: 31 Control: 33	BW <1,250 g and ventilated at >15 cycles/minute at 7 days of life	Major congenital malformation or who were ventilated for surgical reasons	(Long group) 0.5 mg/kg/day for 3 days, reduced to 0.3 mg/kg/day for 3 days and thereafter reduced by 10% every 3 days to wean over 42 days	(Pulse group) 0.5 mg/kg/day for 3 days, repeated every 10 days until infants no longer required ventilatory support or supplemental oxygen or until 36 weeks of age	At 7 days of life	ND	ND	ND	Eleven babies received steroids outside the study protocol and were not randomized
Merz (53)	Intervention: 15 Control: 15	BW <1,250 g, GA <30 weeks, ventilator dependent at 7 days	Sepsis, congenital anomalies, suspected chromosomal abnormalities, or evidence of systemic hypertension	At 7 days of life (early treatment group). Starting dose of 0.5 mg/kg per day on the first 3 days followed by 0.3 mg/kg on days 4–6. From day 7 0.1 mg/kg, given alternatively every 2nd day from days 10 to 16	At 14 days of life same doses of the intervention group (late treatment group)	From day 7 or day 14 of life	Intervention: 14 Control: 24	10–16	ND	ND
Bloomfield (54)	Intervention: 21 Control: 19	BW <1,250 G and ventilated At >15 cycles/min at 7 days of life	Congenital malformation or who were ventilated for surgical reasons	(Long group) 0.5 Mg/Kg/Day for 3 days, reduced to 0.3 Mg/Kg/Day for 3 days and thereafter reduced by 10% every 3 days to wean over 42 days	(Pulse group) 0.5 Mg/Kg/Day for 3 days, repeated every 10 days until infants no longer required ventilatory support or supplemental oxygen or until 36 weeks of age	At 7 days of life	Intervention: 42 Control: 34	ND	ND	ND

ND, not declared; GA, gestational age; BW, birth weight; BPD, bronchopulmonary dysplasia.

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TABLE 4 Randomized controlled trials comparing hydrocortisone vs. placebo.

Reference (authors, year)	Extubation	Reintubation	BPD	Others respiratory outcome	Systemic hypertension	HG	Sepsis/ infection	PDA	IVH	NEC	ROP	Long-term NDV	Long-term growth
Halbmeijer (16)	+	NE	NE	+	−	−	NE	NE	NE	NE	NE	NE	NE
Watterberg (17)	+	NE	=	=	−	=	=	=	=	=	=	At 22–26 months =	At 22–26 months =
Onland (18)	+	NE	=	ND	=	−	+[a]	=	=	=	NE	NE	NE
Baud (19)	ND	NE	+[b]	=	ND	ND	−[b]	+[b]	=	=	ND	At 2 years: +[b]	NE
Baud (20)	+	NE	=	=	=	=	−[b]	+	=	=	=	NE	NE
Parikh (21)	NE	NE	=	NE	NE	NE	NE	NE	=[c]	NE	NE	18 months of corrected age =	18 months of corrected age =
Parikh (22)	=	NE	=	=	=	=	=	NE	=[c]	=	NE	NE	NE
Peltoniemi (23)	NE	NE	=	NE	NE	NE	NE	+	=	−[d]	=	At 2 years: =	At 2 years: =
Watterberg (24)	NE	NE	=	NE	NE	NE	NE	NE	=	=[d]	=	Adjusted age 20 months +	Adjusted age 20 months =
Bonsante (25)	NE	NE	=	+	=	=	=	=	=	=	=	NE	NE
Ng (26)	NE	NE	=	+	=	=	=	NE	=	=	=	NE	NE
Peltoniemi (27)	=	NE	=	+	=	=	=	+	=	−[d]	=	NE	NE
Efird (28)	NE	NE	=	=	=	=	=	=	=	=	=	NE	NE
Watterberg (29)	NE	NE	=	=	=	=	=	=	=	−[d]	=	NE	NE
Watterberg (30)	ND	ND	+	+	=	=	=	=	=	=	=	NE	NE

+, Better outcome for intervention group (steroids administration); −, worse outcome for intervention group (steroids administration); =, no differences between intervention and control groups; NE, not evaluated; ND, not declared; BPD, bronchopulmonary dysplasia; HG, hyperglycemia; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; NDV, neurodevelopment; GA, gestational age; BW, birth weight.

[a]Pneumonia.

[b]For those born at 24–25 weeks of gestational age.

[c]White matter injury.

[d]Gastrointestinal perforation.

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TABLE 5 Outcomes of randomized controlled trials comparing dexamethasone vs. placebo.

Reference (authors, year)	Extubation	Reintubation	BPD	Others respiratory outcome	Systemic hypertension	HG	Sepsis/ infection	PDA	IVH	NEC	ROP	Long-term NDV	Long-term growth
Doyle (31)	NE	NE	NE	=	NE	NE	NE	NE	NE	NE	NE	At 2 years =	At 2 years =
Doyle (32)	+	=	=	+	=	=	=	=	=	=	=	NE	NE
Yeh (33)	NE	NE	+	+	NE	NE	=	NE	=	NE	=	At 8 years −	At 8 years −
Walther (34)	+	ND	=	=	=	−	=	NE	=	=	NE	NE	NE
Romagnoli (35)	NE	NE	+	NE	NE	NE	=	=	=	=	NE	24 and 36 months of life =	24 and 36 months of life =
Romagnoli (36)	+	ND	+	+	=	−	=	=	=	=	=	NE	NE
O'Shea (37)	NE	NE	+	NE	NE	NE	NE	NE	−[a]	NE	NE	At 1 year −[b]	At 1 years =
Kothadia (38)	ND	ND	+	+	=	=	=	NE	−[a]	=	=	NE	NE
Lin, 1999 (39)	=	ND	+	+	−	−	=	NE	=	NE	NE	NE	NE
Yeh (40)	+	ND	+	+	−	−	−	+	=	=	=	NE	NE
Suske (41)	+	ND	+	+	=	=	=	=	=	=	+	NE	NE
Brozanski (42)	ND	ND	+	+	NE	=	=	=	+	=	=	NE	NE
Durand (43)	+	ND	+	+	=	=	=	=	=	=	=	NE	NE
Kari (44)	ND	ND	NE	+	−	=	=	=	=	=	NE	NE	NE
Couser (45)	ND	+	ND	+	=	=	NE	NE	NE	NE	NE	NE	NE
Cummings (46)	+	=	NE	+	=	=	=	NE	NE	NE	=	6 And 15 Months +	6 And 15 Months =

[a]Abnormal cranial ultrasound.

[b]Cerebral palsy.

+, Better outcome for intervention group (steroids administration); −, worse outcome for intervention group (steroids administration); =, no differences between intervention and control groups; NE, not evaluated; ND, not declared; BPD, bronchopulmonary dysplasia; HG, hyperglycemia; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; NDV, neurodevelopment; GA, gestational age; BW, birth weight.

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TABLE 6 Randomized controlled trials comparing different doses of dexamethasone.

Reference (authors, year)	Extubation	Reintubation	BPD	Others respiratory outcome	Systemic hypertension	HG	Sepsis/ infection	PDA	IVH	NEC	ROP	Long-term NDV	Long-term growth
Marr (47)	+	+	=	=	=	=	=	ND	=	=	=	7 years +	7 years: =
Odd (48)	=	ND	NE	=	=	=	=	NE	=	NE	NE	9 and 18 months of postnatal age =	NE
Malloy (49)	=	ND	=	=	–	=	NE	NE	=	=	=	At 1 years –	NE
McEvoy (50)	NE	NE	=	+	=	=	=	NE	=	=	=	At 1 years =	NE
Durand (51)	NE	NE	=	+	=	=	=	NE	=	=	=	NE	NE
Armstrong (52)	ND	ND	+	=	=	NE	NE	NE	=	NE	NE	18 months of =	18 months of =
Merz (53)	+	ND	=	+	=	=	=	NE	NE	=	=	NE	NE
Bloomfield (54)	NE	NE	+	+	=	=	=	NE	NE	=	=	NE	NE

+, Better outcome for intervention group (steroids administration); –, Worse outcome for intervention group (steroids administration); =, no differences between intervention and control groups; NE, not evaluated; ND, not declared; BPD, bronchopulmonary dysplasia; HG, hyperglycemia; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; NDV, neurodevelopment; GA, gestational age; BW, birth weight.

Primary outcome: long-term NDV effects and growth

A graphical representation of the percentage of the studies evaluating the outcomes of interest for this study is shown in Figure 2 (16–54).

Of the 38 RCTs, 15 performed a follow-up program considering NDV, growth, or both (17, 19, 21, 23, 24, 31, 33, 35, 37, 46–50, 52).

Eight studies did not find statistically significant long-term neurological differences (17, 21, 23, 31, 35, 48, 50, 52). Malloy et al. (49) found an increased risk of NDV delay, and O'Shea et al. (37) showed an increased risk of cerebral palsy at 1 year in the groups receiving dexamethasone (different doses vs. placebo, respectively). A long-term follow-up study performed by Yeh et al. (33) showed worse effects on neuromotor and cognitive function at school age in newborns who received dexamethasone compared to the placebo group. Watterberg et al. (24) (hydrocortisone vs. placebo), Cummings et al. (46) (dexamethasone vs. placebo), and Marr et al. (47) (different doses of dexamethasone) found an improved long-term NDV. Baud et al. (19) found better NDV outcomes at 2 years in newborns who received hydrocortisone if they were born at 24–25 weeks of GA, while no statistical difference considering those born at 26–27 weeks of GA. All the RCTs that considered growth parameters did not find differences between the two groups (17, 23, 24, 31, 35, 37, 46, 47, 52). Only Yeh et al. (33) found that newborns who received dexamethasone were significantly shorter than the controls and had a significantly smaller head circumference, evaluated at school age. However, the long-term NDV and growth outcomes evaluated in these 15 RCTs were measured at different time points (Tables 4–6).

To better characterize the effects of corticosteroids on long-term neurological outcomes, we performed also a sub-analysis separating the studies for early (before 7 days of life) and late (after 7 days of life) administration. The graphical representation of this sub-analysis is reported in Supplementary Figure S1. We excluded the studies of Baud et al. (19, 20) for this analysis, because the starting age of the intervention was before 10 days of life, and based on the definition of early and late administration of corticosteroids considered, we were not able to add these studies in the analysis.

Secondary outcome: respiratory outcome, metabolic effects, and morbidity during hospital stay

Despite most of the studies not finding differences for all the outcomes evaluated for both hydrocortisone and dexamethasone, systemic hypertension and HG appear to be the most frequent side effects, especially for dexamethasone compared with hydrocortisone (Figure 2). Both have an important effect on respiratory outcome and time to extubation (Figure 2). The reintubation rate has been rarely evaluated (Figure 2).

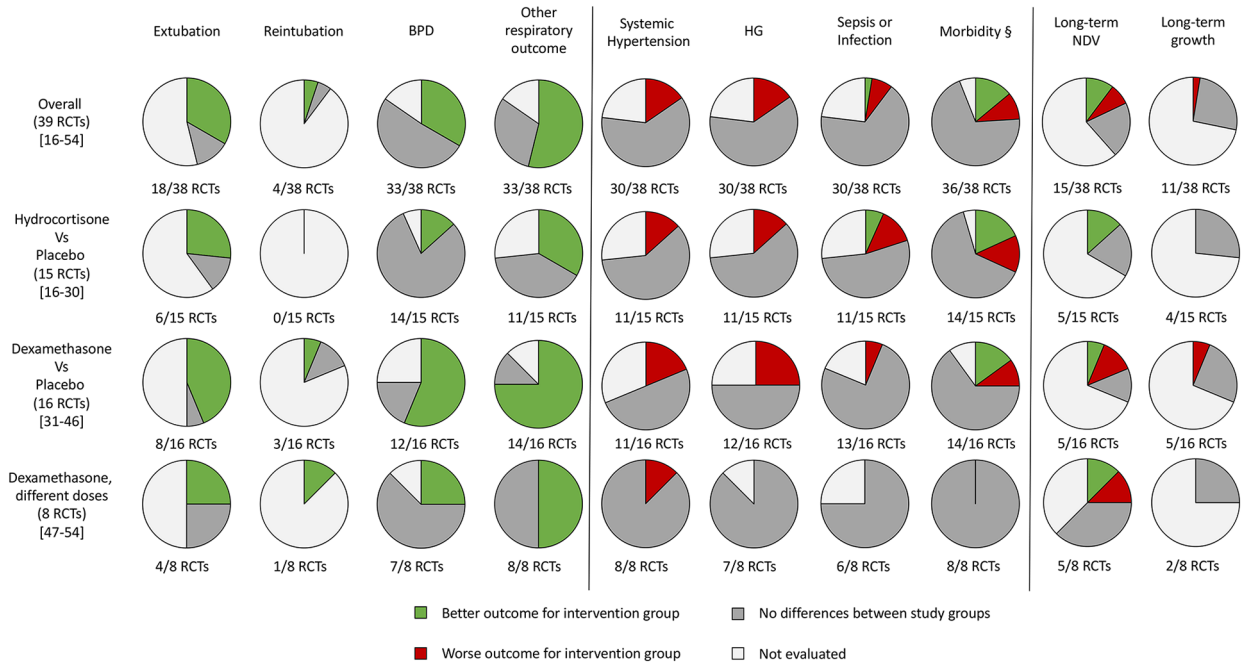

FIGURE 2
Graphical representation of the randomized controlled trials that evaluated the outcomes of the systematic review. RCTs, randomized controlled trials; BPD, bronchopulmonary dysplasia; HG, hyperglycemia; NDV, neurodevelopment; §, at least one between patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis (or gastrointestinal perforation) and retinopathy of prematurity.

We found that 18 studies evaluated the early extubation rate (16–18, 20, 22, 27, 32, 34, 36, 39–41, 43, 46–49, 53). Five of 18 RCTs found no differences between intervention and control groups (2 hydrocortisone vs. placebo, 1 dexamethasone vs. placebo, and 2 with different doses of dexamethasone) (22, 27, 39, 48, 49), while 13 found an early time of extubation in newborns who received system corticosteroids (4 hydrocortisone vs. placebo, 7 dexamethasone vs. placebo, and 2 with different doses of dexamethasone) (16–18, 20, 32, 34, 36, 40, 41, 43, 46, 47, 53). A total of 21RCTs did not evaluate this outcome or declare the rate of extubation in relation to the administration of systemic corticosteroids (19, 21, 23–26, 28–31, 35, 37, 38, 42, 44, 45, 50–52, 54). Only four studies declared the rate of reintubation, specifically two RCTs found a better reintubation rate for newborns treated with systemic corticosteroids (one dexamethasone vs. placebo and one with different doses of dexamethasone) (45, 47), and two studies found no differences for newborns treated with dexamethasone (32, 36). A total of 33 studies evaluated the rate of BPD (17–30, 32–43, 47, 49–54). Thirteen of 33 found a better outcome (2 hydrocortisone vs. placebo, 9 dexamethasone vs. placebo, and 2 with different doses of dexamethasone) (19, 30, 35–40, 42, 43, 52, 54), while 20 studies did not find differences (17, 18, 20–29, 32, 34, 41, 47, 49–51, 53). Baud et al. found a better outcome for babies born at 24–25 weeks of GA whereas no differences for those born at 26–27 weeks of GA (19, 20). No studies found an increased rate of BPD between the groups. Thirty-three of 39 studies evaluated the pulmonary function (16, 17, 19, 20, 22, 25–34, 36, 38–54). In addition, 21 of 33 RCTs found an improved respiratory outcome for intervention groups (5 hydrocortisone vs. placebo, 12 dexamethasone vs. placebo, and 4 with different doses of dexamethasone) (16, 25–27, 30, 32, 33, 36, 38–46, 50, 51, 53, 54). Twelve did not find a difference (17, 19, 20, 22, 28, 29, 31, 34, 47–49, 52), whereas six did not evaluate this outcome (18, 21, 23, 24, 35, 37).

Systemic hypertension was evaluated in 30/39 studies (16–18, 20, 21, 25–30, 32, 34, 36, 38–41, 43–54). Six of 30 found an increased rate of systemic hypertension in the intervention group (2 hydrocortisone vs. placebo, 3 dexamethasone vs. placebo, and 1 with different doses of dexamethasone) (16, 17, 39, 40, 44, 49). Nine did not evaluate this outcome (19, 21, 23, 24, 31, 33, 35, 37, 42), while the rest of the 24 RCTs found no differences between the study groups (9 hydrocortisone vs. placebo, 8 dexamethasone vs. placebo and 7 with different doses of dexamethasone) (18, 20, 22, 25–30, 32, 34, 36, 38, 41, 43, 45–48, 50–54). As with systemic hypertension, a quasi-totality of the study (30/39) evaluated the outcome HG (16–18, 20, 22, 25–30, 32, 34, 36, 38–51, 53, 54). Six of 30 found an increased rate of HG in intervention groups (2 hydrocortisone vs. placebo and 4 dexamethasone vs. placebo) (16, 18, 34, 35, 39, 40) compared with control, while 24 did not find differences (17, 20, 22, 25–30, 32, 38, 41–51, 53, 54). Brozanski et al. (42) found no differences in the rate of HG, but newborns in the intervention group (dexamethasone vs. placebo) received more statistically significant insulin therapy. Ng et al. (26) and Couser et al. (45) found an increased incidence of glycosuria in the intervention group (hydrocortisone vs. placebo and dexamethasone vs. placebo, respectively), despite no difference in HG rate. Thirty

studies considered the risk of sepsis or other infections (17–20, 22, 25–30, 32–36, 38–44, 46–48, 50, 51, 53, 54). Despite the almost total of the study (26/30) did not find differences (17, 22, 25–30, 32–36, 38, 39, 41–44, 46–48, 50, 51, 53, 54), the two RCTs of Baud et al. found a statistically increased risk for babies that received hydrocortisone, born at 24–25 weeks of GA (19, 20). Onland et al. found a statistically reduced incidence of pneumonia for the group of babies that received hydrocortisone (18). Only one study that compared dexamethasone vs. placebo, found an increased risk for the intervention group (40). For the outcome PDA, we considered the incidence and the treatment (medical or surgery ligation) as PDA. Eighteen RCTs considered this outcome (17–20, 23, 25, 27–30, 32, 35, 36, 40–44). Five/18 found a better outcome for treated newborns (4 hydrocortisone vs. placebo and 1 dexamethasone vs. placebo) (19, 20, 23, 27, 40). Specifically, Baud et al. found a better outcome for babies born at 24–25 weeks of GA, treated with hydrocortisone (19, 20). Thirteen RCTs did not find differences between treated and not treated newborns (17, 18, 25, 28–30, 32, 35, 36, 41–44), whereas no studies found a worse outcome. None of the studies that compared different doses of dexamethasone evaluated this outcome. IVH was considered in 33 of the 39 studies (17–30, 32, 34–44, 47–52). Only O'Shea et al. (37) and Kothadia et al. (38) demonstrated an increased risk of abnormal cranial ultrasound for neonates that received corticosteroids, whereas Brozanski et al. (42) showed a reduced risk of IVH in intervention groups. All three studies compared dexamethasone vs. placebo (37, 38, 42). The rest of the 29 studies found no statistical differences for IVH or white matter injury (17–26, 28–30, 32, 34–36, 39–41, 43, 44, 47–52). Of the 29 studies that evaluated NEC, the studies of Watterberg et al. and Peltoniemi et al. found an increased risk of gastrointestinal perforation in neonates that received corticosteroids (specifically hydrocortisone) (23, 27, 29). The other 26 RCTs did not find statistically significant differences between the two groups for NEC or gastrointestinal perforation (17–20, 22, 24–26, 28, 30, 32, 34–36, 38, 40–44, 47, 49–51, 53, 54). The risk of ROP was evaluated by 25/39 RCTs (17, 20, 23–30, 32, 33, 36, 38, 40–43, 46, 47, 49–51, 53, 54). Twenty-four did not find any statistical differences between the two trial groups (17, 20, 23–30, 32, 33, 36, 38, 40, 42, 43, 46, 47, 49–51, 53, 54), but only Suske et al. (41) demonstrated a reduced risk of ROP for newborns of the intervention groups, who were administered dexamethasone.

Risk of bias

The quality of the studies was assessed by risks of bias, as shown in Figure 3. We judged the risk of selection bias as low in all uncontrolled studies, unclear for 14, and high for 2 RCTs. Performance bias and detection bias were high for four and three studies, respectively, and unclear for one and five, respectively. The rest of the 34 and 31 RCTs were judged as low risk of performance and detection bias, respectively. Attrition bias was judged as low for 29 studies, high for 2, and unclear for 8 RCTs. Considering our outcome, reporting bias was judged high for 8, low for 29, and unclear for the remaining 2 RCTs. Other sources of bias were not evaluable for 6 controlled trials, while was high for 23 studies and low only for 10.

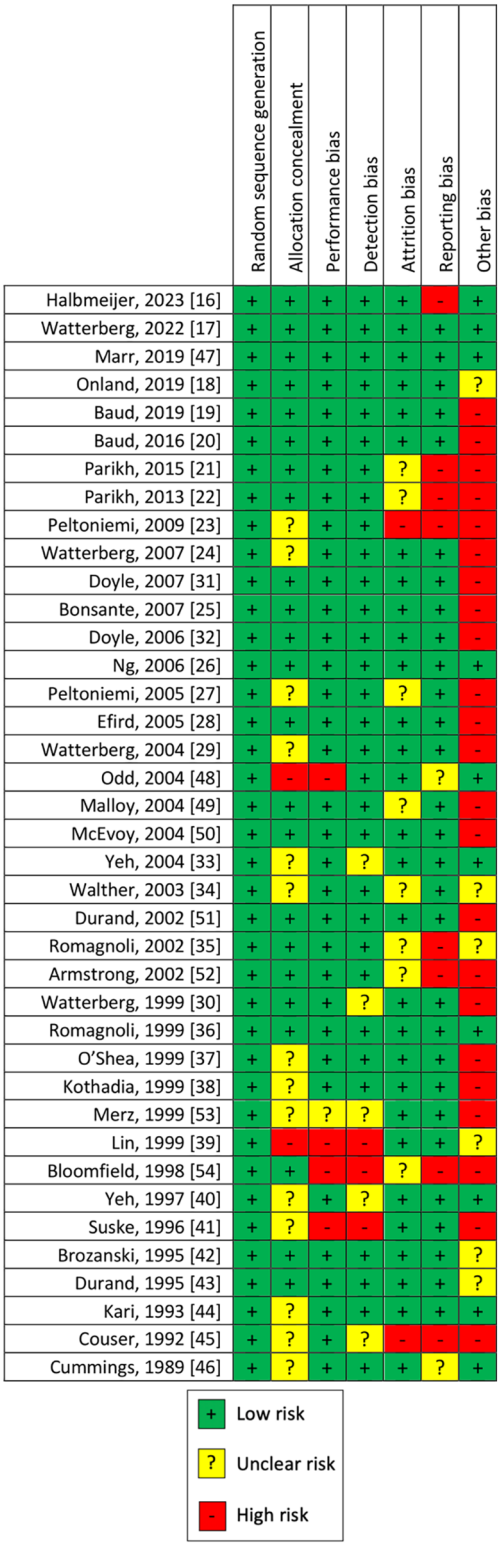

FIGURE 3
Risk of bias of the evaluated randomized controlled trials.

Discussion

Despite many studies exploring the effects of corticosteroid administration in postnatal life for preterm newborns, the optimal modality of administration remains to be defined. The high heterogeneity of the included RCTs regarding dosages, timing of administration, and outcome measures, discourages the mathematical analysis of the data (55). A recent meta-analysis and network meta-analysis included only one study for a therapeutic regiment or more than one study but with different timing of administration and were focused primarily on BPD (11). In this systematic review, we evaluated the efficacy of steroid therapy on other respiratory outcomes, including extubation rate, reintubation, BPD, and related side effects, considering separately hydrocortisone, dexamethasone, and different doses of dexamethasone. Despite the analyzed studies suggesting an overall favorable effect of steroids on respiratory outcomes, a well-designed large RCT is urgently needed to establish the optimal indication and modalities of administration. Among the steroids used for preterm newborns, early and high doses of dexamethasone have a better impact on the respiratory outcome, while hydrocortisone is related to fewer side effects such as systematic hypertension or HG.

Long-term NDV effects and growth

A major limitation in the analysis of the studies including the use of steroids in the neonatal period is represented by the lack of data for long-term outcomes. Only a few studies evaluated neurological and growth outcomes of preterm newborns receiving steroids in early life (17, 19, 21, 23, 24, 31, 35, 37, 46–50, 52). Only one-third of the trials on hydrocortisone evaluated the long-term effects on NDV up to 2 years of life (17, 19, 21, 23, 24). In these studies, neurological outcomes seem to be not influenced by the use of hydrocortisone. Two RCTs found an improvement in neurological outcomes, particularly in ELGAN and newborns with extremely low birth weight (19, 24). Almost half of studies on dexamethasone evaluated neurological outcomes up to 1–2 years of life (31, 35, 37, 46–50, 52). The results of these studies are controversial. If the majority of the RCTs demonstrated that there is no influence of dexamethasone on long-term NDV (31, 35, 48, 50, 52), O'Shea et al. (37) reported an increased rate of cerebral palsy at 1 year for newborns treated with dexamethasone (42 days of therapy, starting doses at 0.25 mg/kg twice a day for 3 days) compared with placebo. Malloy et al. (49) found a worse NDV long-term outcome for newborns in the high doses of dexamethasone groups (0.5 mg/kg/day for 3 days followed by 0.3 mg/kg/day for 4 days every 12 h vs. 0.08 mg/kg/day for 7 days every 12 h). In addition, Yeh et al. (33) showed that children treated with two doses per day of dexamethasone for 28 days (0.25 mg/kg/dose up to 7 days and then the dose was tapered) had significantly poorer motor skills, motor coordination, visual–motor integration, and significantly lower full IQ, verbal IQ, and performance IQ scores. The frequency of clinically significant disabilities was significantly higher among children in the dexamethasone group compared with controls (39% vs. 22%, p value 0.04) (33). However, O'Shea et al. did not power the study for long-term NDV and selection bias because differential survival rates across the two study groups could explain the greater risk of cerebral palsy among the intervention group; Malloy et al. performed a trial with a very low sample size (8 vs. 8). On the other hand, Cummings et al. and Marr et al. found a better long-term neurological outcome for babies treated with dexamethasone (42 days of therapy, starting dose at 0.5 mg/kg/day for the first 3 days, 0.3 mg/kg/day for the next 3 days, and then reduced by 10% every 3 days until a dose of 0.1 mg/kg was reached at day 34) (46, 47). They enrolled newborns born ≤30 weeks of GA (and ≤1,250 g) and ≤27 weeks of GA, respectively. Thus, it could be possible that ELGAN should benefit more than other newborns from steroid treatment. In addition, Marr et al. performed a study with a long time follow-up evaluation of 7 years. Most of the studies did not consider long-term growth as an outcome. The available studies suggest a low impact of early steroid treatment and long-term growth (17, 23, 24, 31, 35, 37, 46, 47, 52). Only Yeh et al. demonstrated that dexamethasone could negatively influence height and head circumference, evaluated at school age (33).

Respiratory outcome, metabolic effects, and morbidity during hospital stay

Postnatal steroid treatment is beneficial for respiratory outcomes, such as extubation, reduced risk of BPD or duration of invasive or non-invasive MV, supplemental oxygen therapy, FiO2, and/or other specific ventilatory/respiratory data. Dexamethasone has a better impact compared to hydrocortisone, but the optimal therapeutic regiment remains to be defined. For the reintubation rate outcome, a conclusion cannot be made, since it has been evaluated only in a few, unpowered studies (32, 45–47). In addition, in all these studies, dexamethasone was used as an intervention, while none of them considered hydrocortisone.

Our analysis showed that BPD is the most studied respiratory outcome. The majority of the studies demonstrated that dexamethasone had a positive effect on the BPD rate, whereas hydrocortisone appears to not improve this outcome. The study with a lower risk of bias showed that the therapeutic regiment of dexamethasone in early life (0.5 mg/kg/day for the first 3 days, 0.25 mg/kg/day for the next 3 days, and 0.125 mg/kg/day on the day 7) had the best impact on BPD (36).

Steroids work as anti-inflammatory agents, which can explain their rationale in the prevention of BPD. One of the main risk factors for developing BPD is prolonged oxygen exposure and MV, which induce a pulmonary local inflammatory response (4, 5). Postnatal corticosteroids decrease inflammation and edema, improving gas exchange and lung protective mechanisms (56, 57).

To the best of our knowledge, there are no RCTs that evaluated the long-term pulmonary outcome of preterm newborns treated

with corticosteroids in neonatal life. On the other hand, studies aimed at investigating long-term respiratory function in preterm babies were mainly focused on BPD and did not independently evaluate the role of postnatal steroid treatment on the final outcome (58).

Not all studies evaluated side effects associated with the use of steroids in preterm newborns.

Despite the majority of the RCTs found no difference between the study groups (17, 18, 20, 22, 25–30, 32, 34, 36, 38, 41–54), some studies suggested an increased risk of systemic hypertension and/or HG.

Systemic hypertension was analyzed in the majority of the studies included in this systematic review. Few studies (~16%) reported an increased risk of hypertension in newborns treated with steroids. The administration of dexamethasone has been associated with systemic hypertension more frequently compared to hydrocortisone. Treatment regimens of more than 0.25 mg/kg of dexamethasone, especially for more than 10 days, appear to increase the risk of systemic hypertension.

HG is an independent risk factor for mortality and NDV delay in newborns (59, 60); thus, all efforts should be made to reduce the risk of this condition. A higher number of studies on dexamethasone reported an increased risk of HG compared with studies on hydrocortisone. However, all the studies that compared two different doses or timing for dexamethasone administration found no difference for HG (47–54). When steroid treatment is needed, neonatologists should minimize the other conditions that induce an increased risk of HG (such as nutrition) (60, 61), or they should improve continuous glucose monitoring to maintain euglycemia (62).

Sepsis remains the major cause of morbidity and mortality in preterm newborns (63). Our analysis showed a relevant increased risk of sepsis in newborns treated with steroids, more for hydrocortisone compared with dexamethasone. However, a recent study demonstrated a reduced risk of pneumonia (18) in newborns treated with hydrocortisone, probably due to an improvement in respiratory outcome and a reduced time of invasive ventilation support.

Data regarding the relationship between steroid administration and morbidity conditions are controversial. Most studies suggested no relation (about 69%), while others demonstrated an increased rate of prematurity-related morbidities (about 14%); finally, about 10% suggested a better outcome. We speculated that this result depends on the different modalities of administration of corticosteroids, different therapeutic regiments, and different morbidity definitions of the studies. Based on our findings, more than 42 days of dexamethasone therapy, more than 1 mg/kg starting dose, or more than 10 days of hydrocortisone therapy might increase the risk of morbidity.

We speculate that part of the reduction in morbidity might be related to the improvement in PDA closure, associated with steroid use. Some studies demonstrated that steroids (especially hydrocortisone) could improve the PDA outcome, reducing the need for medical or surgical treatment (19, 20, 23, 27, 40). Several reasons may explain this effect: (1) *in vitro* studies demonstrated that hydrocortisone treatment decreases the sensitivity of the ductus arteriosus to the relaxing action of prostaglandin E2, which explains the beneficial effects *in vivo* of steroids (64, 65), and (2) the relationship between PDA and BPD, especially for ELGAN, has been demonstrated (66). Despite this topic is not well evaluated, it could be possible that the effects of steroid administration on PDA also improve BPD. However, future studies should evaluate this aspect.

Brozanski et al. (42) found a reduced risk of IVH for preterm receiving steroids. The authors administered a pulse dose of 0.25 mg/kg/dose of dexamethasone to newborns at 7 days of life for 3 days, repeated every 10 days until 36 weeks of postmenstrual age or up to weaning of ventilation/oxygen support. In addition, they affirmed that the decreased rate of IVH in the intervention (pulse) group could be associated with a better stabilization of capillary membranes or alteration of cerebral blood flow by corticosteroids or by an improvement in the ventilatory status of the infants (42). However, two RCTs underline the effects of steroids on early brain damage (37, 38). They administered 0.25 mg/kg twice a day for 3 days, 0.15 mg/kg twice a day for other 3 days, and then a 10% reduction in the dose every 3 days until the dose of 0.1 mg/kg was reached on day 34 and after 3 days on this dose. However, all three studies are not powered for this outcome. Thus, considering the different therapeutic regiments and this limitation, further studies are needed to clarify this aspect.

Concerns remain regarding the risk of spontaneous gastrointestinal perforations in newborns treated with hydrocortisone (23, 27, 29). In particular, Peltomieni et al. (23, 27) administered hydrocortisone 2.0 mg/kg for 2 days, 1.5 mg/kg for 2 days, and 0.75 mg/kg for 6 days, started before 36 h of life (duration therapy 10 days), and Wetterberg et al. (29) 1 mg/kg/day divided twice daily for 12 days starting at randomization (12–48 h of life), followed by 0.5 mg/kg/day for 3 days (duration therapy 15 days). In both studies, The authors stopped the studies because of the higher rate of spontaneous gastrointestinal perforation, limiting the power of the studies (23, 27, 29). Studies with similar treatment did not find differences. In addition, the majority of the analyzed RCTs did not find differences in terms of NEC or spontaneous gastrointestinal perforations between treated and placebo groups (17–20, 22, 24–26, 28, 30, 32, 34–36, 38, 40–44, 47, 49–51, 53, 54).

Risk of bias

Given that some studies with concerns about the overall risk of bias have been included, our results need to be confirmed by further RCTs with a low risk of bias. Blinding bias was low for most of the studies analyzed. Attrition and reporting bias were judged low for most of the studies reviewed. Major concerns are about the risk of other bias (early interruption of the trial due to data-dependent process or bias related to the specific study design), which was judged high for 23 of 38 studies. In addition, the studies presented a high heterogeneity of inclusion criteria (e.g., GA and/or BW) and intervention (different doses, timing of administration, and duration therapy), which could have

influenced the results. We included only RCTs, despite some of these enrolling a small number of patients with low power of the study. Some of the studies included adopted a non-optimal blinding method or were unclear.

Strengths and limitations

Our results should be interpreted considering the limitations of the studies analyzed and of the review process. First, we decided not to perform a meta-analysis because of the extreme variability in methodology, modality of administration of steroids, and outcome of the studies (55). We systematically collected evidence and after a deep evaluation and discussion between the authors, we decided not to make a meta-analysis considering the wide differences in methodology used in different studies included in this manuscript. In particular, the studies vary regarding inclusion and exclusion criteria, enrollment, dose of treatment, starting days and duration of steroids, type of steroids administered, timing of follow-up, and assessment scales (Tables 1–3). The data deriving from current evidence, including meta-analyses, are inconclusive on the long-term effects either to exclude completely that there may be consequences on the central nervous system. Thus, we believe that steroids should be used in trial settings and to collect data in large databases to verify the consequences of this therapy.

We believe that there are no minimal criteria to perform a meta-analysis and that conclusions deriving from published meta-analyses were not supported by robust statistical data. Our data might contribute to better define the modality of steroid therapy and the target population to reduce the risk of brain damage. Whether meta-analyses suggested deleterious effects of steroids on NDV, our study demonstrated that further well-designed studies are needed to reach conclusions regarding the relationship between steroid treatment in preterm newborns and long-term NDV.

We synthesized the results of different studies on NDV. However, the long-term outcomes were not analyzed at the same time point and with different NDV assessment scales. We selected articles published in the English language; thus, it is possible that some gray literature has not been analyzed. In addition, studies showing positive results have a greater likelihood of being published. Finally, in some studies, other medications were administered, based on the clinical conditions of patients, in some studies treatment was interrupted prematurely, and others were not powered for the long-term outcomes.

Conclusion

Postnatal administration of systemic corticosteroids is an important tool for neonatologists to improve respiratory outcomes. Based on published RCTs, dexamethasone appears to be more effective than hydrocortisone for extubation, prevention of BPD, and improvement of respiratory outcomes. However, considering the deleterious effects such as HG, caution should be made during administration of dexamethasone. In addition, long-term effects on NDV and growth remain undefined. Considering that data deriving from current evidence, including meta-analyses, are inconclusive on the long-term effects to exclude completely that there may be consequences on the central nervous system, further studies are advocated to define the optimal therapeutic regiment, to improve the positive effects and reduce the side effects of steroid administration in preterm newborns.

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.

Author contributions

GB: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, writing – review and editing. VC: writing – review & editing. MGC: validation, writing – review & editing. FL: data curation, investigation, writing – review and editing. PR: writing – review and editing. PP: writing – review and editing. GT: conceptualization, data curation, formal analysis, methodology, project administration, software, supervision, validation, visualization, writing – original draft, writing – review and 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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Publisher's note

Supplementary material

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SUPPLEMENTARY FIGURE S1
Graphical representation of the randomized controlled trials that evaluated neurological outcomes in relation to early (before 7 days of life) or late (after 7 days of life) administration of steroids. RCTs, randomized controlled trials; *the studies of Baud et al. were excluded (19, 20).

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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
An Eerdekens,
University Hospitals Leuven, Belgium
Enrique Gomez-Pomar,
University of Kentucky, United States

*CORRESPONDENCE
Carla Madeleine Cuya
ccuya@ucsm.edu.pe

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Multisensory stimulation and its effect on breast milk volume production in mothers of premature infants

Carla Madeleine Cuya[1]*, Carlos Barriga[2], Maria del Carmen Graf[3], Mirta Cardeña[1], María del Pilar Borja[1], Richard Condori[4], Moises Azocar[5] and Carlos Cuya[4]

[1]Nursing Faculty, Universidad Católica de Santa María, Arequipa, Peru, [2]Social Sciences and Technologies and Humanities Faculty, Universidad Católica de Santa María, Arequipa, Peru, [3]Nursing, University of Wisconsin Oshkosh, Oshkosh, WI, United States, [4]Medicine Faculty, Universidad Católica de Santa María, Arequipa, Peru, [5]Manuel de Torres Muñoz Hospital (EsSalud), Arequipa, Peru

Introduction: In a significant number of NICUs, mothers are unable to provide enough maternal milk to feed their premature babies, so healthcare workers rely on human milk banks. Unfortunately, this service is not available in many countries, such as Peru, where premature infants receive formula. The aim of this study was to determine the effectiveness of multisensory stimulation on mother's own milk production.
Methods: Participants in this study were postpartum mothers of preterm infants 27–37 weeks gestational age. The participants were assigned to three groups: (1) audiovisual stimulation (SAV) ($n = 17$), (2) audiovisual and olfactory stimulation (SAVO) ($n = 17$), and (3) control ($n = 16$). A questionnaire was used to collect demographic and obstetric data, including a record of mother's own milk volume.
Results: There was no significant difference between the SAV, SAVO and control groups regarding age, marital status, education level, occupation, number of children, mode of delivery, Apgar and birth weight. On the other hand, a significant difference was observed between the SAV and SAVO groups regarding the amount of milk produced, with higher production between the fourth and seventh day (Tukey $p < 0.05$). Similarly, milk volume was significantly greater in the SAVO group compared to the SAV and control groups (OR = 1.032, 95% CI = 1.0036–1.062, $p < 0.027$).
Conclusion: Multisensory stimulation in postpartum mothers of preterm infants caused an increase in the volume of mother's own milk production. However, more research is needed to explain the findings presented in this study.

KEYWORDS

breastfeeding, premature birth, emotions, sensory system, limbic systems

1 Introduction

Mother's own milk is undoubtedly the ideal and first food to promote the healthy growth and development of newborns, constituting a fundamental pillar at the beginning of their lives (1). It is rich in essential nutrients such as proteins, fats, carbohydrates, vitamins and minerals that promote the mental and physical development of premature infants (2). Therefore, the implementation of policies that actively encourage and promote mother's own milk feeding in this context becomes an unavoidable priority for health institutions (3, 4). Although preterm infants face developmental challenges due to their

physiological immaturity, making them susceptible to various health conditions (5), mother's own milk acts as a protective factor due to its abundant immunoglobulins and other bioactive components (6).

One of the most common conditions faced by premature infants is necrotizing enterocolitis (2), an inflammation of the colon that occurs in response to the premature development of the digestive system. Necrotizing enterocolitis can have serious and, in some cases, life-threatening consequences, underscoring the importance of ensuring adequate nutrition from the first moments of life. Despite this, several neonatal intensive care units (NICUs) face a critical challenge: access and availability of mother's own milk (7).

Furthermore, the lack of availability of mother's own milk, in neonatal intensive care units, due to the fact that mothers often do not produce enough maternal milk (8), could be considered as a public health problem. Therefore, the unavailability of mother's own milk for immediate feeding of preterm infants, a common situation in many neonatal intensive care units (NICUs), leads health care providers to rely on donor human milk (2, 8, 9). In this case, the limited number of human milk banks aggravates the problem of neonatal care, as these centers could provide an alternative for feeding premature infants (10). Due to the difficulties in the implementation and operation of this type of basic health service, which could be attributed to the lack of an adequate government management and legal regulation in countries such as Peru (11–13). However, in the absence of a human milk bank, health care institutions feel the need to administer infant formula, which several studies have shown to be detrimental to infant growth and development (14–16). In the study by Moreira et al. (2) it was stated that the main complications of the use of formula in premature neonates in the NICU was the presence of necrotizing enterocolitis, which can be explained from the intestinal microbiota, where babies fed with mother's ow milk have a lower amount of enterobacteria than babies who receive formula or donor human milk. It also showed that babies fed with formula presented other complications, such as sepsis and bronchopulmonary dysplasia, unlike babies who received donor human milk or mother's own milk. This is because mother's own milk has metabolic advantages over formula, resulting in better protein absorption and more significant tissue growth in the newborn (17).

Another difference that has been observed between mother's own milk vs. formula, is the fat mass index, which is lower in newborns who are mother's own milk-fed than in those who are fed formula (17). Thus, mother's own milk should be the feeding source of choice for preterm infants.

In this context, the insufficient amount of milk produced by the mothers of preterm infants is one of the main reasons for the lack of mother's own milk in the NICU (8), a problem that may be due to multiple causes (12, 18). This condition can be explained by failed or delayed lactogenesis II, the second stage of milk production, which occurs after birth (18, 19). Underlying neurophysiological mechanisms such as endocrine, metabolic and obstetric factors are involved in lactogenesis II.

On the endocrine aspect, prolactin, insulin, adrenal cortisol and thyroid hormones can act directly on lactotropic cells and indirectly alter the endocrine response and the supply of nutrients to the mammary gland for milk production (20–22). In addition to these factors, oxytocin plays a pivotal role in both the synthesis and ejection of maternal milk. Oxytocin is synthesized in magnocellular neurons and primarily accumulates in the paraventricular nuclei (PVN) and supraoptic nuclei (23). Its presence extends from the median eminence internal zone to the neurohypophysis (24), as well as collateral projections to the central amygdala and nucleus accumbens (25).

In terms of metabolic and obstetric factors that may delay lactogenesis II in mothers of premature infants, various conditions should be considered, such as retained placenta, cesarean section, type 2 diabetes, gestational diabetes, childbirth stress, polycystic ovarian syndrome, and postpartum hemorrhage, among others (18). Obese women are also more likely to have delayed lactogenesis II due to hormonal influences on milk production (26). Limitations have also been described in the maintenance of breastfeeding in preterm infants (27), which may be due to the immaturity of the sucking and swallowing reflexes of the newborn, who cannot be fed directly from the mother's breast, requiring manual extraction and collection of milk for later delivery to health care personnel (20).

Regarding the problem of insufficient mother's own milk production, several studies have demonstrated the importance of intervening with external and environmental stimuli. For example, the study by Cohen et al. (28), in lactating female mice showed that exposure to the odor of their pups resulted in significant changes in the cortical area of the mice's brains, leading to improved mother-pup behavior. Similarly, Embarek-Hernández et al. (29), report that multisensory stimulation improves feeding behavior in children and may include visual, tactile, oral, vestibular, auditory, or kinesthetic stimulation. Other similar studies, such as Hernández-Gutiérrez et al. (30), show that a combination of tactile, kinesthetic, and oral stimulation stimulates feeding responses in preterm infants compared with oral stimulation alone.

The production of mother's own milk can be influenced by multisensory stimuli at the level of oxytocin neurons (16) in the central amygdala and nucleus accumbens (25). Therefore, multisensory stimuli could induce an emotional and sentimental response (amygdala and hypothalamus) (31), which would result in the production of oxytocin through the action of oxytocinergic nerves originating in the PVN (32), which increase the blood flow of milk to the nipple during breastfeeding (23).

To summarize, the present study aimed to determine the efficacy of these stimulating processes on milk production in mothers of preterm infants.

2 Materials and methods

2.1 Study design

The design of the present study corresponds to case–control study, in accordance with the CONSORT 2010 guidelines (33). The study was conducted in the facilities of the Hospital Goyeneche, located in the city of Arequipa, in the southern region of Peru. Study participants were postpartum mothers with

preterm infants born between 27 and 37 weeks of gestation. The study period was between June and December 2022. It should be noted that during this period there were sanitary restrictions in all Peruvian health facilities due to the COVID-19 pandemic (34). Therefore, maternal contact with the newborns was minimal. Even the kangaroo mother care method could not be applied during the study period due to the health restrictions that existed at the time.

The Institutional Research Ethics Committee of the Catholic University of Santa Maria approved the research project in the city of Arequipa, Peru (code: 099-2022). Prior to data collection, the researchers provided all participants with a detailed verbal and written explanation of the objectives and scope of the study, the data collection process, and their rights and responsibilities. Written informed consent was obtained from all participants. All information obtained during the study was kept strictly confidential. The results were presented anonymously to prevent the disclosure of any personal information about the participants. Participants were also free to withdraw or terminate their participation in the study at any time. However, there were no dropouts during the study.

In the case of the inclusion criteria, the selection of participants was postpartum mothers with premature infants born within 27–37 weeks of gestation, who had not received galactagogues, who did not have comorbidity or health complications in the breasts, and who wished to participate in the study, as well as premature infants who did not have malformations or health complications, who were born with an Apgar score greater than 7, at 5 min, with a weight between 1,000 and 3,900 g. Candidates who did not meet the above criteria were excluded from the study.

2.2 Sampling and recruitment

In the hospital where this study was conducted, 250 premature births were registered from June to December 2022, among which nine newborns presented malformations. According to the inclusion criteria, the mothers were selected in the delivery room. They were asked to sign the informed consent form to confirm their participation. Of the 241 potential participants, 191 mothers did not meet the inclusion criteria. Therefore, the sample was reduced to 50 participants who were recruited and randomly assigned (online random number generator) (35, 36) to three groups: 17 mothers in the visual-auditory stimulation (SAV) group, 17 in the visual-auditory olfactory stimulation (SAVO) group, and 16 mothers who received general care (control group) (see Figure 1).

2.3 Data collection

Two instruments were used to collect data. The first instrument was a questionnaire to collect personal data from the participants (demographics and obstetric history). The second instrument was a form to record daily mother's own milk production. The maternal data collected in the questionnaire included age, marital status, education level, occupation, number of children, comorbidities, mode of delivery, and infant information such as gestational age, sex, birth weight, and Apgar. Sampling was performed for 15 min on each breast for seven consecutive days. All groups in this study received general care from the NICU staff, including educational sessions to teach participants about the importance of mother's own milk, breast massage before extraction, and guidelines on the safe method of expressing and storing breast milk.

The stimuli used in this study took place only in the area designated as a lactation room, an environment designed for the extraction and collection of mother's own milk within the facilities of the Goyeneche Hospital, the stimuli were carried out once a day.

The SAV and SAVO groups watched a video with images and sounds of babies breastfeeding, smiling and crying during the extraction of mother's own milk. The above-mentioned video served as an audiovisual stimulus that was previously validated by two health professionals (a neonatal intensive care specialist and a neonatal nurse) and an expert in social communication. The Delphi method was used and an Aiken V coefficient of 1 was obtained. The video is about 10 min long and includes instrumental music and neonatal crying. The video begins by showing a newborn's hands, feet, and face, then shows babies being breastfed, and ends with an image of a calm newborn. In the video, we included only the faces of healthy babies who were breastfeeding, relaxed, or crying, and excluded the faces of mothers and hospitalized newborns. The video was displayed on a high-definition (HD) 65-inch television screen.

During human milk extraction, the SAVO group, in addition to watching the video, also received an olfactory stimulus consisting of inhaling for approximately 3 min a cotton swab previously rubbed on the newborn's neck, armpits, and groin. NICU staff obtained the cotton swab after the neonate was bathed. They then placed the swabs individually in a hermetically sealed bottle. The control group received only general care from the NICU staff. The amount of milk collected from both breasts was recorded for seven consecutive days after delivery. It is noteworthy that throughout the process of stimulation and milk extraction, the mothers selected for this study did not directly breastfeed their newborns.

2.4 Data analysis

In the case of the statistical analysis of the selected sample of mothers (Figure 1), the power analysis was taken as a reference, according to a comparative study between the effectiveness of massage and the use of hot compresses on the breasts to stimulate milk production, which considers a power of 80% and a significance of 5% (37). Descriptive statistics (averages, standard deviations) are used for analysis of sample characteristics, and inferential statistics are used for analysis of continuous variables for estimation of normality. To evaluate the differences between the groups, they were compared using the ANOVA test for continuous data with the use of Tukey's *post*

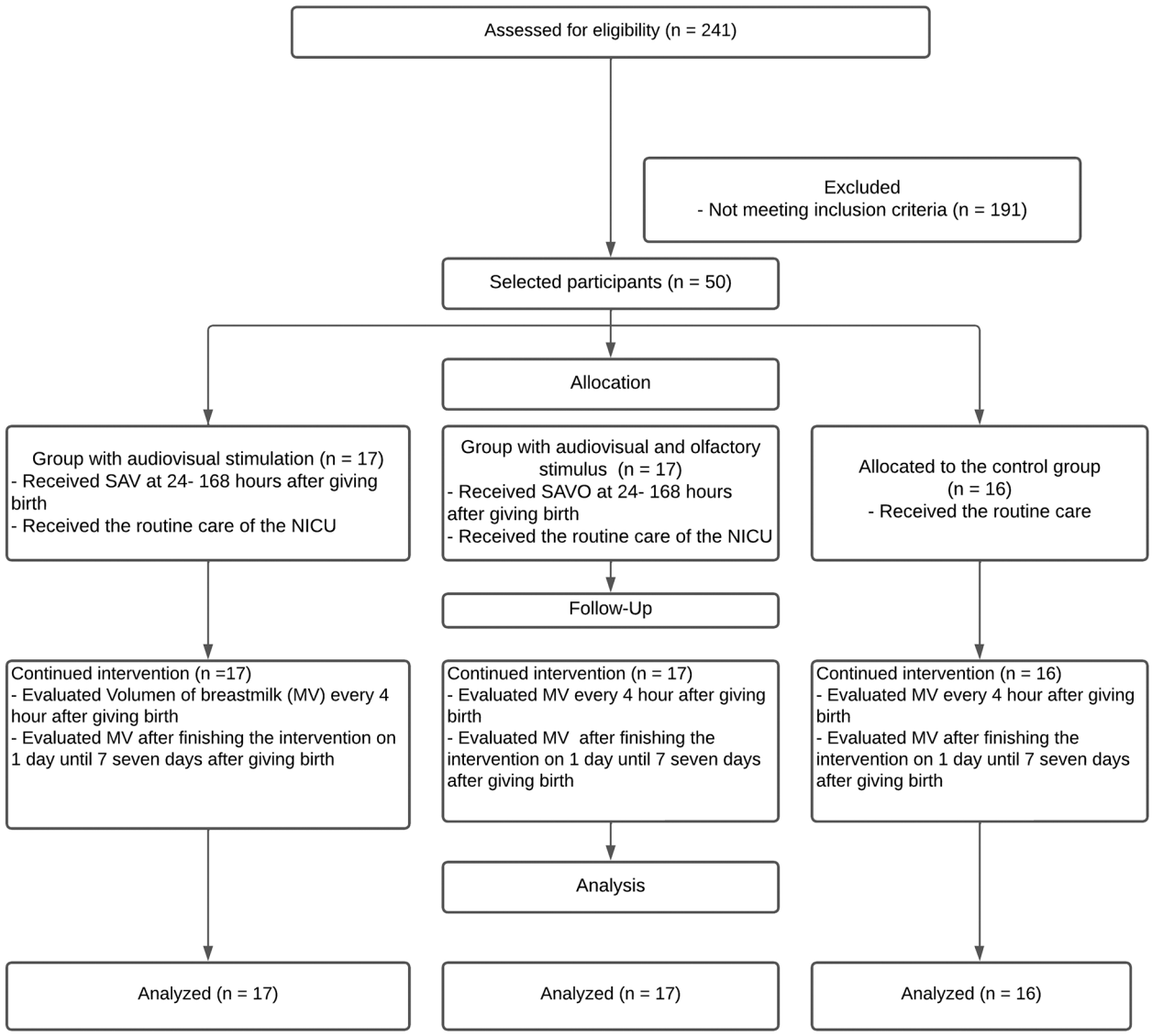

FIGURE 1
A flow diagram summarizing the participant selection process. SAV, audiovisual stimulation; SAVO, audiovisual and olfactory stimulation; NICU, neonatal intensive care unit; MV, breast milk volume.

hoc test and the Pearson's χ^2 test for categorical data. Additionally, multinomial logistic regression analysis was conducted. All *p*-values were two-tailed and significance was set at alpha <0.05. The JAMOVI statistical program, version 2.3.21, was used to analyze all data.

3 Results

3.1 Demographic and obstetric data

Demographic data such as age, marital status, education level, occupation, number of children, and obstetric data such as mode of delivery, Apgar, and birth weight were not significantly different between SAV, SAVO, and the control group (Table 1).

3.2 Mother's own milk volume according to stimulus type during days 1–7 postpartum, between the control group, SAV, and SAVO (*N* = 50)

Depending on the type of stimulation, an increase in mother's own milk volume was observed, with a greater volume from day 4 to day 7 (Table 2) in the SAV and SAVO stimulation groups compared to the control group (Figure 2).

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TABLE 1 Demographic and obstetric data of participants.

Demographic and obstetric data	Control group (*n* = 16)		SAV (*n* = 17)		SAVO (*n* = 17)		F/χ^2	*p*-value
	n	%	*n*	%	*n*	%		
Age (years) mean	29.44		27.12		28.29		0.48[a]	0.62
Marital status								
Single	1	6.25	4	23.53	2	11.76		
Married	4	25.00	1	5.88	5	29.41		
Cohabiting	9	56.25	12	70.59	9	52.94	6.87[b]	0.31
Separated/divorced	2	12.50	0	0.00	1	5.88		
Widow	0	0.00	0	0.00	0	0.00		
Level of education								
Uneducated	0	0.00	0	0.00	0	0.00		
Primary school	1	6.25	3	17.65	0	0.00		
High school	8	50.00	9	52.94	8	47.06	6.34[b]	0.39
Technical college	6	37.50	4	23.53	6	35.29		
Graduate university	1	6.25	1	5.88	3	17.65		
Employment status								
Unemployed	0	0.00	0	0.00	0	0.00		
Student	9	56.25	8	47.06	8	47.06		
Self-employed	5	31.25	8	47.06	7	41.18	1.20[b]	0.88
Employed	2	12.50	1	5.88	2	11.76		
Number of children								
Single parent	6	37.50	6	35.29	7	41.18		
Multipara	7	43.75	11	64.71	10	58.82	7.62[b]	0.11
Grand multipara	3	18.75	0	0.00	0	0.00		
Type of delivery								
Eutopic delivery	4	25.00	4	23.53	3	17.65		
Labor dystocia	12	75.00	13	76.47	14	82.35	0.30[c]	0.86
Apgar mean								
1 min apgar score	6.94		8.06		7.53		2.46[a]	0.10
5 min apgar score	8.56		8.88		8.71		1.25[a]	0.30
Birth weight (grams) mean	1,895		2004		2,084		0.295[a]	0.75
Early initiation of breastfeeding (within 1 h of birth)								
No	12	24.0	11	22.0	11	22.0	0.089[b]	0.54
Yes	4	8.0	6	12.0	6	12.0		

Apgar, Appearance, Pulse, Grimace, Activity, and Respiration; SAV, audiovisual stimulation; SAVO, audiovisual and olfactory stimulation.
[a]One-way ANOVA.
[b]Likelihood ratio.
[c]Rho Spearman.

3.3 One-way ANOVA for between-subject and within-subject comparisons of milk volume between the SAV, SAVO, and control groups

According to mother's own milk volume, significant variance is observed between study groups on day 0 (4 h postpartum) and from day 3 to day 7 (Table 3).

There was a highly significant difference ($p < 0.05$) in the increase of mother's own milk volume in the SAVO group over the 7-day period (Tukey's posthoc test) (Table 4).

In the multinomial logistic regression analysis, the audiovisual and olfactory stimulation (SAVO) group was more likely to have an increase in average mother's own milk volume than the control group. No significant changes were observed in the audiovisual stimulation and control groups. There were also no significant differences between the SAV and SAVO groups (Table 5).

On the other hand, the multivariate linear regression analysis between the sociodemographic and obstetric data of the mothers, the type of stimulus and the volume of milk production showed that the relationship between the age of the

TABLE 2 Comparison of breast milk volume between control group, SAV and SAVO, days 1–7 postpartum (*N* = 50).

Group	Day 0		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Control	14.3	17.7	13.9	17.9	23.4	23.3	30	28.3	43.8	34.7	56.1	33.5	76.9	38.6	95.3	32.5
SAV	3.18	5.51	10.4	12.3	24.8	23.8	37.8	25.3	50	31	75.3	35.3	106	64.9	136	101
SAVO	9.35	10.7	19.2	23.5	35.3	32.9	53.8	35.6	86.2	62.3	133	113	181	152	215	168

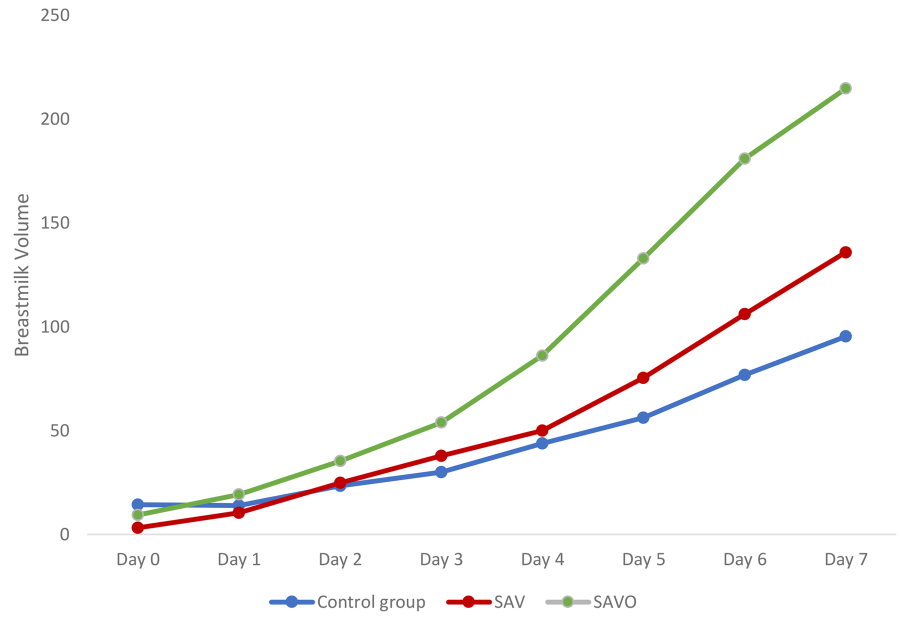

FIGURE 2
Comparison of breast milk volume between the control group, SAV and SAVO.

mother and the multisensory stimulus could intervene in the production of mother's own milk, especially during the first two days (Table 6).

4 Discussion

The present study evaluated the effectiveness of using multisensory stimuli (audiovisual and olfactory) to increase milk production in mothers of preterm infants. The research was based on the neuroscientific basis of the activation of oxytocin, the main hormone in mother's own milk production, as demonstrated by Uvnäs-Moberg et al. (32), who found that this hormone can be activated by non-noxious sensory stimulation (PVN).

In this context, neuroscience (38) emphasizes that external stimuli from the environment intervene in the activation of the limbic system (39) and take advantage of the integration of different sensory channels (kinesthetic, tactile, visual, gustatory, olfactory, auditory and vestibular) for the development of a comprehensive experience (40). The simultaneous use of the senses creates a stimulating experience that effectively captures the recipient's attention and produces more intense emotions. As a result, information retention is enhanced (41) and a lasting experience is generated, creating an emotional connection with the

TABLE 3 One-way ANOVA to compare milk volume, between subjects and within subjects between the SAV, the SAVO and the control groups.

Comparison		Sum of squares	Quadratic mean	*F*	Significance[a]
Day 0	Between groups	1,018.027	509.014	3.402	0.042
	Within groups	7,031.353	149.603		
Day 1	Between groups	670.377	335.189	0.981	0.383
	Within groups	16,060.103	341.704		
Day 2	Between groups	1,408.883	704.441	0.959	0.391
	Within groups	34,537.938	734.85		
Day 3	Between groups	4,900.179	2,450.089	2.704	0.077
	Within groups	42,584.941	906.063		
Day 4	Between groups	17,569.029	8,784.515	4.319	0.019
	Within groups	95,601.471	2,034.074		
Day 5	Between groups	53,306.899	26,653.45	5.234	0.009
	Within groups	2,39,350.221	5,092.558		
Day 6	Between groups	95,776.015	47,888.007	4.875	0.012
	Within groups	4,61,681.985	9,823.021		
Day 7	Between groups	1,22,411.768	61,205.884	4.572	0.015
	Within groups	6,29,158.732	13,386.356		

[a]Significance level at 0.05.

TABLE 4 Multiple comparisons regarding the type of stimulation (SAV, SAVO and the control group) in the average volume of breast milk, over a period of 7 days.

Group comparison	Mean (SD)			Mean difference	SE	*F*	*P*
	SAVO group	SAV group	Control group				
	n = 17	*n* = 17	*n* = 16				
SAVO with SAV	91.5 (68.3)	55.4 (29.6)		−36.1	0.69	4.93	0.064
SAVO with control	91.5 (68.3)		44.2 (24.1)	−47.3	0.84		0.012
SAV with control		55.4 (29.6)	44.2 (24.1)	−11.2	0.77		0.759

recipient (31). Furthermore, a study by Rolls et al. (38), reported a link between visual, olfactory and auditory stimuli and the learning process, as both the amygdala and the hippocampus interact with the emotion produced by the stimulus, generating learning that is demonstrated in social and emotional behavior (42).

The literature found so far includes studies with *ad hoc* protocols of multisensory stimulation of preterm and term infants in the areas of mother's own milk production (43), weight gain, length of hospital stay (44) and neuromotor development (45, 46). However, we did not find any studies on mothers of preterm infants related to measurement of milk volume.

It is worth noting that there are only three human milk banks in Peru, none of which are located in the city of this study (Arequipa). However, the Neonatal Intensive Care Unit where the research took place has highly specialized personnel who take care of premature babies and their nutritional needs. Similarly, a multidisciplinary team educates mothers about the importance of feeding their milk to their babies to promote their growth and development.

The results of the present study suggest that the group of mothers who received visual-auditory olfactory stimulation (SAVO) positively increased the volume of milk production (Table 2). This increase could be due to the hormonal role in pregnancy and childbirth. During pregnancy, hormones intervene to facilitate childbirth (47). According to Larsen et al. (48), prolactin regulates neurogenesis in the mother's brain during pregnancy, creating new neuronal networks in the lateral subventricular zone of the brain that enhance the sense of smell. Similarly, Uvnäs-Moberg et al. (32), and Olza et al. (47), reported that oxytocin affects neuroendocrinological, physiological, and psychological processes during labor, delivery, and the early postpartum period and determines maternal behavior.

On the other hand, our study found an increase in milk volume on day 4 in mothers who received visual, auditory, and olfactory stimulation, in contrast to the control group (Table 3). Therefore, it was suggested that multisensory stimulation may positively influence milk production in mothers of preterm infants from the fourth day of lactation. These findings were in agreement with Yu et al. (18), who indicated that lactogenesis II is delayed in mothers of preterm infants, and milk volume is lower in the first 24 h after birth. Therefore, for a higher increase in volume, the stimuli should be applied 48 h after delivery.

Conversely, Mullen et al. (19), suggest that early breastfeeding (before 6 h after birth) is a primary factor in milk production in mothers of preterm infants. In this study, there was no significant difference in the type of multisensory stimulus used (Table 6). Yu et al. (18), found that late lactogenesis II was associated with the type of delivery, particularly cesarean delivery. However, Heller et al. (49), pointed out that this information is inconclusive for preterm birth. Regarding the type of delivery, there was no significant differences between stimulation type and milk production (Table 6).

The parity of the mother is a controversial factor, as some studies, such as Zachariassen et al. (50), suggest a significant association between being primiparous and successful initiation of breastfeeding. On the contrary, Maas-trup et al. (51), suggests that multiparity is associated with successful breastfeeding. However, in this study, no significant differences were found in stimulation and mother's own milk volume with parity of the mother. However, a significant difference was found between multisensory stimulation, mother's own milk volume on days 1 and 2, and maternal age. There were no conclusive studies on the association between maternal age and mother's own milk production. However, we found evidence of an association between maternal age and successful breastfeeding after discharge of a preterm infant. In this regard, Pineda et al. (52), found that young mothers were less successful in maintaining breastfeeding. Similarly, Casey et al. (53), indicated that maternal age is a predictor of failure to maintain exclusive breastfeeding.

Other sociodemographic factors, such as maternal marital status, education level, and occupation, did not show significant

TABLE 5 Multinomial logistic regression according to stimulus and average milk volume.

Group	Estimator[a]	SE[b]	*Z*[c]	*p*	OR	IC 95%	
SAV—control group	0.016	0.0142	1.123	0.261	1.016	0.9881	1.045
SAVO—control group	0.0319	0.0144	2.211	0.027	1.032	1.0036	1.062
SAVO—SAV	0.0159	0.00924	1.718	0.086	1.016	0.9978	1.03

IC, confident interval; OR, odds ratio.
Model: AIC = 108, R^2 McF = 0.0901, $p < 0.05$.
[a]Constant coefficient of the logistic regression.
[b]Standard error.
[c]Measures the distance between the estimated coefficient and the null.

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TABLE 6 Multivariate linear regression for sociodemographic and obstetric data according to the volume of breast milk production.

Origin	Dependent variable	Sum of squares type III	DF	Mean square	*F*	Significance
Adjusted model	Day 0	3,893.556[a]	21	185.407	1.249	.287
	Day 1	9,241.576[b]	21	440.075	1.645	.108
	Day 2	19,840.478[c]	21	944.785	1.642	.109
	Day 3	23,939.644[d]	21	1,139.983	1.356	.223
	Day 4	60,968.653[e]	21	2,903.269	1.557	.136
	Day 5	1,60,460.019[f]	21	7,640.953	1.618	.116
	Day 6	2,92,044.657[g]	21	13,906.888	1.467	.170
	Day 7	4,12,037.737[h]	21	19,620.845	1.618	.116
Stimulation vs. mother's age	Day 0	161.124	3	53.708	.362	.781
	Day 1	3,384.022	3	1,128.007	4.217	.014
	Day 2	6,889.859	3	2,296.620	3.993	.017
	Day 3	3,506.734	3	1,168.911	1.390	.266
	Day 4	14,240.719	3	4,746.906	2.546	.076
	Day 5	9,171.626	3	3,057.209	.648	.591
	Day 6	30,517.425	3	10,172.475	1.073	.376
	Day 7	71,640.433	3	23,880.144	1.969	.141
Stimulation vs. marital status	Day 0	290.000	3	96.667	.651	.589
	Day 1	1,170.901	3	390.300	1.459	.247
	Day 2	2,399.310	3	799.770	1.390	.266
	Day 3	2,781.950	3	927.317	1.103	.364
	Day 4	8,867.649	3	2,955.883	1.585	.215
	Day 5	5,349.478	3	1,783.159	.378	.770
	Day 6	11,182.766	3	3,727.589	.393	.759
	Day 7	11,678.976	3	3,892.992	.321	.810
Stimulation vs. mother's level of education	Day 0	249.739	3	83.246	.561	.645
	Day 1	1,528.211	3	509.404	1.905	.152
	Day 2	3,898.211	3	1,299.404	2.259	.103
	Day 3	1,171.622	3	390.541	.464	.709
	Day 4	3,638.633	3	1,212.878	.651	.589
	Day 5	16,075.698	3	5,358.566	1.135	.352
	Day 6	29,563.338	3	9,854.446	1.040	.390
	Day 7	14,926.963	3	4,975.654	.410	.747
Stimulus vs. employment	Day 0	63.022	3	21.007	.142	.934
	Day 1	511.625	3	170.542	.638	.597
	Day 2	147.117	3	49.039	.085	.968
	Day 3	1,585.365	3	528.455	.628	.603
	Day 4	618.075	3	206.025	.111	.953
	Day 5	22,914.347	3	7,638.116	1.618	.208
	Day 6	32,515.745	3	10,838.582	1.143	.349
	Day 7	25,267.459	3	8,422.486	.695	.563
Stimulus vs. number of children	Day 0	263.340	3	87.780	.591	.626
	Day 1	372.804	3	124.268	.465	.709
	Day 2	1,260.493	3	420.164	.730	.543
	Day 3	1,389.152	3	463.051	.551	.652
	Day 4	722.533	3	240.844	.129	.942
	Day 5	5,601.936	3	1,867.312	.396	.757
	Day 6	6,993.697	3	2,331.232	.246	.864
	Day 7	11,048.214	3	3,682.738	.304	.822
Stimulus vs. delivery type	Day 0	144.757	3	48.252	.325	.807
	Day 1	218.665	3	72.888	.273	.845
	Day 2	1,216.143	3	405.381	.705	.557
	Day 3	1,685.480	3	561.827	.668	.579
	Day 4	9,796.012	3	3,265.337	1.751	.179
	Day 5	20,566.263	3	6,855.421	1.452	.249
	Day 6	42,636.508	3	14,212.169	1.499	.236
	Day 7	42,851.376	3	14,283.792	1.178	.336
Stimulation vs. early initiation of breastfeeding	Day 0	991.740	3	330.580	2.227	.107
	Day 1	526.062	3	175.354	.656	.586
	Day 2	287.380	3	95.793	.167	.918

(*Continued*)

TABLE 6 Continued

Origin	Dependent variable	Sum of squares type III	DF	Mean square	*F*	Significance
	Day 3	559.507	3	186.502	.222	.880
	Day 4	7,029.460	3	2,343.153	1.257	.308
	Day 5	28,932.153	3	9,644.051	2.043	.131
	Day 6	65,473.426	3	21,824.475	2.302	.099
	Day 7	91,552.002	3	30,517.334	2.517	.079

[a]R^2 = .484 (R^2 adjusted = .096).
[b]R^2 = .552 (R^2 adjusted = .217).
[c]R^2 = .552 (R^2 adjusted = .216).
[d]R^2 = .504 (R^2 adjusted = .132).
[e]R^2 = .539 (R^2 adjusted = .193).
[f]R^2 = .548 (R^2 adjusted = .210).
[g]R^2 = .524 (R^2 adjusted = .167).
[h]R^2 = .548 (R^2 adjusted = .209).

differences in stimulation with mother's own milk volume. Nevertheless, several studies have demonstrated the association of the above-mentioned variables with the success of maintaining exclusive breastfeeding in preterm infants after discharge from hospital (49, 52).

According to Mitha et al. (54), the factors that promote breastfeeding in preterm infants in the NICU are skin-to-skin contact using the kangaroo position during the first week of life, continuous information to mothers about the importance of breastfeeding, expressing their milk within 6 h of birth, the provision of a designated room (in the NICU) for expressing their milk, and support from staff trained in breastfeeding. In contrast, Heller et al. (49), did not find a significant association between the duration of breastfeeding in preterm infants and health care provider information, availability of a lactation room and staff trained in breastfeeding. Therefore, further studies are needed to determine the relationship between these factors and mother's own milk production.

Due to the hospital's COVID-19 protocol, postpartum mothers with preterm infants in the NICU were not able to perform skin-to-skin contact (kangaroo method). The absence or delay of this method is considered to be a risk factor for the successful establishment of exclusive breastfeeding at discharge (54–56). Therefore, it would be essential to implement the multisensory stimuli proposed in this study with mothers who use the kangaroo method, in order to evaluate its impact on mother's own milk production.

Despite the limitations imposed by the context of the COVID-19 pandemic, the study was rigorously conducted. Thus, the limitations did not affect our findings.

Finally, the results found in this study may have relevant clinical implications for neonatal intensive care units that are faced with insufficient mother's own milk to feed premature infants and lack access to human milk banks. The incorporation of multisensory stimulation would represent an innovative approach to mother's own milk production and mother-infant care.

5 Conclusion

Multisensory stimulation in postpartum mothers of preterm infants may influence an increase in mother's own milk production, according to the findings of this study. However, more research is needed in this area to clarify the reported findings.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Universidad Catolica de Santa María, Arequipa, Peru (protocol code 099-2022; 18 July 2022). 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. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. CB: Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. MG: Data curation, Investigation, Validation, Writing – review & editing. MC: Conceptualization, Funding acquisition, Writing – review & editing. MB: Conceptualization, Funding acquisition, Writing – review & editing. RC: Investigation, Resources, Writing – review & editing. MA: Investigation, Resources, Validation, Writing – review & editing. CC: Investigation, Resources, 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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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Claudio Pellegrino,
Agostino Gemelli University Polyclinic (IRCCS), Italy
Luciana Teofili,
Fondazione Policlincio Universitario A. Gemelli IRCCS, Italy

*CORRESPONDENCE
Gerhard Pichler
gerhard.pichler@medunigraz.at

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Acid base and metabolic parameters of the umbilical cord blood and cerebral oxygenation immediately after birth

Martin Dusleag[1,2], Berndt Urlesberger[1,2], Bernhard Schwaberger[1,2], Nariae Baik-Schneditz[1,2], Christoph Schlatzer[1,2], Christina H. Wolfsberger[1,2] and Gerhard Pichler[1,2]*

[1]Division of Neonatology, Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria, [2]Research Unit for Neonatal Micro- and Macrocirculation, Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

Objective: Aim was to investigate whether acid-base and metabolic parameters obtained from arterial umbilical cord blood affect cerebral oxygenation after birth in preterm neonates with respiratory support and in term neonates without respiratory support.
Study design: This was a post-hoc analysis of secondary outcome parameters of a prospective observational study including preterm neonates with and term neonates without respiratory support. Non-asphyxiated neonates with cerebral oxygenation measured with near-infrared spectroscopy during the first 15 min and with blood gas analyses from arterial umbilical cord blood were included. Arterial oxygen saturation (SpO_2) and heart rate (HR) were monitored with pulse oximetry. Potential correlations were investigated between acid-base and metabolic parameters (pH-value, bicarbonate, base-excess, and lactate) and $crSO_2$/cFTOE 5 min after birth.
Results: Seventy-seven neonates were included: 14 preterm neonates with respiratory support (mean gestational age [GA] 31.4 ± 4.1 weeks; mean birth weight [BW] 1,690 ± 640 g) and 63 term neonates without respiratory support (GA 38.7 ± 0.8 weeks; BW 3,258 ± 443 g). Mean $crSO_2$ 5 min after birth was 44.0% ± 24.2% in preterm and 62.2% ± 20.01% in term neonates. Mean cFTOE 5 min after birth was 0.46 ± 0.06 in preterm and 0.27 ± 0.19 in term neonates. In preterm neonates with respiratory support higher lactate was significantly associated with lower $crSO_2$ and SpO_2 and tended to be associated with higher cFTOE. In term neonates without respiratory support no significant correlations were found.
Conclusion: In non-asphyxiated preterm neonates with respiratory support, lactate levels were negatively associated with $crSO_2$ and SpO_2, whereas in term neonates without respiratory support no associations were observed.

KEYWORDS

neonates, acid-base and metabolic parameters, cerebral oxygenation, immediate neonatal transition, near-infrared spectroscopy

1 Introduction

The transition from fetus to newborn represents a highly complex physiological process (1). Initial clinical assessment of the newborn is routinely performed using the Apgar score introduced by Virginia Apgar in 1953 (2). Especially in preterm infants, monitoring by pulse oximeter and/or electrocardiogram is recommended to ensure continuous monitoring of heart rate (HR) and arterial oxygen saturation (SpO_2) (3–5).

However, brain monitoring is not routinely used yet, even though the brain is the organ, which might be mostly affected by hypoxia. Brain function of the newborn immediately after birth is usually assessed just by clinical evaluation of muscle tone and reflexes (3). Monitoring systems such as Doppler ultrasonography and electroencephalography are of limited value due to their lack of feasibility during immediate neonatal transition (3, 6). Near-infrared spectroscopy (NIRS) represents a method with increasing importance to measure cerebral oxygenation. Based on different absorption spectra of oxygenated and deoxygenated hemoglobin regarding the emitted infrared light, relative changes of these parameters can be measured and cerebral regional oxygen saturation ($crSO_2$) can be derived. Further, cerebral fractional tissue oxygen extraction (cFTOE) can be calculated using the equation (SpO_2-$crSO_2$)/SpO_2 (7). This non-invasive continuous monitoring of $crSO_2$ represents a mixed arterial, capillary, and particularly venous saturation and reflects the balance between oxygen supply and oxygen consumption of the brain (6, 8). Within the first minutes after birth, $crSO_2$ has been shown to rise to a plateau earlier than peripheral arterial oxygen saturation in term infants, even if the data on this is not fully conclusive (8, 9). In addition, $crSO_2$-guided therapy in extremely immature neonates results in a significant reduction in cerebral hyperoxia and hypoxia, although this is not associated with a significantly lower incidence of death and brain injury (8, 10, 11).

$crSO_2$ depends on cerebral blood flow (CBF), which is a result of cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR), on cerebral oxygen consumption (cVO_2) and on arterial oxygen content (CaO_2), which mainly depends on arterial oxygen saturation and hemoglobin level (Hb). Several of these parameters are influenced by acid-base balance (pH, HCO_3, BE and lactate) (12).

Acid-base parameters of arterial umbilical cord blood such as pH, HCO_3, BE and lactate provide information about the metabolic status of neonates at birth. Severe metabolic acidosis—defined by a pH below 7.0 and a base deficit above 12 mmol/L—is associated with increased neonatal mortality and morbidity (13). Acid-base parameters obtained from venous umbilical cord blood show higher pH values than arterial umbilical cord blood due to the placental origin, whereas samples from heel capillary blood usually indicate lower pH values than arterial umbilical cord blood because of poor peripheral microcirculation (14–16).

The aim of the present study was to analyze the possible impact of acid-base status, measured from a blood sample of the umbilical artery at birth on cerebral oxygenation 5 min after birth in non-asphyxiated preterm neonates with respiratory support and in stable term neonates without respiratory support.

2 Material and methods

2.1 Design

This was a post-hoc-analysis of secondary outcome parameters of prospective observational studies conducted from October 2015 to September 2018 at the Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria. The Regional Ethics Committee approved the study and written parental consent was obtained before birth (EC number: 27–465 ex 14/15).

2.2 Inclusion and exclusion criteria

Preterm neonates with respiratory support and stable term neonates without respiratory support delivered by Cesarean section, who were included in the prospective observational study were eligible. Neonates with missing data of the monitoring parameters or acid-base and metabolic parameters were excluded. Neonates with major congenital malformations, and laboratory signs of asphyxia (umbilical artery pH <7.0, BE >12 mml/L or Lactate >2.9 mmol/L) were excluded.

2.3 Measurements during immediate transition

After delivery, the neonates were immediately taken to the resuscitation desk and placed supine under an overhead heater. Plastic wraps were used to prevent hypothermia in preterm neonates <29 weeks' gestation. Neonatal stabilization was performed according to neonatal resuscitation guidelines (4, 5) by specialized resuscitation teams (neonatologist/experienced resident and nurse) who were not involved in the study. Respiratory support was provided by continuous positive airway pressure or positive pressure ventilation using a T-piece device (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand). Oxygen levels were titrated according to neonatal resuscitation guidelines (4, 5). SpO_2 and HR were monitored by a pulse oximetry probe (IntelliVue MP30 Monitor, Philips, Amsterdam, The Netherlands) placed around the right wrist/hand. $CrSO_2$ was measured using an INVOS 5100 monitor (Covidien, Minnesota, USA) with a neonatal sensor fixed on the left forehead of each neonate. Averaging time of SpO2, HR and crSO2 was 8 s and values were stored every second. cFTOE was calculated with the following formula: (SpO_2-$crSO_2$)/SpO_2. Cerebral oxygenation was monitored during the first 15 min after birth. Measurements were recorded by the multi-channel system alpha-trace digital MM (BEST Medical Systems, Vienna, Austria) for subsequent analyses. The acid-base and metabolic parameters from arterial umbilical cord blood were analysed with a blood gas analyser (ABL 800 Flex; Fa.Drott, Wiener Neustadt, Austria).

2.4 Statistical analysis

Demographic and clinical data are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Data of preterm neonates with respiratory support and term neonates without respiratory support were compared using t-test for independent samples, Mann-Whitney-U or Chi-square test as appropriate.

Mean of values of minute 5 after birth of SpO_2, HR, $crSO_2$ and cFTOE values were correlated to pH, bicarbonate (HCO_3), base

excess (BE) and lactate using Spearman's rank correlation coefficient or Pearson's correlation, as appropriate. This time-point was chosen to be close to the blood sample time-point. The analyses were performed in an explorative sense. Therefore, no correction for multiple testing was performed.

A *p*-value <0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics 27.0.0 (IBM Corporation, Armonk, NY, USA).

3 Results

Out of 224 eligible neonates 77 were included (Figure 1): 14 preterm neonates with respiratory support and 63 stable term neonates without respiratory support. Most neonates were excluded due to missing NIRS data at minute five or missing acid-base and metabolic parameters of umbilical artery. Demographic data of preterm and term neonates are presented in Table 1.

Concerning monitoring parameters (Table 1) preterm neonates receiving respiratory support showed significantly lower values of $crSO_2$ and SpO_2 and higher values in cFTOE than term neonates without respiratory support, whereas there was no statistically significant difference in HR. Besides lactate levels, which were statistically significantly higher in preterm neonates with respiratory support, no statistically significant differences were observed regarding pH, HCO_3 or BE between the two groups (Table 1).

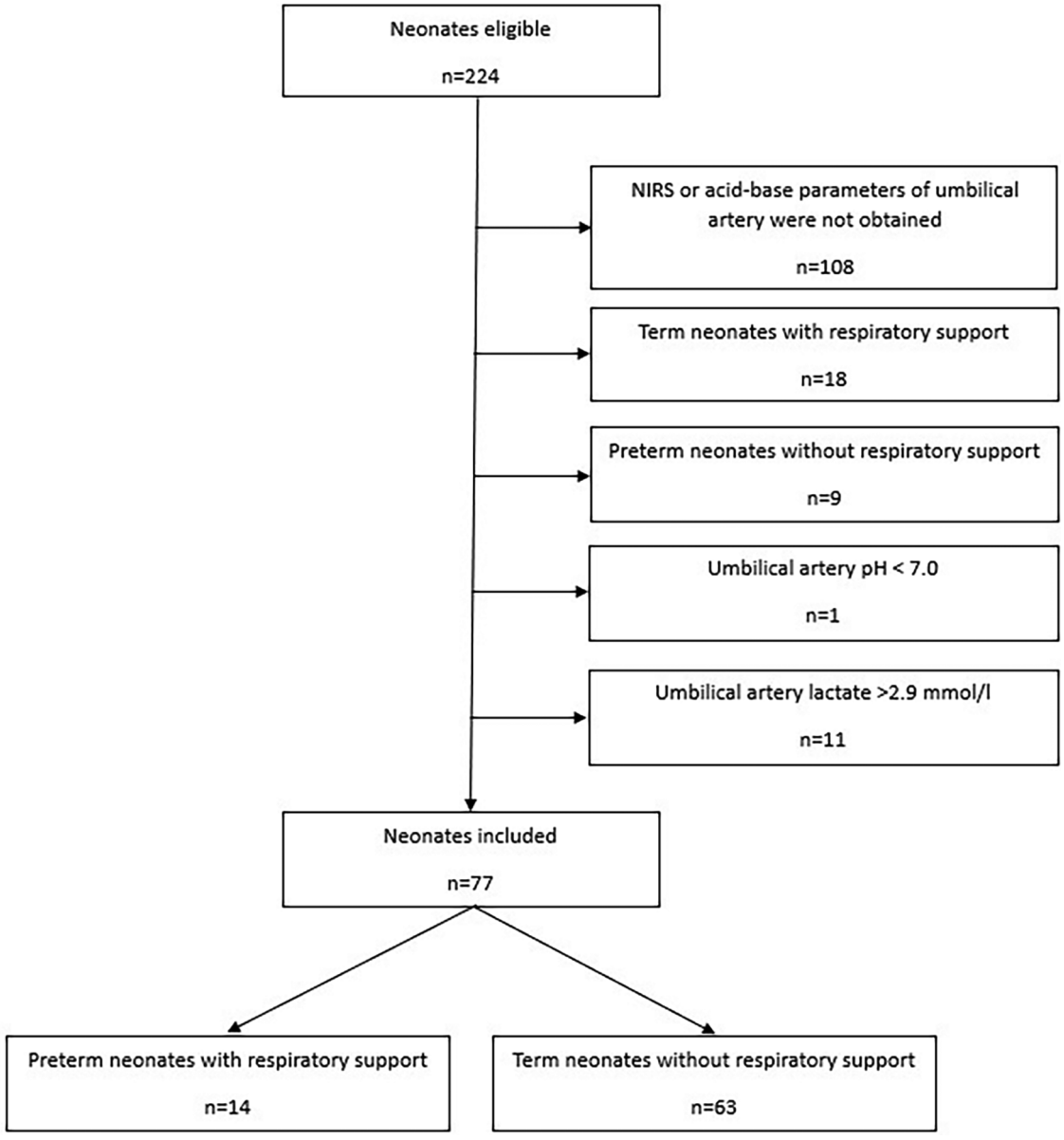

FIGURE 1
Patient flow diagram. NIRS, near infrared spectrometry.

TABLE 1 Demographics, monitoring data 5 min after birth and acid base metabolism of the umbilical artery in preterm neonates with respiratory support and stable term neonates without respiratory support.

		Preterm ($n = 14$)	Term ($n = 63$)	p-value
Demographics	Gestational age (weeks)	31.4 ± 4.1	38.7 ± 0.8	<0.001
	Birth weight (g)	1.690 ± 640	3.258 ± 443	<0.001
	Female sex (%)	4 (29)	24 (38)	0.693
	Apgar 1 min	8 (6.75–8)	9 (9–9)	<0.001
	Apgar 5 min	9 (8–9)	10 (10–10)	<0.001
	Apgar 10 min	9 (9–9.25)	10 (10–10)	<0.001
Monitoring	SpO_2 (%)	66 ± 12	83 ± 9	<0.001
	Pulse (bpm)	148 ± 16	154 ± 17	0.275
	$CrSO_2$ (%)	44.0 ± 24.2	62.2 ± 20.01	0.012
	FTOE	0.46 ± 0.2	0.27 ± 0.19	0.011
	pH	7.32 ± 0.06	7.32 ± 0.03	0.815
Acid-base metabolism	Bicarbonate (mmol/L)	22.9 ± 2.5	23.0 ± 1.20	0.839
	Base excess (mmol/L)	0.70 ± 2.89	1.37 ± 1.55	0.418
	Lactate (mmol/L)	2.6 ± 1.5	1.7 ± 0.42	0.012

Data are presented as mean values ± SD or median (IQR). SpO_2, arterial oxygen saturation; $CrSO_2$, cerebral regional oxygen saturation; FTOE, fractional tissue oxygen extraction.

In preterm neonates with respiratory support lactate levels correlated significantly negatively with $crSO_2$ and SpO_2 5 min after birth (Table 2). In term neonates no correlations were observed.

4 Discussion and conclusion

In the present study we have demonstrated that $crSO_2$ and SpO_2 5 min after birth were associated with lactate levels in compromised preterm neonates with respiratory support, whereas in stable term neonates without respiratory support no associations were observed. In addition, lactate in preterm neonates also tended to be associated with cFTOE. Apart of lactate no further parameters of acid-base status were associated with SpO2, HR, crSO2 or cFTOE, neither in preterm neonates with respiratory support nor in stable term neonates.

SpO_2 represents the percentage of hemoglobin saturated with oxygen in peripheral arterial blood (17). Our findings regarding SpO_2 values in term neonates 5 min after birth are consistent with those of Rabi et al. (18), who described median SpO_2 values of 81% (75–83).

Lactate is produced as a metabolite in anaerobic glycolysis and is elevated in case of impaired cellular oxygenation (19). The correlations in the present study were observed despite the fairly narrow lactate range within the study population with values <2.9 mmol/L. Similar findings with negative correlations between lactate levels obtained from capillary blood and $crSO_2$ and with positive correlations between lactate levels and cFTOE in preterm neonates 15 min after birth were published by Mattersberger et al. (20) as well as by Janaillac et al. (21) in extremely preterm infants in the first 72 h after birth. The observed correlations could be explained by the fact that lactic acidemia induces pulmonary vasoconstriction and decreases cardiac stroke volume as a result of impaired cardiac contractility (22). Subsequently, low cardiac output leads to reduced oxygen supply of peripheral tissue and diminished peripheral oxygen saturation. The association between elevated lactate levels and poor hemodynamics has also been described in previous studies (23, 24). Considering lactate as a parameter of hemodynamics, the observed association between lactate levels and cerebral oxygenation may reflect impaired cerebrovascular autoregulation in preterm neonates. Intact cerebrovascular autoregulation allows constant CBF over a wide range of blood pressure, resulting in CBF independency of CPP. Impaired cerebrovascular autoregulation leads to a pressure-dependent CBF due to its linear correlation with CPP, resulting in deleterious CBF fluctuations in response to CPP variations (12, 25–28). Several studies have already indicated impaired cerebrovascular autoregulation in compromised preterm neonates (25–27, 29–33). Considering that in the present study cFTOE also tends to be associated with lactate in preterm neonates, low $crSO_2$ may not only be a result of diminished oxygen content -in terms of low SpO_2-, but also due to increased oxygen extraction in the cerebral microcirculation. In contrast, studies of infants diagnosed prenatally with congenital heart disease (34) and of critically ill neonates and of infants without cerebral damage (35) do not indicate associations between lactate levels and cerebral oxygenation. However, they showed negative correlations between cerebral oxygenation and SpO_2. Since these studies included

TABLE 2 Correlation analyses of SpO_2, pulse, $CrSO_2$ and FTOE measured 5 min after birth with umbilical artery pH, bicorbonate, base excess and lactate and in preterm neonates with respiratory support and stable term neonates without respiratory support.

		pH		Bicarbonate		Base excess		Lactate	
		r	p-value	r	p-value	r	p-value	r	p-value
Preterm ($n = 14$)	SpO_2	0.402	0.154	0.051	0.863	0.013	0.964	**−.540***	0.046
	HR	−0.167	0.644	−0.248	0.489	−0.367	0.267	0.146	0.687
	$crSO_2$	0.461	0.131	0.344	0.273	0.253	0.428	**−0.589***	0.044
	FTOE	−0.38	0.279	0.003	0.994	−0.039	0.914	0.59	0.073
Term ($n = 63$)	SpO_2	−0.008	0.952	0.104	0.423	0.145	0.261	0.112	0.393
	HR	−0.118	0.368	−0.112	0.398	−0.149	0.256	0.257	0.052
	$crSO_2$	0.085	0.515	0.139	0.290	0.085	0.514	0.024	0.854
	FTOE	−0.19	0.147	−0.133	0.316	−0.068	0.603	0.077	0.566

SpO_2, arterial oxygen saturation; $CrSO_2$, cerebral regional oxygen saturation; FTOE, fractional tissue oxygen extraction.
*p-value <0.05.

cerebral oxygenation measurements beyond the immediate fetal to neonatal transition and differentiation between preterm and term neonates was not considered, the differences in their findings could be result of a better cerebral autoregulation.

As far as other acid-base and metabolic parameters are concerned, these were slightly more alkaline compared to previous publications, which mostly included neonates born by vaginal delivery (19, 36). This is most probably due to the effect that neonates with laboratory signs of asphyxia were excluded, since we wanted to analyse the effect of blood gases and lactate in non-asphyxiated neonates. Furthermore, differences might be due to differences in the metabolic stress of the fetus caused by repeated uterine contractions during vaginal delivery (19) and Cesarean section.

Measurement of umbilical cord blood pH, HCO_3 and BE provides essential information about acid-base metabolism and extrauterine adaption of newborns (13). In accordance to the present study no correlations between $crSO_2$ and pH were found in children during cardiopulmonary bypass surgery (37), in infants diagnosed prenatally with congenital heart disease during the first 72 h (34) and in stable preterm neonates in neonatal intensive care (38). HCO_3 is the physiologically most important buffer system in the human body (39). BE is used for quantification of changes in metabolic acid-base status and together with umbilical artery pH it is crucial to estimate the risk for newborn cerebral damage (40, 41). Mattersberger et al. (20) indicated positive correlations between HCO_3 measured 15 min postnatally and cFTOE in term neonates and correlations of lower pH and BE also measured 15 min postnatally with lower $crSO_2$ and higher cFTOE in preterm neonates. A point of innovation of the present study compared to Mattersberger et al. is the fact that by using umbilical cord blood the blood sampling is immediately after birth and might help to predict changes in the transition period and especially predict cerebral oxygenation in this vulnerable period (42). Furthermore capillary blood gas measurements do not always predict arterial blood gas values in an accurate way (13). In contrast, neither in stable preterm neonates in neonatal intensive care (38) nor in critically ill neonates and infants without cerebral damage (35) correlations were found between $crSO_2$ and BE. Aldrich et al. (43) showed, that $crSO_2$ is positively correlated with pH and negatively with BE shortly before birth and negative correlations between $crSO_2$ and BE and HCO_3, respectively were reported by Nissen et al. (44) in term-born infants with hypertrophic pyloric stenosis. A possible explanation of the differences to our findings are different study populations, comorbidities but also the fact, that in contrast to the present study, blood gas analysis were obtained from capillary blood. Samples obtained from arterial blood or umbilical cord blood tend to have more alkaline pH values than those of capillary blood (45). The present study was a post-hoc-analysis with all its inherent limitations. The small sample size of preterm neonates with respiratory support and possible interactions between the investigated acid-base and metabolic parameters and cerebral oxygenation mark further shortcomings. However, the described correlations in preterm neonates could be interpreted as an impaired cerebral autoregulation and are therefore an important finding.

In conclusion, in non-asphyxiated preterm neonates with respiratory support lactate levels were significantly associated with $crSO_2$ and SpO_2, whereas in stable term neonates without respiratory support no associations were observed.

Future studies will be necessary to evaluate causal relationships between acid-base and metabolic parameters and cerebral oxygenation during the period of transition from fetal to neonatal life.

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 Regional Ethics Committee of the Medical University of Graz. 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

MD: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. BU: Resources, Writing – review & editing, Validation, Methodology, Formal Analysis, Conceptualization. BS: Investigation, Data curation, Writing – review & editing, Validation, Formal Analysis. N-BS: Writing – review & editing, Validation, Investigation, Formal Analysis, Data curation. CS: Project administration, Writing – review & editing, Investigation, Data curation. CW: Validation, Formal Analysis, Writing – review & editing, Investigation, Data curation. GP: Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Conceptualization, Writing – review & editing, Validation, Investigation, Formal Analysis, Data curation.

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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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Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Jiang-Qin Liu,
Shanghai First Maternity and Infant Hospital, China
Nunzia Molinaro,
Campus Bio-Medico University, Italy

*CORRESPONDENCE
Libor Svoboda
libor.svoboda@med.uni-jena.de

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Contactless assessment of heart rate in neonates within a clinical environment using imaging photoplethysmography

Libor Svoboda[1]*, Jan Sperrhake[2], Maria Nisser[2], Luca Taphorn[1] and Hans Proquitté[1]

[1]Department of Pediatric and Adolescent Medicine, University Hospital Jena, Jena, Germany, [2]Xsight Optics GmbH, Jena, Germany

Introduction: In neonatology, the accurate determination of vital parameters plays a pivotal role in monitoring critically ill newborns and premature infants, as well as aiding in disease diagnosis. In response to the limitations associated with contact-based measurement methods, substantial efforts have been directed toward developing contactless measurement techniques, particularly over the past decade.

Methods: Building upon the insights gained from our pilot study, we realized a new investigation to assess the precision of our imaging photoplethysmography-based system within a clinical environment of the neonatal intermediate care unit. We conducted measurements in 20 preterm infants or newborns requiring therapeutic interventions. As a point of reference, we employed a conventional pulse oximeter. To analytically predict measurement artifacts, we analyzed the potential influence of confounding factors, such as motion artifacts, illumination fluctuations (under- and overexposure), and loss of region of interest prior to heart rate evaluation. This reduced the amount of data we evaluated for heart rate to 56.1% of its original volume.

Results: In artifact-free time segments, the mean difference between the pulse oximetry and the imaging photoplethysmography-based system for 1 s sampling intervals resulted in −0.2 bpm (95% CI −0.8 to 0.4, LOA ± 12.2). For the clinical standard of 8 s averaging time, the mean difference resulted in −0.09 bpm (95% CI −0.7 to 0.6, LOA ± 10.1). These results match the medical standards.

Discussion: While further research is needed to increase the range of measurable vital parameters and more diverse patient collectives need to be considered in the future, we could demonstrate very high accuracy for non-contact heart rate measurement in newborn infants in the clinical setting, provided artifacts are excluded. In particular, performing *a priori* signal assessment helps make clinical measurements safer by identifying unreliable readings.

KEYWORDS

contactless monitoring, non-invasive, imaging photoplethysmography, heart rate, newborns, vital parameters, neonatology, preterm infants

Abbreviations

bpm, beats per minute; CI, confidence interval; ECG, electrocardiography; HR, heart rate; IMC, intermediate care unit, iPPG, imaging photoplethysmography; LED, light-emitting diode; LOA, limits of agreement; NICU, neonatal intensive care unit; PPG, photoplethysmography; RGB, red, green, blue; ROI, region of interest; SpO_2, pulsoxymetrically measured oxygen saturation.

Introduction

Determining vital parameters is a crucial aspect of neonatology and broader medical practice. One fundamental parameter assessed is the heart rate (HR), which yields critical clinical information. HR assessment commences shortly after birth, providing initial insights into postnatal adaptation success. Resuscitation may be warranted if HR falls below specific thresholds (1, 2).

Compromised newborns, especially preterm infants, necessitate continuous vital parameter monitoring. Electrocardiography (ECG) serves as the gold standard for HR determination, particularly shortly after birth, offering the most rapid and accurate measurement (3–5). Pulse oximetry-based photoplethysmography (PPG), employed for arterial oxygen saturation (SpO_2) and HR determination, may exhibit slight delays compared to ECG, especially during neonatal resuscitation (6). Typically, PPG signals within neonatal intensive care units (NICUs) use 8 s default averaging time to optimize data accuracy and relevance (7).

Both methods usually involve contact-based sensors, presenting general and age-related drawbacks. Insufficient perfusion, as seen in vasoconstriction or hypotension, may render pulse oximetry-based sensors ineffective (8, 9). Additionally, pain, skin irritation, pressure ulcers, and infections caused by adhesive electrodes or sensors are notable concerns, particularly for premature infants (10–15). Additionally, Anton et al. 's review (16) suggests that several studies have shown that the time between birth and successful establishment of HR using ECG or PPG frequently exceeds 1–2 min.

In response to these limitations and the diverse applications of vital parameter monitoring, research on contactless monitoring methods has intensified, primarily over the last decade. Many non-contact HR measurement methods rely on imaging photoplethysmography (iPPG) principles (17, 18). The iPPG method derives HR measurements by employing the same fundamental principles as conventional pulse oximetry-based photoplethysmography (PPG), which entails the detection and amplification of subtle cyclic changes in skin color associated with each cardiac cycle. Several studies, including our pilot study (19), have demonstrated the feasibility of contactless HR measurement in neonates using iPPG (11–13, 19–28). However, it is essential to note that the iPPG signal is susceptible to various sources of interference, including motion artifacts, changes in ambient light, skin pigmentation variations, and obstruction of the region of interest (ROI) by other equipment or healthcare professionals (4, 11, 17, 22, 25, 29).

In our pilot study (19), we evaluated the accuracy and feasibility of a multimodal 3D camera system using iPPG to measure HR in healthy term and late preterm infants under standardized conditions. Our approach, incorporating 2D and 3D vision, demonstrated feasibility when compared to a reference (*Masimo Rad-97 Pulse CO-Oximeter®*). Notably, the 2D-based method showed a mean difference of only +3.0 bpm compared to the reference, while the 3D-based method revealed a mean difference of +8.6 bpm. Due to accuracy and data volume considerations, we chose to focus on 2D-based methods and discontinuing 3D imaging.

This study aims to validate the accuracy and feasibility of an adapted camera-based system for assessing HR in preterm or compromised newborn infants within the neonatal intermediate care unit (IMC) clinical environment. Additionally, the study seeks to identify and quantify potential disruptive factors to increase the robustness and suitability of iPPG-based HR measurement for everyday use.

Materials and methods

Structure and function of the camera sensor

The iPPG camera system utilized in this study is a simplified version of the multi-modal setup implemented in our pilot study. This system consists of two near-infrared (NIR) Genie Nano M1280-NIR cameras equipped with filters at 750 nm and 950 nm, along with a standard RGB Bayer-pattern Genie Nano C1280-IRC camera for color sensing. All three cameras recorded at a frame rate of 30 Hz. To adjust brightness, we turned on ceiling lights when there was insufficient sunlight, relying on ambient illumination as a visible light source. As ceiling lights emit low intensity at 750 nm and no detectable intensity at 950 nm, the system includes three light-emitting diodes (LEDs). Two of these LEDs operate at 950 nm, which is undetectable by the human eye, while the other operates at 750 nm, which is barely visible.

The cameras were arranged in a horizontal line, with the RGB camera in the center and the 950 nm and 750 nm cameras on its left and right, respectively. The RGB camera sets a fixed optical axis normal to the front plane of the sensor. The two NIR cameras were tilted towards the optical axis to center their field of view on a measurement target at a distance of 50 cm. The LED lights were located directly beneath the camera array, with the 950 nm LEDs located on the outside and the 750 nm LED positioned in the center. The geometric arrangement in this study was identical to that shown in Figure 1 of our pilot study (19).

Our primary source of image data for iPPG HR evaluation was the RGB camera. The two near-infrared (NIR) cameras provided supplementary image data regardless of ambient light. Additionally, the NIR data gathered in this study serves as a foundation for possible iPPG SpO_2 assessments, given that the 750 nm and 950 nm wavelengths encompass the point where the extinction coefficients of oxygenated and deoxygenated hemoglobin intersect (30). Although the study did not aim to assess SpO_2 levels due to the absence of patients with significant oxygen saturation deviations, we collected data for potential follow-up research.

The camera system was securely enclosed in a 3D-printed spherical shell that housed essential electronics for device control and protection. The cameras transmitted the data via Ethernet to an auxiliary computer for data storage. All elements of the system were mounted onto a medical cart (Figure 1) to enable mobility. Compared to our previous wall-mounted setup in the

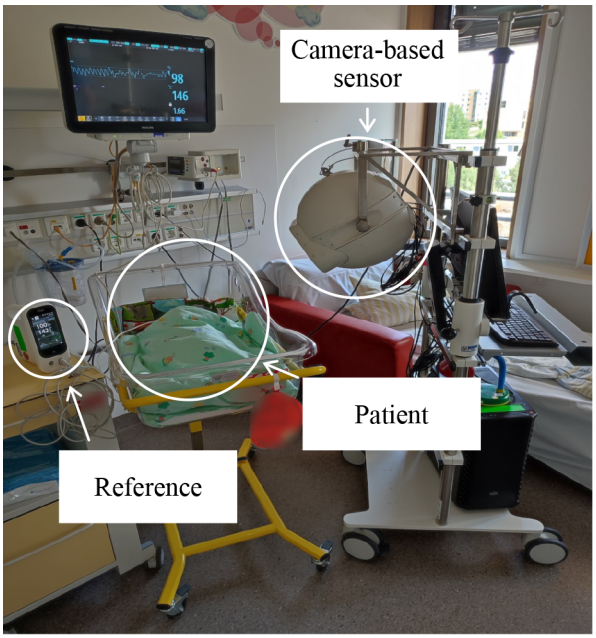

FIGURE 1
The camera-based sensor deployed within the neonatal intermediate care ward (IMC) positioned close to the patient's bed during the data acquisition process.

pilot study, our new setup provided us with the freedom to move between rooms and adjust the camera.

A priori evaluation of the measurement condition

Prior to estimating and analyzing any HR data, we evaluated the reliability of each recording based on the properties of the ROI. By processing the collected data in this order, we avoided bias toward physiological plausibility. The *a priori* evaluation of the ROI involved three characteristics: motion within the ROI, illumination of the ROI, and validity of the ROI (as explained further). All of which are based on color averages of the ROI.

Motion was determined by the temporal standard deviation of the color signals within an interval, weighted by their respective mean, giving a threshold for motion within the ROI. If the motion was too high within a ROI, the corresponding time intervals were denoted as invalid. Next, the illumination of a ROI was classified by minimal and maximal boundary conditions of average color values within a time interval. If values were below or above the boundaries, the interval was labeled invalid. Finally, the validity of the ROI is a measure whether the fixed image box still contains the desired region of interest of the patient. An invalid ROI could be caused by movement or occlusion. It was measured as the angular difference in color space between the average color of the ROI within a time interval and the global color average of the ROI. If the difference exceeded a threshold value, the ROI was identified as inaccurate, and the corresponding time interval was labeled invalid.

If any of these properties were invalid, the corresponding time intervals were discarded from the HR evaluation. An example measurement from this study is shown in Figure 2, comparing the reference to the iPPG results while segmenting the measurement into valid and invalid intervals.

Heart rate estimation from camera images

To extract HR-related signals from the video recordings of patients acquired with our camera system, we used bounding boxes as regions of interest (ROI) that were placed in areas with visible skin pixels. Each recording contained image sequences of a patient's head and upper body. Because head positions and tilt angles of patients' heads varied between measurements, we placed the ROIs manually on the forehead and lateral or posterior head regions. We opted against the tracking of the ROI because it brought no benefits to our approach in this setting. Since most patients had a relatively stable resting position, selecting a fixed bounding box was an adequate choice. Each evaluation involved averaging the pixel values within the ROI for each color channel of each frame and combining them to a 3-dimensional vector in color space, which served as the basis for signal calculation. The time sequence of color vectors was split into small time windows with temporal overlap. The pulse wave signal was then retrieved for each time window using XminaY demixing from the chrominance-based method described in (31).

Initially, we estimated a temporary HR corresponding to the expected value of a normal distribution adapted to the power spectrum of the pulse wave signal. The reliability of the estimate was measured using the width of the distribution. Subsequently, the HR of the current interval was calculated as a weighted average of several successive estimates. By applying this method to an entire recording, we derived a time-dependent HR signal that could be matched to a reference with comparable sampling intervals.

Setting and participants

Our research was conducted as a single-center observational study at the University Hospital Jena in Germany. We secured ethical approval for our research from the local ethics committee (Ethics Committee Reference No. 2020-1891-MV), including an amendment dated 19th August 2021. Our clinical trial adhered strictly to the principles outlined in the Declaration of Helsinki and complied with Good Clinical Practice (GCP) guidelines.

The study population comprised cardiopulmonary stable late preterm newborns and full-term compromised newborns at the Neonatal Intermediate Care Ward (IMC) that did not require respiratory support during data collection.

We conducted measurements on a cohort of 20 patients utilizing a simplified version of the camera-based sensor system described in our prior publication (19). Before commencing any measures, we diligently obtained written informed consent from the parents to record image data.

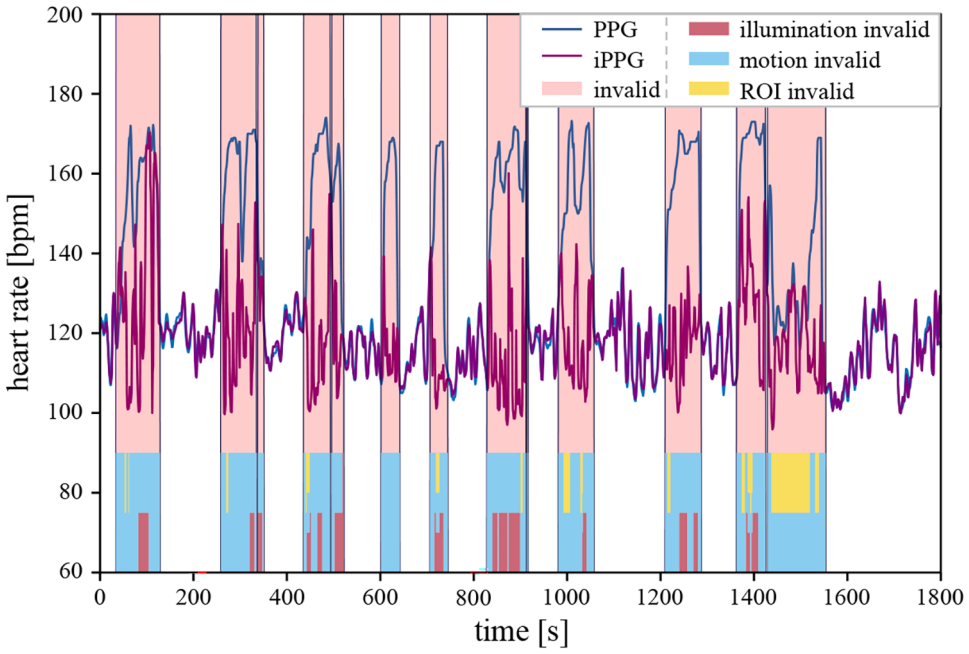

FIGURE 2
A graphical representation of measurement including heart rate curves from both systems (blue line PPG, purple line iPPG), with light red intervals marking invalid segments, which were excluded from the subsequent statistical analysis. The color bars within the segments at the bottom of the plot indicate the identified disruptive factors. Red, blue, and yellow denote invalid illumination, motion, and ROI conditions, respectively. Multiple colors are shown in the plot if more than one disruptive factor was identified over a time segment.

Data collection occurred within the time frame of 19th January 2022 to 30th May 2022. Importantly, data acquisition was executed within the confines of the patients' rooms, eliminating the need to displace them from their familiar surroundings. Throughout the measurement process, patients were positioned either in the embrace of a parent or in their beds, as illustrated in (Figure 1).

We set the standard measurement interval to 30 min, whereby in 3 cases, multiple measurements could be carried out. On the other hand, we terminated measurements in many instances earlier, either because of increasing restlessness of the infant or on parental request. This resulted in a total of around 676 min of video material. The videos were recorded at 30 frames per second, generating a total of 162,000 images for each 30-min measurement interval.

As previously described in the manuscript under "Structure and function of the camera sensor", the camera sensor was attached to a mobile trolley. The mobile design allowed the system to get the best viewing position. Because the ROIs were localized on a child's head, they did not have to be undressed or moved. The nursing and medical care of the children were also guaranteed at any time.

We positioned the sensor at approximately 50 cm from the child's head. This distance ensured that the child's head was equally visible by all three cameras, given by their respective viewing angle as per the construction of the camera sensor.

We obtained the reference values for HR using a pulse oximeter (*Masimo Rad-97 Pulse CO-Oximeter ®, mcu: 1.068, Prozessor: V 1.4.6.2 i-ss; Techboard: 7e94*). The pulse oximeter sensor was attached to either the patient's wrists or feet. To synchronize the time stamps of measurement intervals from our system with those of the reference, we manually adjusted the system clock of the PC recording the videos to match the system time of the pulse oximeter with an approximate alignment down to a second.

Without the use of an additional external light source, ambient illumination varied between individual measurements. Because measurements were performed in a realistic clinical environment and standard patient rooms, they were particularly exposed to prevailing weather conditions from open window blinds. If the exposure was too low, we switched on the overhead lighting. If the exposure was too high, we lowered the window blinds. However, it was challenging to ensure ideal measurement conditions across all measurements. Therefore, some data was affected by variations in ambient illumination, movement of the patients, and random obstructions of the patient's head.

Statistical methods

In analyzing the study population, we employed descriptive statistics to summarize the data. For normally distributed data, we presented the mean ± standard deviation. We reported the median along with the 25th and 75th percentiles for non-normally distributed data, specifically HR. Gender distribution was summarized using absolute and relative frequencies.

We utilized a linear mixed model to assess the agreement between the measurements obtained from the Masimo sensor

and the camera-based sensor. This model incorporated a random intercept per patient to account for multiple measurements per patient and the associated correlation among these observations. We reported the estimated mean difference between the two systems (Masimo sensor minus camera-based sensor) along with a 95% confidence interval. This mean difference serves as an estimate of bias, indicating the degree of disagreement between the two methods. The 95% confidence interval provides a range of values to quantify the uncertainty associated with this estimate, encompassing possible values for the bias.

Additionally, we assessed the level of agreement between the HR measurements obtained from the Masimo sensor and the camera-based sensor using Bland-Altman plots. Figure 3A presents the results for the 1 s sampling intervals, while Figure 3B displays those for the averaging time of 8 s.

The percentage distribution of the reasons for signal failures was summarized using relative frequencies.

The significance level was set at $\alpha = 0.05$ for all analyses. All statistical procedures were executed using SPSS software (IBM Corp. Released 2022. IBM SPSS Statistics for Windows, Version 29.0.0.0 Armonk, NY: IBM Corp.).

Results

At the end of the measurement phase, we collected 23 measurements of different lengths from 20 patients for evaluation. The recordings were frequently monitored during the measurement phase. For six of them, it was subsequently determined that, despite diligent preparation of the measurements, conditions for a successful acquisition of HR data were not met.

In three measurements, the ROI could not be placed accurately. The videos of two other measurements were overexposed due to strong ambient light, and the video of a third measurement was underexposed. The three cases in which the illumination conditions prevented any evaluation were carried out early in the measurement phase. The illumination conditions and video exposure were more closely monitored and regulated during subsequent measurements. The following measurements resulted in 17 recordings from 14 patients available for evaluation.

These 17 measurements covered 485 min of data material and, thus, 71.7% of the original data volume. As mentioned, these measurements were checked for possible disruptive factors. In this analysis, 272 min of the 485 min of data material could be identified as fault-free, which corresponds to 56.1% of the evaluable data. From all originally recorded measurements, 40.2% could be evaluated. 43.9% of the evaluable data were excluded from further statistical analysis due to the presence of essentially three confounding factors. These were motion artifacts, illumination fluctuations (under- and overexposure), and loss of region of interest. As summarized by Figure 4, more than one confounding factor could be present at the same time.

Of the 14 patients whose measurements contributed to the HR evaluation, 11 were female (78.6%), while 3 were male (21.4%). All study participants exhibited characteristics consistent with individuals of Caucasian ancestry, characterized by predominantly fair or white skin pigmentation. Their corrected gestational age ranged from 27.4 to 41.9 weeks, with a mean of 33.7 weeks. Their weight at the time of measurement ranged from 1,580 to 3,710 g, with a mean weight of 2,353 g. The median HR, as measured by Masimo, was 144 beats per minute (bpm), ranging from 61 to 199 bpm. The 25th and 75th percentiles were at 125 bpm and 154 bpm, respectively. Further details are available in Table 1.

We compared HR data obtained from our camera-based sensor and pulse oximetry reference. We evaluated the data over 1 s sampling intervals and 8 s time averaging. The mean difference between the two methods for 1 s sampling intervals was −0.2 bpm (95% CI −0.8 to 0.4, LOA ± 12.2). For the 8 s time averaging, the mean difference was −0.09 bpm (95% CI −0.7 to 0.6, LOA ± 10.1). Notably, the differences between the methods for both sampling intervals did not achieve statistical significance ($p = 0.396$ for 1 s averaging time, respectively $p = 0.772$ for 8 s averaging time) (see Table 2).

Discussion

Our study addressed various questions assembled on the results of our pilot study (19), where the measurement accuracy of our camera-based sensor in a patient collective of healthy newborns and late premature infants was tested using two different measurement methods. The 2D measurement yielded similar results ($p = 0.359$) to the reference system, with an average difference of +3.0 bpm and a range of ±36.6 bpm. With the 3D measurement, we found that the results differed significantly from each other ($p = 0.010$), and there was a mean difference of +8.6 bpm (LOA ± 44.7 bpm). We then abandoned the 3D measurement method for further study phases.

In this study, we aimed to test the measurement accuracy of our adapted 2D system and, simultaneously, test the feasibility for longer observational periods as might be required in IMC. Therefore, we chose measurement times of 30 min and advanced to a more challenging group of patients comprised by sick newborns and premature infants who were in the neonatal IMC for therapeutic purposes.

It is important to note that we achieved a significant increase in agreement with the pulse oximetry reference, with an average difference of −0.24 bpm, with associated LOA of ±12.16 bpm. Compared to our pilot study, this is an order of magnitude more accurate.

In standard practice at the neonatal IMC, default sampling intervals are set to 8 s in order to avoid unnecessary alarms (7). For this reason, we also time averaged over 8 s and again evaluated the mean difference in the HR data between the two systems used. Using the 8 s time average further reduced the mean difference between the iPPG results and the reference to −0.09 bpm and an associated LOA of ±10.12 bpm. In this way, values that have changed significantly in the short term can better be eliminated from the analysis, and unnecessary alarm signals can be prevented.

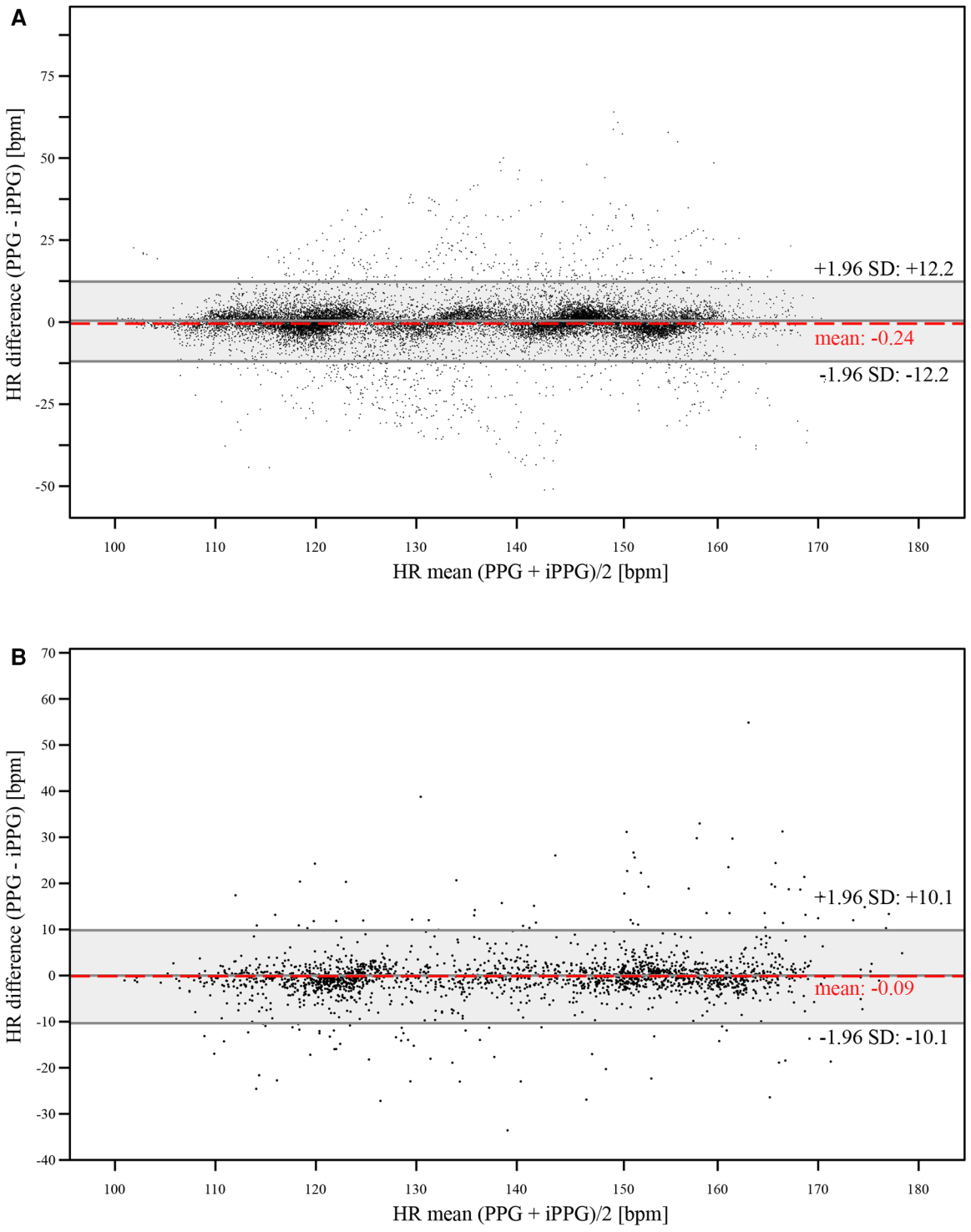

FIGURE 3
The Bland-Altman plots show the measured HR values derived from the reference and the iPPG system (**A**) with a 1 s sampling interval, (**B**) with an averaging time of 8 s. The *y*-axis shows the HR differences between the two methods in beats per minute (bpm), while the *x*-axis shows their mean HR in beats per minute (bpm).

Another question we could not answer in our pilot study was which disruptive factors influence our measurements and to what extent. In the current study, a total of 43.9% of the data that could be evaluated was perturbed by external factors. An evident and significant confounding factor is patient motion. This often includes the patient turning or covering the front of their head, leading to an invalid ROI. This accounted for most of the signal dropouts. While proper camera positioning is essential, contactless

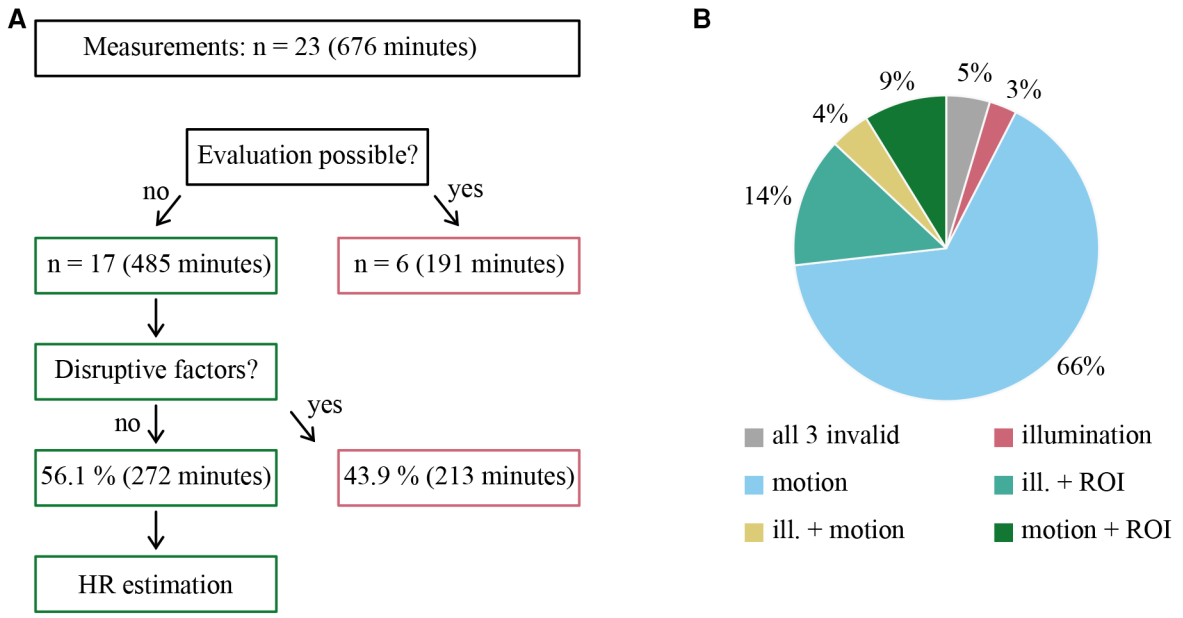

FIGURE 4
(A) Flowchart summarizing the selected recordings that could be evaluated, where *n* corresponds to the number of the respective measurements. (B) Distribution of *a priori* identified disruptive factor described in the text. These can be divided into invalidity due to motion, illumination, ROI inaccuracy, and combinations thereof.

TABLE 1 The demographic and clinical characteristics of the studied population are summarized as follows.

Parameter	*N*	Mean ± SD[a]/ Median (25th–75th percentile)[b]
Gestational age [weeks]	14	33.7 ± 4.1[a]
Age [hours]	14	641.6 ± 805.4[a]
Weight [g]	14	2,352.9 ± 694.6[a]
Temperature [°C]	14	37.0 ± 0.2[a]
Bilirubin [µmol/L]	14	50.1 ± 62.5[a]
Heart rate [bpm]	14	144 (125–154)[b]

Data marked with [a]correspond to mean ± SD. Data marked with [b]correspond to the median (25th/75th percentile).

TABLE 2 Mean HR difference in beats per minute and limits of agreement (LOA) comparing Masimo vs. iPPG.

Parameter	Estimate	95% confidence interval	*p* value	LOA
Mean difference Masimo vs. iPPG 1 s sampling intervals [bpm]	−0.2	−0.8 to 0.4	0.396	±12.2
Mean difference Masimo vs. iPPG 8 s time averaging [bpm]	−0.09	−0.7 to 0.6	0.772	±10.1

methods are susceptible to such disturbances, which can currently only be addressed procedurally and depending on the setting.

A further factor was the illumination on the station. As mentioned earlier, we did not carry out the measurements under standardized conditions. In the course of the measurement phase, we adapted the illumination as each individual situation demanded. However, under- and overexposed images still accounted for 25.5% of the data that could not be evaluated. This can be improved using adaptive exposure settings and defining limits for device operation.

While further research is needed to understand and limit the confounding factors of contactless measurement schemes, new technological opportunities arise. The camera-based approach allows the gathering of data on measurement conditions during ongoing recordings. This means that data acquired in this way can be labeled to give feedback on the validity of measurements during ongoing clinical monitoring.

Another aspect that needs to be addressed in the future is the ability of conventional contact-based monitors to measure several vital signs in parallel. In addition to HR, this also includes SpO_2, respiratory rate, and blood pressure. However, the same confounding factors as for HR estimation will also apply to these parameters.

Finally, up to this point, our results can only be applied to newborns and premature infants who are cardiopulmonary stable. In the future, our approach should be tested in the patient group of cardiopulmonary unstable patients.

Limitations

Our findings are subject to limitations arising from various factors, which we shall discuss below.

Firstly, it is crucial to acknowledge that the high precision of the iPPG sensor in artifact-free intervals is significantly constrained by a notably high rate of missing intervals. This limitation arose from various disruptive factors encountered

during data collection, including motion artifacts, varying ambient light intensity, and loss of ROI. Additionally, user-induced errors, particularly during the initial measurement phases, contributed to this limitation.

Similar to our pilot study, we could not utilize ECG for reference due to the unavailability of devices capable of storing data at the required intervals. ECG is considered the gold standard for HR determination. A potential solution for addressing this challenge in future studies involves simultaneously recording an ECG monitor using an additional webcam.

Another limitation is that the population of this study exclusively encompassed late preterm infants and newborns that are clinically stable and do not need intensive care. Additionally, this excluded extending our dataset to extremely preterm infants or those with an unstable circulatory status. These populations need to be explored in a subsequent study within the neonatal intensive care unit.

Finally, all study participants exhibited characteristics consistent with individuals of Caucasian ancestry, characterized by predominantly fair or white skin pigmentation. Consequently, we could not assess possible inaccuracies stemming from variations in skin pigmentation.

Conclusions

In neonatology, the accurate monitoring of vital parameters is essential for critically ill newborns. Building on a previous pilot study, we evaluated contactless imaging photoplethysmography (iPPG) within a neonatal intermediate care ward. Evaluating 20 cardiopulmonary stable, late preterm newborns and full-term compromised newborns, we compared a camera-based measurement system to a conventional pulse oximeter, considering potential artifacts like motion, variation in illumination, and accuracy of regions of interest. Although 43.9% of the data were excluded due to *a priori* evaluated confounding factors, our results demonstrated high accuracy, with mean differences of −0.2 bpm (1 s sampling) and −0.09 bpm (8 s averaging), aligning with medical standards (32). These findings support the efficacy of non-contact HR measurement in clinical settings, emphasizing the importance of *a priori* identifying potential artifacts for safer clinical measurements. While further research is warranted to expand parameter range and patient diversity, our study underscores the promising accuracy of contactless measurement schemes for neonatal vital sign monitoring.

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

Author contributions

LS: Writing – original draft, Writing – review & editing, Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision. JS: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. MN: Conceptualization, Methodology, Project administration, Resources, Writing – review & editing. LT: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. HP: Conceptualization, Methodology, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The affiliation of JS and MN with Xsight Optics GmbH poses a potential conflict of interest. As Xsight Optics GmbH is a company that partially financed the study, commercial interest could be a source of a conflict of interest. Although the authors were diligent in their effort to minimize any such effect, it cannot be ruled out completely.

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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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Daniel Vijlbrief,
University Medical Center Utrecht, Netherlands
Tuuli Metsvaht,
University of Tartu, Estonia

*CORRESPONDENCE
Ling Sun
✉ sunny70mail@163.com
Qiu-Qin Xu
✉ xuqiuqin922@163.com

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A predictive model for patent ductus arteriosus seven days postpartum in preterm infants: an ultrasound-based assessment of ductus arteriosus intimal thickness within 24 h after birth

Xin-Lu Hu[1], Ting-Ting Zhu[2], Hui Wang[1], Cui Hou[1], Jun-Cheng Ni[1], Zhuo-Fan Zhang[1], Xiao-Chen Li[1], Hao Peng[3], Hong Li[2], Ling Sun[1]* and Qiu-Qin Xu[1]*

[1]Department of Cardiology, Children's Hospital of Soochow University, Suzhou, Jiangsu, China, [2]Department of Neonatology, Children's Hospital of Soochow University, Suzhou, Jiangsu, China, [3]Department of Epidemiology, Suzhou Medical College of Soochow University, Suzhou, Jiangsu, China

Objectives: To develop a predictive model for patent ductus arteriosus (PDA) in preterm infants at seven days postpartum. The model employs ultrasound measurements of the ductus arteriosus (DA) intimal thickness (IT) obtained within 24 h after birth.

Methods: One hundred and five preterm infants with gestational ages ranging from 27.0 to 36.7 weeks admitted within 24 h following birth were prospectively enrolled. Echocardiographic assessments were performed to measure DA IT within 24 h after birth, and DA status was evaluated through echocardiography on the seventh day postpartum. Potential predictors were considered, including traditional clinical risk factors, M-mode ultrasound parameters, lumen diameter of the DA (LD), and DA flow metrics. A final prediction model was formulated through bidirectional stepwise regression analysis and subsequently subjected to internal validation. The model's discriminative ability, calibration, and clinical applicability were also assessed.

Results: The final predictive model included birth weight, application of mechanical ventilation, left ventricular end-diastolic diameter (LVEDd), LD, and the logarithm of IT (logIT). The receiver operating characteristic (ROC) curve for the model, predicated on logIT, exhibited excellent discriminative power with an area under the curve (AUC) of 0.985 (95% CI: 0.966–1.000), sensitivity of 1.000, and specificity of 0.909. Moreover, the model demonstrated robust calibration and goodness-of-fit (χ^2 value = 0.560, $p > 0.05$), as well as strong reproducibility (accuracy: 0.935, Kappa: 0.773), as evidenced by 10-fold cross-validation. A decision curve analysis confirmed the model's broad clinical utility.

Abbreviations

AO, aortic root diameter; DA, ductus arteriosus; GA, gestational age at birth; hsPDA, hemodynamically significant PDA; IT, intimal thickness of the DA; LA, left atrial diameter; LD, lumen diameter of the DA; LogIT, the logarithm of IT; LVDb, body surface area corrected left ventricular end-diastolic diameter; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; Vmax, the peak velocity of the left to right shunt; Vdif, the maximum difference of the shunt velocity throughout the cardiac cycle.

Conclusions: Our study successfully establishes a predictive model for PDA in preterm infants at seven days postpartum, leveraging the measurement of DA IT. This model enables identifying, within the first 24 h of life, infants who are likely to benefit from timely DA closure, thereby informing treatment decisions.

KEYWORDS

patent ductus arteriosus, intimal thickness, preterm infants, echocardiography, predictive model

Introduction

Functional closure of the ductus arteriosus (DA) usually occurs within three days after birth. Patent ductus arteriosus (PDA) has a high incidence in preterm infants, and its influencing factors, the mechanisms of which are not fully elucidated, include molecular, hemodynamic, and structural factors (1). The left-to-right shunt of a PDA in preterm infants causes adverse hemodynamic effects, resulting in complications including periventricular/intraventricular hemorrhage, pulmonary hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis (2).

While non-selective cyclooxygenase inhibitors, including ibuprofen and indomethacin, for PDA closure are widely demonstrated (3), pharmacological interventions do not improve outcomes compared with expectant management, and harm (including increased risk of acute kidney injury or GI bleeding) may outweigh benefit (4–6). Treatment decisions regarding prophylactic, very early, or early administration of these agents also varied considerably among centers (7). Evidence is lacking to identify which preterm infants are most likely to benefit from PDA treatment, and more effective selective treatment options for PDA remain to be elucidated (8). Some studies have investigated the relationship between serum markers, echocardiographic indicators, and hemodynamically significant PDA (hsPDA) in the neonatal period (9–11). However, few have yielded a simple predictive model for PDA in preterm infants. To date, no study has evaluated structural predictors of DA closure beyond DA diameter, length, and shape.

Recently, our group found that the intimal thickness (IT) of the DA, which can be measured by echocardiography, tended to be thinner and have a slower growth rate in newborns in whom the DA failed to close by three days of life. They also had a smaller ratio of IT to lumen diameter of the DA (LD) within 24 h after birth than that of infants with spontaneous closure (12). In this study, we describe creating a predictive model that integrates IT measurements—obtained within the first 24 h postpartum—alongside conventional echocardiographic parameters and established clinical risk factors. This comprehensive model assesses the risk of PDA at seven days postpartum. By facilitating early identification of high-risk infants, the model aids clinical decision-making and enables timely interventions to alleviate left ventricular volume load. Conversely, for infants classified as low-risk, the model allows for avoiding unnecessary pharmacologic interventions, thereby minimizing the potential for adverse side effects and reducing overall harm.

Methods

Study design and participants

This was a prospective cohort study focusing on preterm infants conducted from July 2020 through December 2022. A total of 105 preterm infants admitted to the Children's Hospital of Soochow University within the first 24 h following birth were enrolled in the study. Eligibility criteria included a gestational age of less than 37 weeks and a patent DA confirmed by echocardiography within the initial 24-hour postpartum window.

Exclusion criteria

Infants were excluded from the study for any of the following reasons:

- Presence of an atrial shunt exceeding 5 mm or other forms of congenital heart disease.
- Diagnosis of arrhythmia.
- Anatomical malformations of other systems.
- Poor quality echocardiographic images.
- Uncertain clinical outcomes owing to hospital discharge or mortality within seven days of birth.

Clinical risk factors

The gender, gestational age (GA), birth weight, birth length, and body surface area (BSA) at birth were recorded. The presence of neonatal asphyxia, respiratory distress syndrome (RDS), or the use of mechanical ventilation within 24 h after birth were collected.

Echocardiography examination

GE Vivid E90 and E95 (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasonic diagnostic machines were used with a 2.9–5.8 MHz phased-array probe. Echocardiographic images were collected within 24 h after birth in the supine position in a quiet state.

M-mode ultrasound data measured in real time included aortic root diameter (AO), left atrial diameter (LA), left ventricular end-diastolic dimension (LVEDd), and left ventricular ejection fraction (LVEF). The LA/AO was calculated, and body-surface-area-

corrected left ventricular end-diastolic diameter (LVDb) was calculated by LVEDd/BSA.

Dynamic images of the DA were obtained in the long-axis view at the superior sternal fossa. The direction of the shunt was recorded, the peak velocity of the left to right shunt (Vmax), and the maximum difference of the shunt velocity throughout the cardiac cycle (Vdif) were measured. (When the DA shunt is left-to-right, Vdif is the velocity difference above the spectrum baseline. When the DA shunt is bidirectional, Vdif is the absolute difference between the upper and lower baseline velocities.) The ratio of Vdif to Vmax was calculated. LD and IT were measured using an Echopac workstation off-line as described (12). Figure 1 shows the measurement of IT.

Image acquisition was performed by two trained sonographers, and measurement of DA data was performed by one experienced sonographer. All data were measured for three cardiac cycles, and the mean value was calculated. The sonographers were unaware of the clinical characteristics of the participants and the outcomes of DA closure.

Complete closure or non-closure of the DA of preterm infants by seven days after birth was confirmed by echocardiography.

Statistical analysis

Data were analyzed using R statistical software, version 4.1.3. A two-tailed $p < 0.05$ was considered statistically significant.

Baseline characteristics

A two-independent sample *t*-test, the Wilcoxon rank sum test, or the χ^2 test was used to compare the data between the two groups. As a normal distribution was not present, the Wilcoxon rank sum test was used to compare the mean levels of IT between the two groups, and then log transformation was used to convert IT to an approximately normal distribution.

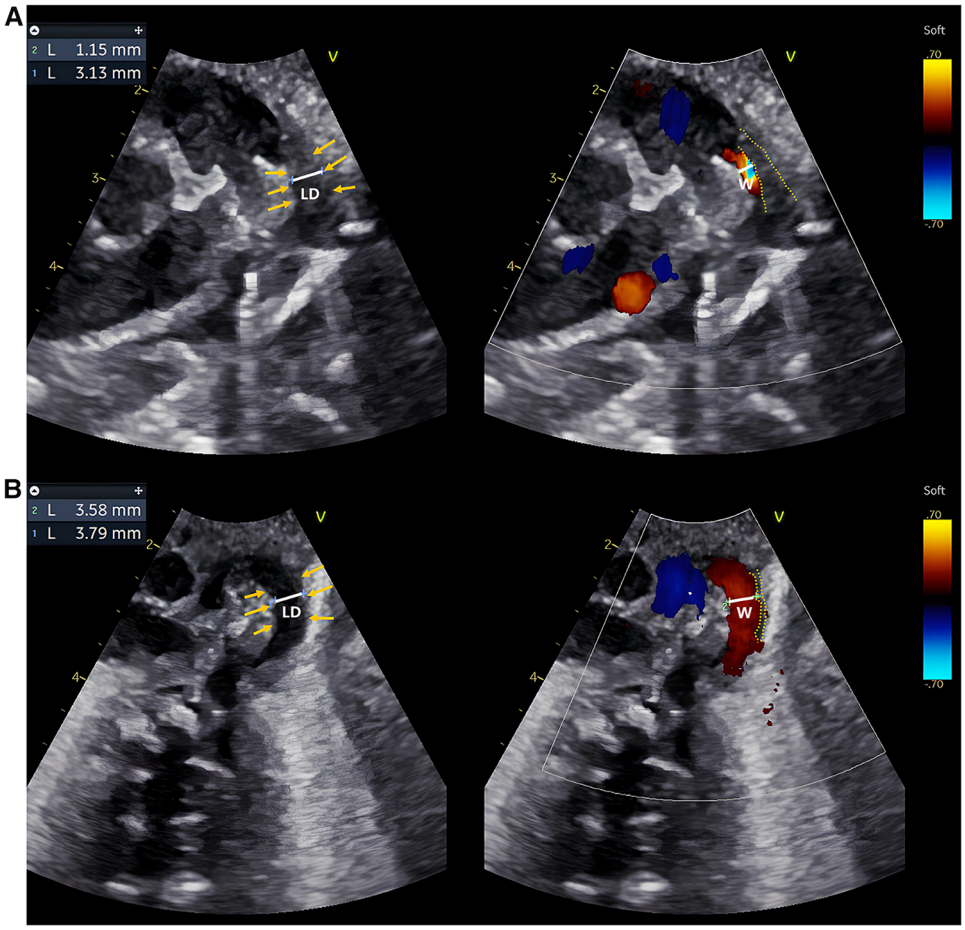

FIGURE 1
Echocardiographic IT measurements of two typical preterm infants within 24 h after birth. (**A**,**B**) are echocardiographic images obtained within 24 h after birth of a preterm infant in the DA-closure group and a premature infant in the DA-open group, respectively. Caliper 1: LD; Caliper 2: The width of the transcatheter flow bundle (W); Yellow arrows: inner margin of the wall of the DA; Yellow dashed line: the outline of the intima of the DA. The LD and W were measured at the same level at the narrowest point of the DA, and IT = (LD−W)/2. The intima of the DA appears hypoechoic, uneven, and loose. The IT of the preterm infant in the DA-closure group was thicker than in the DA-open group.

Association of It and PDA in preterm infants seven days after birth

Univariate and multivariate logistic regression models were used to evaluate the association between IT within 24 h after birth and PDA seven days after birth in preterm infants. Given the risk factors for PDA that have been characterized, potential covariates including gender, GA, birth weight, mechanical ventilation, LA/AO, Vmax, and LD were included in the multivariate model to calculate the univariate- and multivariate-adjusted OR and 95% CI of IT on DA opening outcomes in preterm infants seven days after birth, respectively.

Model development

Candidate predictors such as birth weight, application of mechanical ventilation, LVDb, the ratio of differential to maximum velocity (Vdif/Vmax), and LD were incorporated along with logIT into a multivariate logistic regression model. The final predictors were identified through bidirectional stepwise regression analysis. To assess multicollinearity among the predictors, VIFs were calculated. Once the final predictors were ascertained, they were employed to construct the definitive predictive model. An ANOVA was conducted to assess the improvement in fit between the initial and final models. A nomogram was subsequently created using the R package "rms" to represent the final logistic regression model graphically. This nomogram elucidates the predicted probability of PDA in preterm infants at seven days postpartum.

Model validation

The R package "caret" was used for internal validation of the predictive model using 10-fold cross-validation, and the reproducibility of the model was tested by accuracy and Kappa value.

Evaluation of model

The R package "riskRegression" was used to draw the receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was used to evaluate the discrimination of the model. The cut-off value of the prediction probability was determined using the ROC curve. Its validity was evaluated using sensitivity, specificity, Youden index, and likelihood ratio. The positive and negative predictive values were estimated. The calibration curve was drawn, and the relationship between the observed probability and the predicted probability was used to evaluate the calibration of the model. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the model. The R package "rms" was used to calculate the Brier score to quantify the calibration of the model. The R package "rmda" was used to conduct decision curve analysis (DCA) to evaluate the clinical utility of the predictive model based on net benefit at different risk thresholds. Net reclassification improvement (NRI) was used to compare the incremental value of single predictor logIT on the prediction power of the model.

Results

Baseline characteristics

Initially, a total of 118 preterm infants were prospectively included, but one infant with ventricular septal defect, one with pulmonary atresia, one with pericardial effusion, two with arrhythmia, one with omphalocele, four with poor image quality, and three that were discharged from hospital within seven days after birth were excluded. Finally, 105 preterm infants were enrolled in the study, of which 56 were males and 49 were females. GA ranged from 27.0 to 36.7 weeks, with a mean GA of 33.1 weeks. The rates of spontaneous DA closure and PDA were 83.8% (88/105) and 16.2% (17/105), respectively. None of the 118 preterm infants were initially treated with ibuprofen or indomethacin or underwent surgical ligation of the DA. Eight of the 17 preterm infants in the DA-open group of enrolled infants were given oral ibuprofen suspension to promote PDA closure at 8–16 days of age (median 9 days of age). None of the 105 preterm infants underwent surgical ligation of the DA. The baseline characteristics are summarized in Table 1. Compared to the DA-closure group, the DA-open group had significantly lower GA and birth weight ($p < 0.001$). Additionally, the DA-open group exhibited a higher incidence of neonatal asphyxia, RDS, and reliance on mechanical ventilation within 24 h after

TABLE 1 Characteristics of DA-closure group and DA-open group at seven days after birth in preterm infants.

	DA-closure group	DA-open group		
	$n = 88$	$n = 17$	$X^2/t/w$	p value
Male	46 (52.3%)	10 (58.8%)	0.052	0.818
GA (weeks)	34.1 (32.3, 35.1)	30.3 (29.3, 31.1)	1,338.500	<0.001
Weight (g)	2,026 ± 480	1,392 ± 313	7.048	<0.001
Asphyxia	26 (29.5%)	11 (64.7%)	6.254	0.012
RDS	14 (15.9%)	12 (70.6%)	20.024	<0.001
Ventilation	34 (38.6%)	17 (100.0%)	19.091	<0.001
LVEF (%)	68.9 ± 5.1	68.1 ± 8.8	0.353	0.728
LVDb (mm)	117.4 (105.1, 133.1)	149.8 (141.2, 168.4)	248.000	<0.001
LA/AO	1.5 (1.4, 1.7)	1.5 (1.4, 1.7)	676.000	0.534
Vmax (m/s)	2.1 (1.6, 2.4)	1.0 (0.7, 1.4)	1,270.500	<0.001
Vdif/Vmax	0.6 (0.4, 1.3)	1.7 (1.4, 2.0)	259.000	<0.001
LD (mm)	2.4 (2.1, 3.0)	3.1 (2.5, 3.7)	416.500	0.004
IT (mm)	0.17 (0.08, 0.32)	0.03 (0.01, 0.08)	1,202.500	<0.001
LogIT	−1.8(−2.5, −1.1)	−2.5(−3.4, −1.3)	1,203.000	<0.001

GA, Gestational age at birth; RDS, respiratory distress syndrome; LVEF, left ventricular ejection fraction; LVDb, body surface area corrected left ventricular end-diastolic diameter; LA/AO, the ratio of left atrial diameter to aortic root diameter; Vmax, peak velocity of left to right shunt of DA; Vdif/Vmax, the ratio of the difference of the shunt velocity of ductus arteriosus to the peak velocity; LD, lumen diameter of DA; IT, the intimal thickness of DA; logIT, the logarithm of IT.

birth ($p < 0.05$). Echocardiographically, the DA-open group demonstrated significantly lower Vmax) and elevated LVEDb and Vdif/Vmax ratio ($p < 0.001$). Moreover, the DA-open group had a significantly larger LD ($p < 0.05$) and a thinner IT ($p < 0.001$). Figure 1 showcases echocardiographic images from both the DA-closure and DA-open groups taken within 24 h after birth, highlighting the contrasting features of intimal thickness between the two groups.

Repeatability and reproducibility of IT

In our previous research, we evaluated inter-and intra-observer variability for IT measurement. The data are shown in Table 2. Our analyses showed good repeatability and reproducibility for IT measurement by echocardiography (12).

Association of IT and PDA in preterm infants seven days after birth

Univariate analysis revealed that a smaller IT (or logIT) was significantly associated with PDA in preterm infants seven days post-partum, with an OR of 0.369 (95% CI: 0.216–0.587), ($p < 0.001$). After adjusting for GA, gender, and multiple traditional risk factors, including GA, weight, ventilation, LA/AO, Vmax, and LD, having a smaller IT (or logIT) was an independent risk factor for PDA in preterm infants at seven days post-partum, with an OR of 0.383 (95% CI: 0.188–0.691), ($p = 0.003$), and OR of 0.192 (95% CI: 0.027–0.723), ($p = 0.004$), respectively.

Model development

Univariate logistic regression analysis revealed that weight, LVDb, Vdif/Vmax, LD, and logIT were significantly associated with PDA in preterm infants seven days after birth. Six predictors, including weight, ventilation, LVDb, Vdif/Vmax, LD, and logIT, were included in the model [there was no multicollinearity among the variables (vif > 2)]. After multivariate stepwise regression, five predictors, weight, ventilation, LVDb, LD, and logIT, were entered into the final model (Table 3). The fit of the final model was consistent with that of the initial model ($p = 0.759$). The final model-predicted probabilities were as follows:

$$\text{Probability} = \exp\left(\sum 5i = 1\right)/1 + \exp\left(\sum 5i = 1\right)$$

where

$$\begin{aligned}\sum 5i &= 1 \\ &= -28.497 - 0.007\,\text{weight} + 17.459\,\text{ventilation} \\ &\quad + 0.047\text{LVDb} + 3.163\text{LD} + 0.164\text{logIT}\end{aligned}$$

To facilitate the clinical application of the predictive model, the nomogram can be used to manually obtain the prediction probability of PDA in preterm infants seven days after birth (Figure 2).

Model validation

Using 10-fold cross-validation, we found that the accuracy of the predictive model was 0.935, and the Kappa value was 0.773, indicating that the model had good reproducibility.

Evaluation of the model

Figure 3 and Table 3 show that the AUC of the final predictive model (model 1) is 0.985 (95%CI: 0.966–1.000), indicating good discrimination. Using ROC curve analysis, we found that the sensitivity, specificity, and Youden index of its diagnostic score

TABLE 2 Repeatability and reproducibility of intimal thickness measurement.

	Mean ± SD	Mean ± SD	Bias	95% confidence interval (bias)	*p*	95% limits of agreement
Inter-observer variability	0.16 ± 0.13	0.17 ± 0.03	−0.01	−0.05 to 0.04	0.83	−0.14 to 0.13
Intra-observer variability	0.16 ± 0.03	0.19 ± 0.03	−0.03	−0.09 to 0.03	0.26	−0.18 to 0.13

TABLE 3 Odds ratios from the final predictive model for PDA at seven days after birth in preterm infants.

Variables		*β*	Univariate OR (95% CI)	*p* value	*β*	Multivariate OR (95% CI)	*p* value
Weight (g)		−0.007	0.995 (0.994–0.998)	<0.001	−0.007	0.993 (0.986–0.998)	0.048
Ventilation	No						
	Yes	17.539	1.57×10^{8} (7.73×10^{-33}–NA)	0.990	17.459	3.822×10^{7} (1.24×10^{-128}–NA)	0.995
LVDb (mm)		0.047	1.062 (1.034–1.099)	<0.001	0.047	1.048 (1.000–1.112)	0.071
Vdif/Vmax		−0.259	4.851 (2.266–11.902)	<0.001			
LD (mm)		3.410	3.319 (1.580,7.801)	0.003	3.163	23.649 (3.886–383.885)	0.005
LogIT		−1.913	0.013 (0.002–0.057)	<0.001	−1.808	0.164 (0.026–0.553)	0.017

Ventilation, the use of mechanical ventilation within 24 h after birth; LVDb, body surface area corrected left ventricular end-diastolic diameter; Vdif/Vmax, the ratio of the difference of the shunt velocity of DA to the peak velocity; LD, lumen diameter of DA; LogIT, the logarithm of IT.

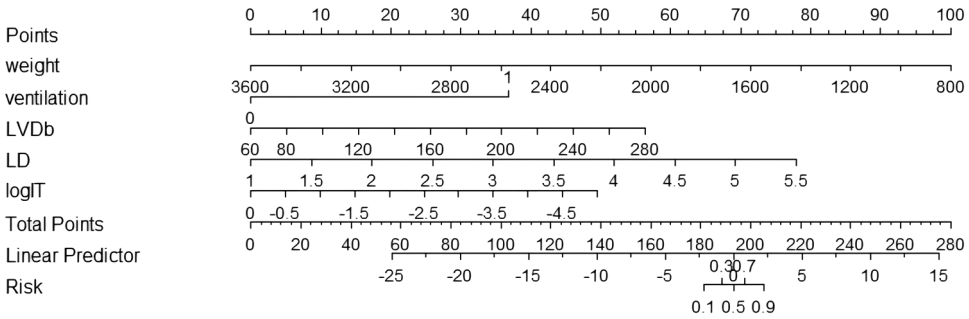

FIGURE 2
Nomogram for predicting the probability of PDA at seven days after birth in preterm infants. Ventilation, the use of mechanical ventilation within 24 h of life; LVDb, body surface area corrected left ventricular end-diastolic diameter; Vdif/Vmax, the ratio of the difference of the shunt velocity of DA to the peak velocity; LD, lumen diameter of DA; LogIT, the logarithm of IT.

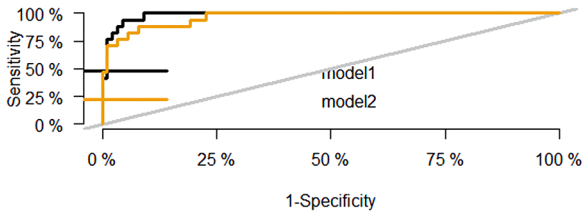

FIGURE 3
ROC curve of the predictive model for PDA at seven days after birth in preterm infants. The black curve is the ROC curve of the final predictive model based on logIT (model 1), and the yellow curve is the ROC curve of the predictive model without logIT (model 2).

TABLE 4 The evaluation of the cut-off value of the predictive model for PDA at seven days after birth in preterm infants.

Evaluation indicators	Model 1	Model 2
Cut-off value	0.114	0.251
AUC	0.985 (0.966–1.000)	0.963 (0.925–1.000)
Sensitivity	1.000	0.882
Specificity	0.909	0.920
Youden's index	0.909	0.802
Positive likelihood ratio	11.000	11.092
Negative likelihood ratio	0.000	0.128
Positive predictive value	0.680	0.682
Negative predictive value	1.000	0.976

Model 1 is the final predictive model based on logIT, and model 2 is the model with logIT removed.

were 100.0%, 90.9%, and 0.909, respectively, which were better than those of the predictive model without logIT (model 2) (AUC = 0.963, sensitivity = 88.2%, specificity = 92.0%, Youden index = 0.802), confirming that logIT had a significant effect on the diagnostic performance of the predictive model. In addition, both model 1 and model 2 had large positive and small negative likelihood ratios, indicating that these diagnostic tests were reliable. Table 4 also shows the positive and negative predictive values of model 1 and model 2.

Using the calibration curve (Figure 4), we found that the observed and predicted PDA probability had a high degree of overlap, indicating that the predictive model had a good calibration. Hosmer-Lemeshow test results showed that the goodness of fit of model 1 (χ^2 value 0.560, $p = 0.9998$) and model 2 (χ^2 value 4.418, $p = 0.8176$) were satisfactory. The Brier score of model 1 was 0.035, indicating that the final model based on logIT had a good calibration, which was better than model 2 (Brier score 0.052).

The DCA curve (Figure 5) shows that between threshold probabilities of 0.1–0.8, the net benefit of model 1 was higher than that of model 2. The final predictive model can be applied to clinical practice with broad applicability.

In addition, the NRI was 1.374, 95% CI: 0.995–1.717 ($p < 0.001$), and the proportion of correct reclassification in model 1 was

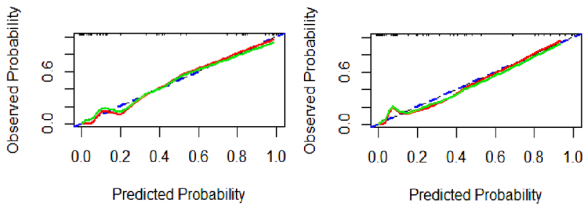

FIGURE 4
Calibration curve of the predictive model for PDA at seven days after birth in preterm infants. Model 1(A), model 2(B). The blue dashed line represents the ideal agreement between the observed and predicted probabilities. The solid red line represents the actual agreement between the observed and predicted probability. The green solid line represents the actual agreement of the correction.

increased by 137.133% compared with model 2. The addition of logIT improved the prediction accuracy of the final predictive model.

Discussion

Current medical treatment of PDA in preterm infants during hospitalization can be divided into preventive treatment delivered

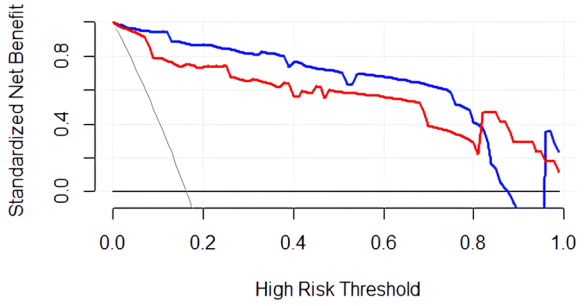

FIGURE 5
DCA curve of the predictive model for PDA at seven days after birth in preterm infants. The blue curve represents the net clinical benefit of model 1. The red curve represents the net clinical benefit of model 2.

within 24 h after birth, very early treatment delivered within the first three days of life, and early treatment delivered within the first seven days of life (13, 14). However, due to the high probability of spontaneous closure of the DA in preterm infants (15), there is controversy about treatment for PDA, both in terms of which infants to treat and when to start medications. Specific treatment options for PDA vary significantly among institutions, and different physicians may make different treatment decisions (7).

A recent meta-analysis of 14 randomized controlled clinical trials comparing the outcome indicators of very early treatment, early treatment, and expectant management of hsPDA found that very early or early drug treatment of hsPDA may not reduce the mortality rate or the incidence of PDA complications in preterm infants, but very early treatment of hsPDA may reduce the length of hospital stay in preterm infants (14). By capturing predictor data within the first 24 h postpartum and correlating them with DA status at seven days postpartum, this study aims to rapidly identify infants who might benefit from early PDA closure. Such early identification enables the initiation of treatment at an exceptionally early stage or even the deployment of preventive measures. The ultimate goals are to minimize hospital stay duration and forgo interventions for preterm infants likely to experience spontaneous DA closure, as either very early or early treatments could prove deleterious.

The clinical variables incorporated into the predictive model developed in this study are readily accessible. In most healthcare settings, echocardiographic evaluations are standard procedures for preterm infants in the first 24 h after admission to neonatal intensive care units. These evaluations routinely gather data on EF, LD, and DA flow parameters, among other metrics. By dedicating just a few additional minutes, a skilled sonographer can directly measure IT on the echocardiography machine itself, obviating the need for an auxiliary workstation. This aspect enhances the model's practical utility in a clinical context. However, IT differed from the pulmonary artery end to aortic end of the DA, and thus, a slight difference in the measured IT could lead to variation. The dynamic images were played back during systole to the frame in which the flow bundle and the intima were best displayed, and then measurements on different frames of the image resulted in differences. Our analyses showed good repeatability and reproducibility, indicating that small differences in the measured level or frame had only a minor influence on the IT results.

In the multivariate logistic regression model, significant differences existed in GA, weight, RDS, ventilation, LVDb, Vmax, Vdif/Vmax, IT, and logIT between the DA-closure group and the DA-open group in the baseline data. Weight was included and GA was not included among the candidate predictors, due to the well-known strong correlation between weight and GA. Ventilation was included and RDS was not included, since ventilation is a common treatment for RDS in neonatal care units. Vdif/Vmax was included and Vmax was not included, due to the apparent collinearity of Vmax and Vdif/Vmax.

Permanent DA closure is a nuanced process involving both functional closure through muscle contraction and anatomical closure via morphological and molecular remodeling. This complex process is modulated by multiple regulatory mechanisms, including but not limited to prostaglandin E2 and arterial oxygen partial pressure (16–18). A series of histological changes ensue, including the deposition of extracellular matrix under the endothelium, disintegration of the inner elastic layer, a loss of elastic fibers in the media, and migration of smooth muscle cells into the media. The contraction of the DA lumen and intimal growth co-occur after birth, eventually forming the arterial ligament (19–21). In our previous study, we described the ultrasonic imaging characteristics of DA structure and measured IT using echocardiography, which previously had been described only by histopathology. We found that neonates without spontaneous DA closure at three days of life tended to have thinner IT and slower IT growth rates. These neonates also had a lower IT/LD within 24 h after birth than those with spontaneous DA closure by three days of life (12). In this study, the predictive model based on IT demonstrated high internal validation accuracy. The final predictive model, including logIT, increased the model's discrimination degree without IT and the diagnostic efficiency. Its clinical diagnostic results are reproducible, and it has good calibration and broad clinical applicability.

Consistent with previous studies, GA and birth weight significantly influenced spontaneous DA closure (8, 22, 23). Since birth weight is directly related to gestational age, only birth weight was included in the model construction. Here, neonatal asphyxia and RDS incidence were higher in the DA-open group. Since asphyxia or RDS is often treated with mechanical ventilation in the neonatal intensive care unit (24), previous studies have found that mechanical ventilation is independently associated with an increased risk of requiring treatment for PDA (25). Invasive respiratory support is an important predictor of requiring surgical intervention for PDA (26). We, therefore, included only the use of mechanical ventilation in the model construction. Both birth weight and mechanical ventilation were used in the final model.

Previous studies have found that abnormal DA flow patterns predict hsPDA, and parameters such as Vmax or ratio of Vmax to end-diastolic velocity can predict spontaneous DA closure (2, 11, 27). Since the shunt volume of the DA is determined by the DA resistance and the pressure gradient between the aorta and the pulmonary artery, the former depends on the intrinsic properties of the DA shape and diameter. The latter can be reflected by Vmax (28, 29). We speculated that Vdif reflects the fluctuation of the pressure gradient between the aorta and the pulmonary artery and could be used as a surrogate for the flow pattern. The larger the Vdif, the more significant the fluctuation and the more tendency toward an abnormal DA flow pattern (i.e., a growing or pulsatile pattern) (2). We introduced a new parameter in this study, Vdif/Vmax, to account for this dual effect. Vdif/Vmax differed significantly between the two groups and significantly correlated with PDA in univariate regression. However, it was omitted in the final regression model. The utility of this new DA flow parameter merits further study.

LD and LA/AO are common echocardiographic parameters used in previous studies to predict a future PDA requiring intervention (27, 30–32). In this study, LD differed significantly between the two groups and entered the final predictive model. Increased LVEDd is associated with hsPDA (1, 2), which was included in the model construction parameters after correction with BSA to account for the effect of birth weight. LVDb was also included in the final predictive model.

Several limitations must be acknowledged in the interpretation of this study's findings. First, the small sample size restricts external validation and call into question the generalizability of the predictive model. This was a single-center study in southern China, and IT was only reported by our team in the study population of our center. We look forward to future multi-center research with different races and across different regions. Furthermore, the study did not conduct subgroup analyses focusing on very premature or low birth weight infants, potentially limiting the model's specificity for high-risk populations. However, the debate over very early treatment, early treatment, and expectant management is an issue faced by all preterm infants younger than 37 weeks of gestation (14). We intend to expand the sample size in future studies with the goal of achieving a model that will be more representative of younger preterm infants in future studies.

In conclusion, this study successfully develops a predictive model for PDA in preterm infants seven days postpartum based on the ultrasound measurement of IT of the DA within 24 h after birth. This model facilitates the early identification—within 24 h postpartum—of infants that may benefit from DA closure, thereby informing treatment decisions.

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 The Ethics Committee of the Children's Hospital of Soochow University approved the study (Ethics Approval Number: 2021CS151). 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

X-LH: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. T-TZ: Data curation, Investigation, Writing – original draft. HW: Conceptualization, Methodology, Writing – review & editing. CH: Data curation, Investigation, Writing – original draft. J-CN: Data curation, Writing – original draft. Z-FZ: Data curation, Writing – original draft. X-CL: Data curation, Writing – original draft. HP: Formal Analysis, Supervision, Writing – review & editing. HL: Resources, Writing – review & editing. LS: Conceptualization, Supervision, Writing – review & editing. Q-QX: Conceptualization, Funding acquisition, Resources, 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

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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Elizabeth Sharpe,
The Ohio State University, United States
Palanikumar Balasundaram,
University of Illinois at Rockford, United States
Alexandra Dinis,
Coimbra Hospital and University Center, Portugal
Hercília Guimarães,
University of Porto, Portugal

*CORRESPONDENCE
Mohammad A. A. Bayoumi
✉ moh.abdelwahab@hotmail.com

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Comparing conventional and modified Seldinger techniques using a micro-insertion kit for PICC placement in neonates: a retrospective cohort study

Matheus F. P. T. van Rens[1,2], Kevin Hugill[3], Robin van der Lee[1], Airene L. V. Francia[2], Fredericus H. J. van Loon[4,5] and Mohammad A. A. Bayoumi[2]*

[1]Neonatal Intensive Care Unit, Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, Netherlands, [2]Neonatal Intensive Care Unit, Women's Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar, [3]Department of Nursing and Midwifery Education, Hamad Medical Corporation, Doha, Qatar, [4]Anesthesiology, Intensive Care and Pain Medicine, Catharina Hospital, Eindhoven, Netherlands, [5]Faculty of PeriOperative Care & Technology, Institute of People and Health Sciences, Fontys University of Applied Sciences, Eindhoven, Netherlands

Objective: This study aims to assess the comparative effectiveness of a conventional splitting needle or a peelable cannula vs. the modified Seldinger technique (MST) by utilizing a dedicated micro-insertion kit across various clinically significant metrics, including insertion success, complications, and catheter-related infections.

Methods: We conducted a retrospective observational cohort study using an anonymized data set spanning 3 years (2017–2019) in a large tertiary-level neonatal intensive care unit in Qatar.

Results: A total of 1,445 peripherally inserted central catheter (PICC) insertion procedures were included in the analysis, of which 1,285 (89%) were successful. The primary indication for insertion was mainly determined by the planned therapy duration, with the saphenous vein being the most frequently selected blood vessel. The patients exposed to MST were generally younger (7 ± 15 days vs. 11 ± 26 days), but exhibited similar mean weights and gestational ages. Although not statistically significant, the MST demonstrated slightly higher overall and first-attempt insertion success rates compared to conventional methods (91 vs. 88%). However, patients undergoing conventional insertion techniques experienced a greater incidence of catheter-related complications ($p < 0.001$). There were 39 cases of catheter-related bloodstream infections (CLABSI) in the conventional group (3.45/1,000 catheter days) and eight cases in the MST group (1.06/1,000 catheter days), indicating a statistically significant difference ($p < 0.001$). Throughout the study period, there was a noticeable shift toward the utilization of the MST kit for PICC insertions.

Conclusion: The study underscores the viability of MST facilitated by an all-in-one micro kit for neonatal PICC insertion. Utilized by adept and trained inserters, this approach is associated with improved first-attempt success rates, decreased catheter-related complications, and fewer incidences of

CLABSI. However, while these findings are promising, it is imperative to recognize potential confounding factors. Therefore, additional prospective multicenter studies are recommended to substantiate these results and ascertain the comprehensive benefits of employing the all-in-one kit.

KEYWORDS

neonate, neonatal intensive care unit (NICU), vascular catheters, modified Seldinger technique (MST), peripherally inserted central catheter (PICC), complications, newborn, central line-associated blood stream infection (CLABSI)

Introduction

Peripherally inserted central catheters (PICC) are routinely used for sick term and preterm neonates. These devices can be conveniently inserted percutaneously at the bedside and represent a sizable proportion of the central vascular access devices (CVAD) used for vascular access (VA) in neonatal intensive care units (NICU) (1–5). Typically, they are inserted to provide reliable intravenous access for prolonged therapy durations and parenteral nutrition or for infusion therapy in cases of difficult intravenous vascular access (DIVA) (1, 4–6). PICCs used in these circumstances are reported to have lower complication rates compared to short peripheral IV catheters (PIVC) or umbilical venous catheters (UVC) (1, 6–13).

Recognizing PICC candidates early, having an experienced inserter with a developed understanding of neonatal anatomy, and choosing the optimal vein using technological aids for vessel selection and catheter tip placement all help increase the likelihood of a successful placement (6, 7, 13, 14–16). However, PICC insertion is often complicated by the neonate's small size, the fragility of their blood vessels, and previous use of peripheral veins for PIVC use (6, 7, 10, 12). Traditionally, in neonates, PICCs were inserted using a combination of split needle or peelable cannula techniques (5, 16). This approach is supported by a range of commercially available and dedicated medical products and remains a popular choice among many clinicians.

The modified Seldinger technique (MST) is a development of the classic Seldinger technique. The classic Seldinger technique, which was named after its developer and exponent, typically involves several distinct steps. The first step is the needle puncture of the target blood vessel and then the insertion and threading of a flexible guidewire to the estimated final tip location, followed by the removal of the puncture needle. Next is the dilation of the vessel using a dilator before passing the catheter over the guidewire to its intended location. The final step is the removal of the guidewire leaving the catheter *in situ*. The MST is subtly different from the classic technique in its steps. It was developed to take advantage of the advances in VA equipment design and address some of the shortcomings of the original technique (6, 7).

The MST is used for the minimally invasive percutaneous placement of CVCs with the assistance of a guidewire inserted into a suitable dilated peripheral blood vessel (6, 7, 16, 17). Typically, the technique involves a needlestick with a puncture needle, followed by the insertion of a short guidewire. The needle is then removed. Using a guidewire and an insertion aid, a combined dilator and peelable cannula are inserted over the guidewire into the blood vessel lumen. The guidewire and insertion aid are then removed. The catheter is fed through the dilator/cannula and threaded to its desired tip position before the dilator/cannula itself is withdrawn and peeled apart to separate it from the catheter for disposal (6, 7, 16–20). Catheter stabilization, securement, dressing, and confirmation of the correct catheter tip location using medical technologies are similar between the two approaches (6, 7).

The MST has been widely adopted in pediatric and adult populations, but minimum blood vessel diameters precluded its use in smaller patients. In recent years, the technological advances in VA device design, particularly with smaller sizes becoming available, have led to this technique being used in NICUs (16). More recently, all-in-one MST kits with micro components suitable for use with neonates have been made commercially available. These kits contain matched micro bore needles, vein dilators, and guidewires supporting the insertion of neonatal-size PICCs into smaller, more superficial peripheral veins while potentially decreasing venous trauma and enhancing first-attempt insertion success rates (4, 16–20). In this article, for clarity, we refer to proprietary all-in-one micro-component MST kits as "micro-MST kit." This phrasing acknowledges the neonate compatible size of its components and relationship to the MST insertion technique and differentiates this kit from more traditional *ad hoc* combinations of equipment for MST.

To date, there are few comparative reports on the use of micro-sized MST kits or factors affecting their use in neonatal populations (14). In this article, we present a study that evaluates the MST using the micro-MST kit against conventional PICC insertion techniques (split needle or peelable cannula). The measures of insertion success, therapy completion or failure (necessitating early unplanned catheter removal), and infection rates, which are clinically important outcomes affecting the overall success or failure of IV therapy, are reported herein.

Materials and methods

A retrospective observational cohort study design was used. The study objective was to evaluate different methods of PICC insertion (i.e., conventional: steel splitting needle or peelable cannula and a modified micro-Seldinger technique insertion kit) in NICU neonates to identify the most effective technique for reducing complication rates (specifically, first-attempt insertion success, therapy completion, and infection) among the study population.

The primary outcome measure consisted of the successful insertion of a PICC, encompassing both the completion of the insertion procedure itself and the accurate positioning of the catheter tip in accordance with international guidelines (6, 7). The process measures involved the percentage reaching the end of therapy without related complications. The study protocol was approved by an institutional review board (MRC-01-22-626).

PICC insertion

Historically, in our unit, all PICCs, except those surgically inserted, were inserted using either a steel splitting needle or peelable cannula, each manufactured/distributed by the medical equipment company, Vygon:

- Microflash, a 20G peelable cannula introducer for 1 and 2Fr PICCs
- Siliconized stainless-steel 24G Splitting needle for the insertion of 1Fr catheters

A review of internal audit data showed a high number of complications related to the stainless-steel splitting needle technique, including infusate leakage, puncture, and breakage of catheters. While the peelable cannula technique had fewer insertion-related issues, the first-attempt success rates were lower. This observation was felt to reflect the clinician's skill level, familiarity with a particular technique, and lack of standardized training. With the formal establishment of a multi-professional neonatal VA team (NeoVAT), this situation changed (14). This team was exposed to evidence-based training and education based on international standards and care bundles (6, 7, 15) and a standardized confirmation of competence assessment. They now provide a dedicated VA service (14). In 2017, following a period of orientation and training, the micro-MST using a Vygon Microsite insertion kit containing a 24G puncture needle, a flexible nitinol guidewire, a guidewire insertion aid, and a 20G peelable combined dilator/cannula was introduced as an option for PICC insertion. Figure 1 illustrates the three PICC insertion devices.

In the study unit, MST using the micro-MST approach follows the established evidence-based standard procedures (6, 7, 15) outlined in the Introduction section and described previously (16). For readers less familiar with neonatal PICC insertion using the MST, short audio–visual presentations are readily available, for example, https://m.youtube.com/watch?v=z4zcmY1DrVE and https://vimeo.com/478943739, which show the steps involved.

During the initial patient assessment, the NeoVAT uses a locally developed mnemonic—the "5 Rights for Vascular Access"—to ensure the selection of the right device for the right vein when administering the right therapy for the right duration and for the right patient (4, 15, 21). This systematic approach used in in-house training programs helped maintain a standardized and patient-centric practice during VA. Evidence-based care bundles of preventative infection control measures for insertion site dressing and dressing changes, catheter-related bloodstream infections (CLABSI) prevention together with a daily consideration of the need for continued VA, and planned removal are implemented and routinely audited.

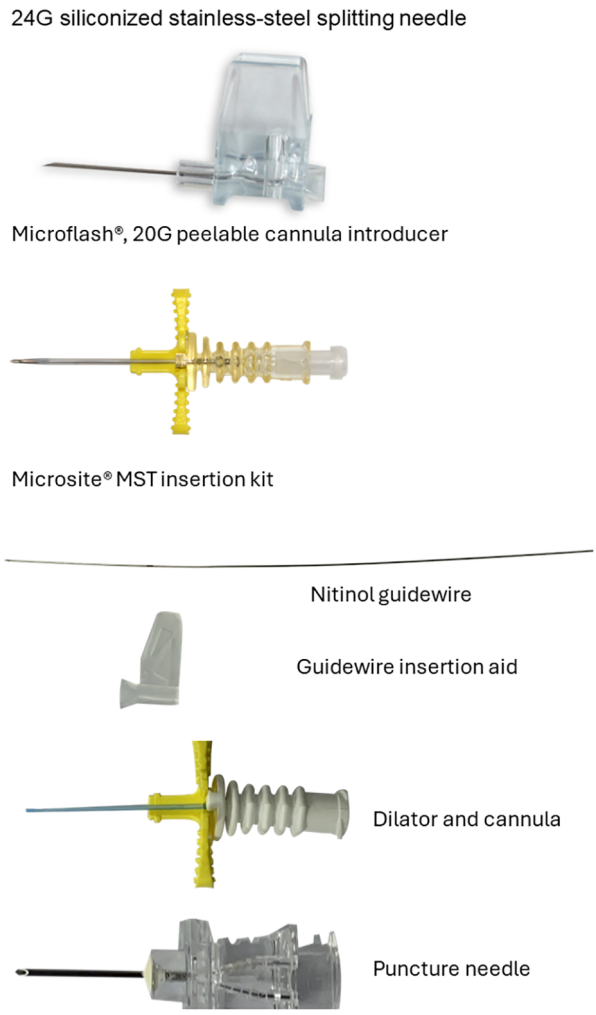

FIGURE 1
Peripherally inserted central catheter (PICC) insertion devices. Images courtesy of and used with permission from Vygon, France.

Data

Routinely collected anonymized VA data were collected between 1 January 2017 and 31 December 2019. The study was carried out in the NICU of the Women's Wellness and Research Centre (WWRC) of the Hamad Medical Corporation (HMC, Doha, Qatar). The data collected were sex, Gestational age (GA) at birth, age at time of insertion, birth weight, reason for insertion, vein used, technique used for insertion, success of insertion, dwell time, reason for removal, and presence of infection.

Participants and sample size

The study site was a large 112-bed tertiary-level NICU with approximately 4,000 admissions yearly. Approximately 500

PICCs are inserted each year. The study population included all neonates admitted to the NICU requiring a PICC for IV fluids, parenteral nutrition, administration of medications, or DIVA defined as requiring more than three PIVCs in 24 h.

Neonates were excluded from the data if VA devices other than PICCs were used (e.g., PIVCs and umbilical or surgically inserted central catheters). To ensure a maximal set of data and the inclusion of all eligible participants, the NeoVAT members checked patient charts each day for any omissions.

Statistical analysis

The data were analyzed based on the PICC insertion method and the device used. The analysis of the patient characteristics and outcome variables was summarized using descriptive measures expressed as mean (standard deviation) or median (minimum–maximum) for continuous variables and frequencies expressed as percentages for categorical variables. The assumption of normal distribution was determined with Kolmogorov–Smirnov testing. To detect the significance between dependent and independent variables, Chi-squared test, unpaired *t*-test, Mann–Whitney *U* test, or one-way analysis of variance was used, as appropriate. *Post hoc* analyses [Tukey honestly significant difference (HSD) test] were used to detect the differences between subgroups. SPSS (version 27.0) was used for all statistical analyses, with $p < 0.05$ representing the level of significance.

Results

Overview

Between 1 January 2017 and 31 December 2019, a total of 1,445 insertion procedures were recorded (Table 1). The patient characteristics were reported for all 1,445 neonates. In addition, data on catheter characteristics, complication rates, associated factors for complications, and number of insertion attempts are reported.

The mean birth weight was 1,269 g (±639) in the conventional insertion group and 1,344 g (±681) in the micro-MST group. The mean GA was 29.5 (±3.9) weeks in the conventional insertion group and 29.8 (±3.9) weeks in the micro-MST group. The most common diagnosis for admission was prematurity.

In Table 2, the reasons for the PICC insertion and the specifics regarding the fluids and DIVA are presented. The larger majority of the inserted PICCs were used for prolonged intravenous therapy either for parental nutrition and/or medication. The patient characteristics were mainly related to weight [≤1,500 g, as per local protocols (15, 20, 22)] and difficult intravenous access. The fluid characteristics of the parental nutrition or related medication included a pH of <5 or >9 and an osmolarity of >600 mOsm/L as per local protocols (16, 21, 23). The analysis of the choice of the "vein inserted" data indicated a difference between the conventional and micro-MST study groups in terms of the selected puncture site/inserted vein ($p = 0.011$). The lower limbs were targeted most often for insertion, and the most common vein used for both groups was the saphenous vein (67% for conventional and 76% for micro-MST).

TABLE 1 Baseline demographic characteristics of the study participants.

		Conventional insertion ($n = 887$)	Micro-MST ($n = 558$)	*p*-value
Sex				
Male	792	479 (54%)	313 (56%)	0.437
Female	653	408 (46%)	245 (44%)	
Age (days) at insertion, mean ± SD		11 ± 26	7 ± 15	0.001
Gestational age (GA) at birth (weeks)				
23–27	359	222 (25%)	137 (25%)	
28–31	655	412 (47%)	243 (44%)	
32–36	224	110 (12%)	114 (20%)	
≥37	207	143 (16%)	64 (11%)	
GA mean ± SD (weeks)		29.5 ± 3.9	29.8 ± 3.9	0.051
Birth weight (g)				
≤999	504	342 (39%)	162 (29%)	<0.001
1,000–1,499	632	383 (43%)	249 (45%)	
1,500–2,499	202	90 (10%)	112 (20%)	
≥2,500	107	72 (8%)	35 (6%)	
Birth weight, mean ± SD		1,269 ± 639	1,344 ± 681	

SD, standard deviation.

PICC insertion success by method and device

In a total of 1,445 insertion procedures, 1,286 catheters (89%) were successfully inserted (Table 3). Table 3 shows the insertion success of the individual devices as per group (i.e., micro-MST and conventional) and as per insertion device type (i.e., Microsite,

TABLE 2 Reason for the peripherally inserted central catheter (PICC) insertion and targeted blood vessel.

Reason for insertion	Total $n = 1,445$	Conventional insertion ($n = 887$)	Micro-MST ($n = 558$)	*p*-value
Duration of therapy	1,368	865 (97.5%)	503 (90.1%)	<0.001
Fluid characteristics[a]	27	7 (0.8%)	20 (3.6%)	
Patient characteristics[b]	50	15 (1.7%)	35 (6.3%)	
Targeted blood vessel				
Limb extremity inserted				
Upper	421	292 (33%)	129 (23%)	<0.001
Lower	1,024	595 (67%)	429 (77%)	
Vein inserted				
Axillary	2	1 (0.1%)	1 (0.2%)	0.011
Basilic	34	21 (2.4%)	13 (2.3%)	
Brachial	10	8 (0.9%)	2 (0.4%)	
Cephalic	56	39 (4.4%)	17 (3.0%)	
Cubital	310	216 (24.4%)	94 (16.8%)	
Dorsal	7	5 (0.6%)	2 (0.4%)	
Femoral	1	0 (–)	1 (0.2%)	
Jugular	2	2 (0.2%)	0 (–)	
Saphenous	1,023	595 (67.0%)	428 (76.7%)	

[After, (15, 20, 22)].

[a]pH (<5 or >9) and/or osmolarity (>600 mOsm/L).

[b]Weight (≤1,500 g) and/or difficult intravenous vascular access (DIVA) (>3 peripheral IV within 24 h).

TABLE 3 Peripherally inserted central catheter (PICC) insertion success by method and device.

		Conventional insertion ($n = 887$ attempts)		Micro-MST ($n = 558$ attempts)	p-value
Successful insertions	1,286 (89%)	781 (88%)		505 (91%)	0.130
Number of attempts of successful insertion (median and IQR)		1.7 1 (1–6)		1.4 1 (1–4)	<0.001
		Conventional insertion		Micro-MST	
		Microflash $n = 485$	Splitting needle $n = 403$	Microsite $n = 558$	
Successful insertions		432 (89%)	349 (87%)	505 (91%)	0.163
Number of attempts of successful insertion (IQR)		1 (1–5)	1 (1–6)	1 (1–4)	

IQR, interquartile range.

Microflash, and Splitting needle). The success rate was slightly higher for MST (91% success vs. 88%). The difference increased when analyzing the used insertion needle type. Microsite used micro-MST as an insertion technique and showed significant differences with either Microflash or the Splitting needle. The same was observed when analyzing the number of attempts to one successful insertion, that is, micro-MST showed a significantly higher success rate.

The use of the Microsite device resulted in the highest first-attempt success rate of insertion when compared to conventional Microflash and Splitting needle. *Post hoc* analyses resulted in the significance between Microsite and Microflash ($p < 0.001$), Microsite and Splitting needle ($p = 0.001$), and Microflash and Splitting needle ($p = 0.013$).

Over the course of 3 years, there was a noticeable change in the pattern of usage of conventional insertion needles, as illustrated in Figure 1. In 2017, the Splitting needle was used in 63% of the cases (302 out of 478), but by 2019, it was utilized in only 6% of cases (28 out of 496). Simultaneously, the use of the Microflash insertion needle increased from 34% (163 out of 478) in the first year to 55% (257 out of 471) in the second year of the study. However, its use experienced a decline in the final study year, dropping to 13% (64 out of 496). Conversely, the use of the micro-MST kit exhibited a consistent upward trend in utilization, starting at 3% (13 out of 478) in 2017 and reaching 81% (404 out of 496) in 2019 (Figure 2).

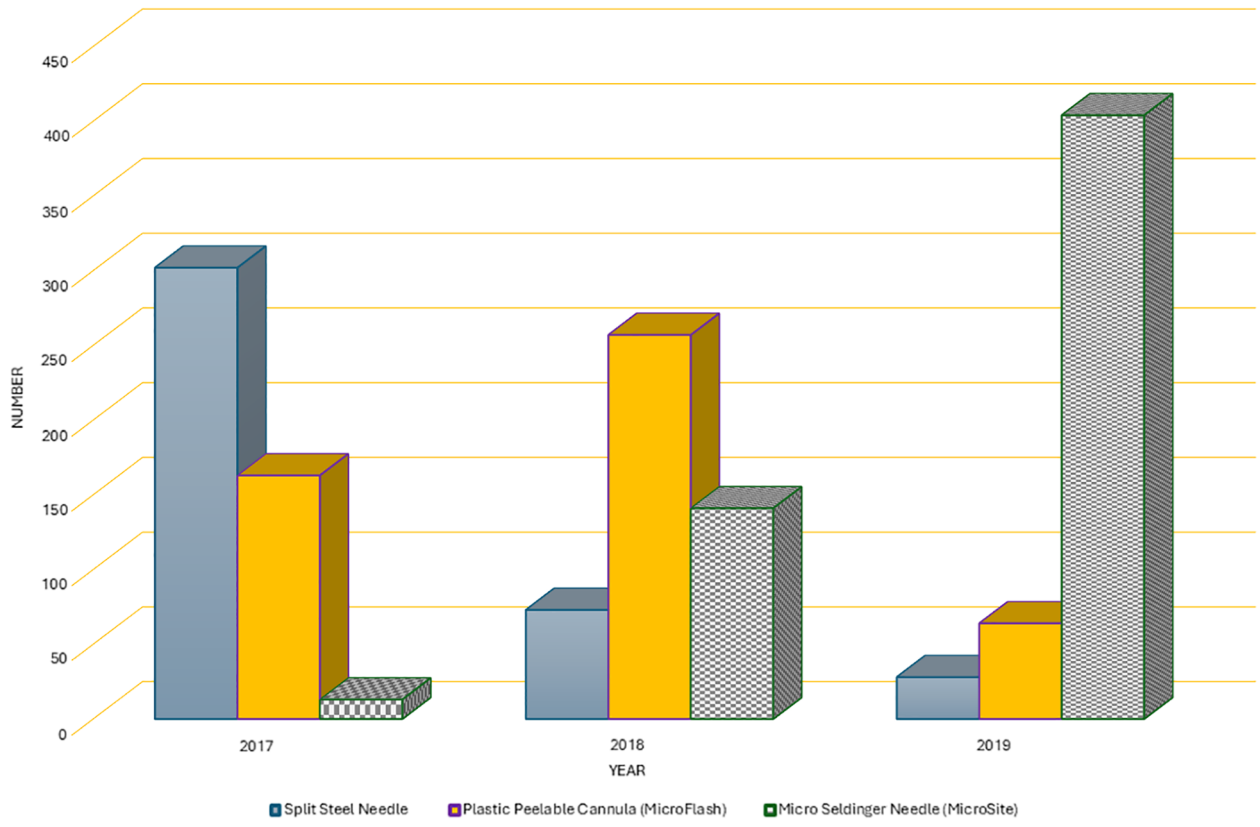

FIGURE 2
Insertion device use over 3 years.

Complications

Comparing conventional insertion techniques with the micro-MST insertion kit, there was a significant difference in the reasons for catheter removal or successful end of therapy (Table 4). Detailed analyses per type of technique device used were in favor of Microsite devices/technique. The failure rate for micro-MST was 14% vs. Microflash with 19% and Splitting needle with 25%. While the dwell time was not significantly different, it demonstrated an improvement when the micro-MST kit was utilized.

Central line-associated bloodstream infection

The definition of a CLABSI diagnosis lacks consistent clinical diagnostic criteria, and the use of that term can vary between settings (7). In this study setting, the definition of CLABSI and the calculation of its incidence rate aligned with the definitions of the US Centers for Disease Control and Prevention (CDC) (24). In essence, CLABSI was confirmed in the presence of a laboratory-confirmed bloodstream infection not associated with any other infection site and developed within 48 h of the central line insertion. The CLABSI rate is defined as the number of CLABSI infections per 1,000 central line days. The occurrences of CLABSI in this study are presented in Table 5. Micro-MST (Microsite) showed the lowest CLABSI rate (1.6%). Combined and individually conventional insertion techniques showed a 5.0% (4.9 and 5.1) CLABSI rate.

TABLE 5 Central line associated bloodstream infection (CLABSI).

	Conventional insertion ($n = 781$)		Micro-MST ($n = 505$)	*p*-value
CLABSI diagnosed[a]	39 (5.0%)		8 (1.6%)	0.001
Incidence[b]	3.45		1.06	
	Conventional ($n = 781$)		Micro-MST ($n = 505$)	
	Microflash ($n = 432$)	Splitting needle ($n = 349$)	Microsite ($n = 505$)	
CLABSI[a]	22 (5.1%)		17 (4.9%)	8 (1.6%)	0.006
Incidence[b]	3.44		3.47	1.06	

[a]CLABSI is defined as a laboratory-confirmed bloodstream infection not associated with any other infection site and developing within 48 h of the central line insertion (21).
[b]CLABSI incidence rate per 1,000 catheter days.

Discussion

The neonates in the micro-MST group generally had a younger mean age compared to that in the conventional insertion group. There was no evidence that inserters chose the micro-MST for younger patients, and the gradual transition to greater use of the micro-MST approach over the study duration did not support this reasoning. It is possible that this observation might reflect greater utility and adherence to the VA route and device selection algorithm used in the study site (16, 21). This tool advocates for earlier selection of central vascular routes, such as PICC, when it is anticipated that intravenous therapy will be prolonged and would affect the age at which PICCs were inserted.

A detailed cost-effectiveness analysis of the two approaches to the PICC insertion was beyond the scope of this study. Some commentaries suggest that despite the additional cost of MST

TABLE 4 Reasons for the removal of the peripherally inserted central catheter (PICC).

	Totals	Conventional insertion ($n = 781$)	Micro-MST ($n = 505$)	*p*-value
Reason for removal				
1. Therapy completed	952 (74%)	551 (71%)	401 (79%)	0.001
2. Therapy failure[a]	242 (19%)	171 (22%)	71 (14%)	
Catheter-related complications[b]	100	72	28	
Maintenance-related complications[c]	142	99	43	
3. Administrative censoring[d]	92 (7%)	59 (7%)	33 (7%)	
Dwell time in days, mean ± SD		14.5 ± 8.7	14.9 ± 8.2	0.356
	Microflash $n = 432$	Splitting needle $n = 349$	Microsite $n = 505$	*p*-value
1. Therapy completed	316 (73%)	235 (67%)	401 (79%)	<0.001
2. Therapy failure[a]	84 (20%)	87 (25%)	71 (14%)	
Catheter-related complications[b]	31	41	28	
Maintenance-related complications[c]	53	46	43	
3. Administrative censoring[d]	32 (7%)	27 (8%)	33 (7%)	
Dwell time in days, mean ± SD	14.8 ± 8.4	14.1 ± 9.0	14.9 ± 8.2	0.343

SD, standard deviation.
[a]Therapy failure = catheter-related and maintenance-related complications.
[b]Catheter-related complications are defined as leaking, infiltration/extravasation, breakage of the catheter, and phlebitis.
[c]Maintenance-related complications are defined as accidental removal, tip migration, and occlusion.
[d]Administrative censoring = death and neonates transferred out to another facility.

equipment, the overall costs are in favor of MST (6). Studies that attempted to analyze the economic effects of using MST for the PICC insertion suggest cost-neutral or slight economies (17, 19) However, when factors, such as the local pricing of MST equipment and staff salary, which vary between hospital facilities and internationally, and fewer insertion attempts are combined with the economic costs related to the local incidence of CLABSI, then the cost-effectiveness analysis becomes more complex. Further study using more sophisticated economic modeling is required to fully articulate the economic cost and benefits of MST.

Insertion success

Both first time and overall PICC insertion success using the micro-MST approach was associated with increased insertion success compared to conventional techniques. However, in this study, the difference was not statistically significant. Wald et al. (18), using a specially modified bespoke MST insertion kit, reported a successful insertion in 14 of 16 cases. Other studies reported statistically significant improvements in insertion success. One example, Gibb and MacLeod et al. (17, 19) reported statistically significant improvements in insertion success when using a micro-MST kit similar to that used in this study compared to the splitting needle technique. However, these results need to be set in context. Gibb et al. and MacLeod et al. (17, 19) reported a comparatively lower first-attempt and overall insertion success rates for both techniques (MST 53% vs. 26% for steel splitting needle, overall, 72% vs. 40%) and more attempts to obtain VA (MST 2.5 vs. steel splitting needle 6.5) when compared to this study. This makes a direct comparison between these studies problematic.

Complications

Two groups of non-infective complication were detailed in this study, that is, catheter related (leaking catheter, infiltration/extravasation, phlebitis, and catheter breakage) and maintenance related (tip migration, accidental catheter removal and occlusion). While these were defined in the database, they were not differentiated and therefore not available for further subgroup analysis. Consequently, we are unable to comment on the relative significance of these subgroups beyond the observation that, taken together, they did not statistically affect the comparative catheter dwell times.

The duration and frequency of clinical procedures, particularly those such as needlesticks associated with pain and discomfort, can have important implications for patient and parent welfare (25–27). The choice of catheter, insertion device, and insertion technique must be based upon a thorough assessment of the need for the prescribed therapy, blood vessel health and suitability for the intended catheter diameter and flow rate, possibility of DIVA (pre-existing or developing), and skill set of the inserter (6, 7, 15, 16), which have a bearing on patient experience, insertion success, and likelihood of complications. Reports (20) suggest that MST approaches involve more preparatory steps, which can be time consuming for those new to this technique and invariably require a period of training and practice for mastery. It might be that ongoing training, increased NeoVAT team cohesion, and the increased familiarity of staff with the micro-MST approach help explain the transition to greater use of this technique over the study time.

Speculatively, several interventions could have contributed to the high rates of first-attempt successful insertion and the lower incidence of catheter-related complications reported in this study. First, these might be related to the nature of the micro-MST approach and the intrinsic design characteristics of the kit, which are intended to inflict less trauma on the blood vessel endothelial wall. Second, these might be related to limiting the PICC insertion to a dedicated and highly trained group of staff (14). Third, it could be that the greater attention to vein preservation strategies and vein assessment, as advocated for by the routinely used 5-Rights mnemonic, was instrumental (4, 16, 21). For example, in this study, incorporating a system for routine systematic vein assessment could have aided insertion success and reduced complications by avoiding suboptimal veins. The embedding of this approach into routine practice might also offer an explanation for the greater selection of the saphenous vein in the micro-MST group as fewer instances of prior vessel use and compromise were likely to be encountered ensuring the vein suitability for the PICC insertion. However, further development of this tool and research to validate it and explore the implications in practice of its use are required.

CLABSI

Reductions in CLABSI rates reported in this study using the micro-MST align with those reported in other neonatal studies (28, 29). Experiencing fewer episodes of skin breakage due to fewer attempts, reduced blood loss, and reduced trauma to the blood vessels due to the dilation technique and guidewire depth reported with MST might explain this finding (16–20). However, it is important to avoid overinterpreting this relationship. In this study, only a limited number of the multifactorial variables known to affect the incidence of CLABSI were included in the analysis. For example, previous studies highlighted the effects of adherence to preventative infection control care bundles (6, 7, 9, 11, 22, 23, 30–32) using closed-circuit infusion sets (32) and cyanoacrylate-based tissue adhesive to secure lines and seal insertion sites (22, 23), which were not analyzed here. Further large-scale interventional studies are required to separate the relationships between CLABSI and the PICC insertion technique in everyday clinical situations.

Strengths and limitations

This study represents a valuable contribution to the limited body of research comparing various PICC insertion techniques specifically within the neonatal population. Despite its strengths, such as the inclusion of a sizable patient cohort, several methodological considerations warrant discussion.

The retrospective, single-center design employed in this study inherently introduces potential biases and limitations. Notably, the lack of randomization and the reliance on retrospective data collection may have introduced selection bias and confounding variables, thereby impacting the internal validity of the findings. Additionally, the retrospective nature of the study limits our ability to control all potential confounders, including changes in practice patterns over time. It is crucial to acknowledge the possibility of inserter variability and unrecorded shifts in procedural techniques or institutional protocols, which could have influenced the observed outcomes. However, the implementation of a dedicated team for PICC insertion, along with standardized training and educational programs, likely helped mitigate some of these potential sources of variability.

Despite the abovementioned limitations, this study provides valuable insights into the comparative effectiveness of different PICC insertion techniques in neonates. Future research endeavors should aim to address these limitations by employing prospective, multicenter study designs with stringent control measures. Such studies would not only validate these findings, but also offer a more nuanced understanding of optimal neonatal PICC insertion practices. Emphasis should be placed on the greater accounting of the multifaceted aspects of PICC insertion and use, as well as the potential impact of adherence to care bundles, promotion of comfort, provision of pain relief, utilization of tissue adhesive, and proactive removal strategies on the likelihood of CLABSI occurrence.

Conclusion

Using the micro-MST kit for PICC insertion in neonates can improve first-attempt and overall insertion success rates and reduce catheter-related complications, leading to unplanned removal, therapy failure, and fewer cases of CLABSI. The micro-MST kit is a safe and effective approach to PICC insertion, and it has become popular among VA practitioners. However, further study is required to demonstrate the superiority of this insertion technique over conventional approaches.

Data availability statement

The datasets generated for this study are available on reasonable request to the corresponding author. Data requests should be made to Dr. Mohammad A. A. Bayoumi by email to moh.abdelwahab@hotmail.com.

Ethics statement

This research study was approved by the Institutional Review Board (IRB) of the Medical Research Center, Hamad Medical Corporation, Doha, Qatar (MRC-01-22-626). A waiver for the requirement of informed consent was granted by the Chair of the IRB on the grounds of being a minimal-risk study. All methods were performed following the relevant guidelines and regulations.

Author contributions

MV: Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing. KH: Writing – review & editing, Conceptualization. RV: Writing – review & editing, Conceptualization. AF: Project administration, Writing – review & editing, Conceptualization. FV: Formal analysis, Methodology, Writing – review & editing, Conceptualization. MB: Conceptualization, Project administration, Supervision, Writing – review & editing, Data curation.

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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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EDITED BY
Minesh Khashu,
University Hospitals Dorset NHS Foundation Trust, United Kingdom

REVIEWED BY
Qingfeng Sheng,
Shanghai Children's Hospital, China
Kai-Sheng Hsieh,
China Medical University, Taiwan

*CORRESPONDENCE
Bin Wu
lx97238@sina.com
Jian Wang
wj196312@vip.163.com

†These authors have contributed equally to this work

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Enhancing surgical decision-making in NEC with ResNet18: a deep learning approach to predict the need for surgery through x-ray image analysis

Zhiqing Wu†, Ran Zhuo†, Xiaobo Liu†, Bin Wu* and Jian Wang*

Department of Pediatric Surgery, Children's Hospital of Soochow University, Suzhou, Jiangsu, China

Background: Necrotizing enterocolitis (NEC) is a severe neonatal intestinal disease, often occurring in preterm infants following the administration of hyperosmolar formula. It is one of the leading causes of neonatal mortality in the NICU, and currently, there are no clear standards for surgical intervention, which typically depends on the joint discretion of surgeons and neonatologists. In recent years, deep learning has been extensively applied in areas such as image segmentation, fracture and pneumonia classification, drug development, and pathological diagnosis.
Objective: Investigating deep learning applications using bedside x-rays to help optimizing surgical decision-making in neonatal NEC.
Methods: Through a retrospective analysis of anteroposterior bedside chest and abdominal x-rays from 263 infants diagnosed with NEC between January 2015 and April 2023, including a surgery group (94 cases) and a non-surgery group (169 cases), the infants were divided into a training set and a validation set in a 7:3 ratio. Models were built based on Resnet18, Densenet121, and SimpleViT to predict whether NEC patients required surgical intervention. Finally, the model's performance was tested using an additional 40 cases, including both surgical and non-surgical NEC cases, as a test group. To enhance the interpretability of the models, the study employed 2D-Grad-CAM technology to describe the models' focus on significant areas within the x-ray images.
Results: Resnet18 demonstrated outstanding performance in binary diagnostic capability, achieving an accuracy of 0.919 with its precise lesion imaging and interpretability particularly highlighted. Its precision, specificity, sensitivity, and F1 score were significantly high, proving its advantages in optimizing surgical decision-making for neonatal NEC.
Conclusion: The Resnet18 deep learning model, constructed using bedside chest and abdominal imaging, effectively assists clinical physicians in determining whether infants with NEC require surgical intervention.

KEYWORDS

NEC, deep learning, pediatric surgery, diagnostic imaging, artificial intelligence in medicine

Abbreviations

NEC, neonatal necrotizing enterocolitis; NICU, neonatal intensive care unit; 2D-Grad-CAM, 2D gradient-weighted class activation mapping; AUC, area under the curve; CI, confidence interval; CNN, convolutional neural network; FC, fully connected; ReLU, rectified linear unit; TL, transfer learning; PPV, positive predictive value; NPV, negative predictive value; CAXR, chest and abdominal x-ray; DRX, digital radiography x-ray.

Introduction

NEC is the leading cause of severe inflammatory disease in newborns post-birth (1), especially among preterm infants, and is a principal contributor to neonatal mortality in the NICU (2). Newborns suffering from NEC, particularly after complications like intestinal perforation and peritonitis (3), often experience worsening conditions necessitating transfer to specialized pediatric hospitals equipped for surgery. In such instances, mortality rates can soar to 30%, and even 50% due to widespread intestinal necrosis. Additionally, up to 9% of children at the age of one who have had NEC require parenteral nutrition (3), and many post-surgery infants exhibit intestinal flora dysbiosis (4). The rapid progression of NEC sometimes calls for multiple short-term assessments to decide on the urgency of surgical intervention (5). Surgical management of NEC aims to mitigate further infection (6) and sepsis by repairing perforations and resecting non-viable bowel sections (6, 7), which is crucial for preventing short bowel syndrome (8) and the prolonged use of parenteral nutrition. Currently, there are no definitive standards for surgical indications, which often rely on the joint discretion of surgeons and neonatologists (9). The presence of free air under the diaphragm on an upright abdominal x-ray and progressive abdominal distension are the gold standards for surgical intervention in acute NEC. Clinically, the ideal surgical window during the acute phase of NEC —when the intestinal wall is fully necrotic but not yet perforated— is highly sought after. Furthermore, severe intestinal strictures post-conservative treatment still warrant surgical indications.

In recent years, deep learning has seen extensive application in diagnosing traumatic bone fractures (10), pulmonary nodules (11), COVID-19 (12), and in classifying pneumonia as well as in image segmentation (13, 14). Deep learning neural networks, by mimicking the human brain, automatically learn and recognize patterns in images, offering an edge in processing complex image data (15). Currently, the use of supine x-ray films in NEC lacks a standardized approach (16). In our research, we have trained deep learning models based on bedside chest-abdominal x-rays using Densenet121, Resnet18, and SimpleViT. Our study underscores ResNet18's potential to refine NEC surgical decision-making. These models are commonly employed in pneumonia classification (11, 17) and the identification of gastrointestinal pathologies (18).

Materials and methods

Materials

From January 2015 to April 2023, bedside chest and abdominal films of 263 neonates aged 0 to 39 days were collected from Children's Hospital of Soochow University for this study. We divided these original images into a 7:3 ratio for training and validation. These infants were treated for NEC either surgically or non-surgically. In addition, we have collected 40 cases of non-surgical and surgical NEC from May 2023 to February 2024 as an independent validation set to assess the model's performance on unfamiliar datasets. Additionally, from May 2023 to February 2024, we collected a total of 40 cases, including 21 non-surgical and 19 surgical NEC cases, as an independent validation set to evaluate the model's performance on unfamiliar datasets. The diagnosis of the non-surgical group was based on the modified Bell staging criteria, and the initial bedside chest and abdominal films in the anteroposterior position, decided for conservative treatment, were used. For the surgical group, the last bedside chest and abdominal films in the anteroposterior position before surgery, which were confirmed as NEC during the surgery, were used. The bedside chest and abdominal films were acquired using the DRX-Revolution Mobile x-Ray System produced by Carestream Health, USA. All images were taken in the supine position. According to the needs of the disease, some patients also underwent anteroposterior and lateral CAXR, but our study did not involve lateral views. As part of a retrospective study, we initially collected a large volume of clinical diagnostic NEC x-ray images from cases that did not undergo surgical treatment for model training. These images were subsequently annotated by experienced pediatric radiologists to select those with relatively distinct radiographic features. For the non-surgical group, images taken prior to antibiotic treatment were used; for the surgical group, images from the last bedside review before surgery were utilized. Surgical indications include cases where the child's upright abdominal x-ray shows signs of pneumoperitoneum, abdominal paracentesis fluid indicates the presence of feces or a large amount of purulent or bloody fluid, and situations where, despite receiving the best medical treatment, the condition continues to worsen or remains unstable. Surgical interventions for these cases involved simple laparotomy, and if necrosis was discovered, resection of the necrotic bowel segments followed by the establishment of an intestinal stoma or anastomosis. Cases diagnosed with NEC preoperatively were included; however, images from cases not confirmed as NEC postoperatively were excluded to enhance the model's diagnostic specificity. The inclusion criteria included (1) NEC patients are diagnosed and treated according to the modified Bell staging.(2) sufficient radiographic image technical quality, (3) imaging field of view (FOV) covering the entire abdomen.(4) During the surgery and in the postoperative pathology, it was confirmed that the children who underwent surgical treatment had NEC. Exclusion criteria include: children with congenital intestinal malformations (congenital megacolon, intestinal atresia, malrotation of the intestines), meconium ileus, spontaneous intestinal perforation, and cases with a large amount of incomplete data. The diagnosis of NEC was confirmed by three senior pediatric radiologists and neonatologists with over five years of experience.

The study was conducted with the consent of the parents of the children and was approved by the Institutional Ethics Committee of Children's Hospital of Soochow University.

Methods

Data augmentation, commonly used in the medical field to increase the size of the dataset, generates additional labeled images without changing the semantics of the image. In this paper, we used various data augmentation methods, such as

random cropping, rotation, and horizontal flipping. In implementation, the CPU generates augmented images while the previous batch of images is being trained on the GPU. Thus, these data augmentation techniques do not affect the time complexity. We also used oversampling to deal with imbalanced data. Deep learning methods automatically extract features from raw data and classify images. The main advantage of this approach is that both feature extraction and classification occur within the same network. Convolutional Neural Network (CNN) models, the most advanced form of DL technology, consist of many stacked convolutional layers that automatically extract features from image data. They have been used in many radiological tasks and can achieve high performance in image-based disease classification (19). The CNN architecture is built with layers including an input layer (producing output from the image as input), convolutional layers (convoluting the input image with filters to produce feature maps), Rectified Linear Unit (ReLU) activation layers (activating neurons above a threshold), pooling layers (reducing the image size while retaining high-level features), and fully connected (FC) layers (producing results) (8). The accuracy of CNNs depends on the design of the layers and the training data. CNNs typically require large labeled medical datasets for training, which are difficult to create due to time and labor costs. Recent studies have shown that transfer learning can address issues with small datasets.

In transfer learning (TL), a Convolutional Neural Network (CNN) is first trained to learn features in a broad domain (e.g., ImageNet), then the trained features and network parameters are transferred to a more specific domain. In CNN models, low-level features like edges, curves, and corners are learned in initial layers, while specific high-level features are learned in the final layer (20). Among different TL models, we chose ResNet for its widespread recognition in medical image classification. We used ResNet-18 due to its relatively shallow structure, allowing faster training of images without sacrificing performance. It consists of a 7×7 convolutional layer, 2 pooling layers, 5 residual modules, and a fully connected (FC) layer. Each residual module contains two 3×3 convolutional layers followed by a batch normalization layer and a ReLU activation function. Inputs can be added directly before the final ReLU activation function by skipping these two convolutional layers. In a recent study (21), the authors evaluated the performance of several neural networks with a Softmax output layer with a ReLU activation layer and verified that Softmax with ReLU activation performs better in classification tasks. Therefore, Softmax was preferred as the output layer in this study to obtain probability predictions.

Due to its use of bottleneck residual blocks, batch normalization (adjusting the input layer), and identity connections (to prevent gradient vanishing in the network), it has high classification accuracy. During the transfer learning and fine-tuning process, we gradually unfroze the top 10 layers of the model and changed the output of the fully connected (FC) layer to binary classification. We tested various optimizers and found the "Adam" optimizer (22) to perform best among all studied optimizers, hence it was applied in our model. To our knowledge, no previous studies have fevaluated the effectiveness of these deep learning models that can directly recognize bedside chest-abdominal x-ray images without the need for delineating regions of interest (ROI) in assessing the need for surgical intervention.

All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all legal guardians of the patients. Personal identifiers were removed from all patient data to protect privacy and confidentiality.

Comparison of deep learning models

In this study, we explored which deep learning model had superior performance in determining the need of NEC surgery by comparing three commonly used deep-learning-based classification methods: ResNet-18 (a 18-layer residual network), DenseNet, and the latest Transformer model architecture, which integrates multi-head attention mechanisms (MHA) in two schemes to enhance model performance. Initially, we conducted a comparative analysis of our ResNet18 model against the deeper ResNet50 and ResNet101 models to evaluate their performance. Surprisingly, we found that the latter two models underperformed, whereas the ResNet18 model demonstrated superior predictive capabilities for our research objectives. Additionally, we employed the 2D-Grad-CAM (23) module for interpretability analysis of the three deep learning models. This module allows for a visual identification of the alignment between intestinal lesions and model prediction focus. We also utilized Decision Curve Analysis (DCA) to evaluate the clinical benefits of different prediction models.

Statistical analysis

We use the following indicators to evaluate the performance of the model and select the best model: accuracy, sensitivity, specificity, F1 score, DCA curve images, where the F1 score is the weighted average of precision and recall. This study used the following tools: Python 3.7.16 (https://www.python.org/downloads/release/python-3716/) and PyTorch third-party libraries (Version: 1.13.1) on Windows 11 operating system {[MSC v.1916 64 bit (AMD64)]}.

Results

In terms of AUC curve performance (Figure 1), the Resnet18 model demonstrates superior classification capability compared to the Densenet121 and SimpleViT models, and it maintains high accuracy on unseen datasets.

As shown in Figure 1A, the Resnet18 model has an AUC of 0.973 on the training set, indicating a high level of classification efficacy. The AUC on the test set is 0.876; although it decreases compared to the training set, it still reflects the model's robust classification capability.

Additionally, the Resnet18 model demonstrated good performance in predictive decision applications, outperforming

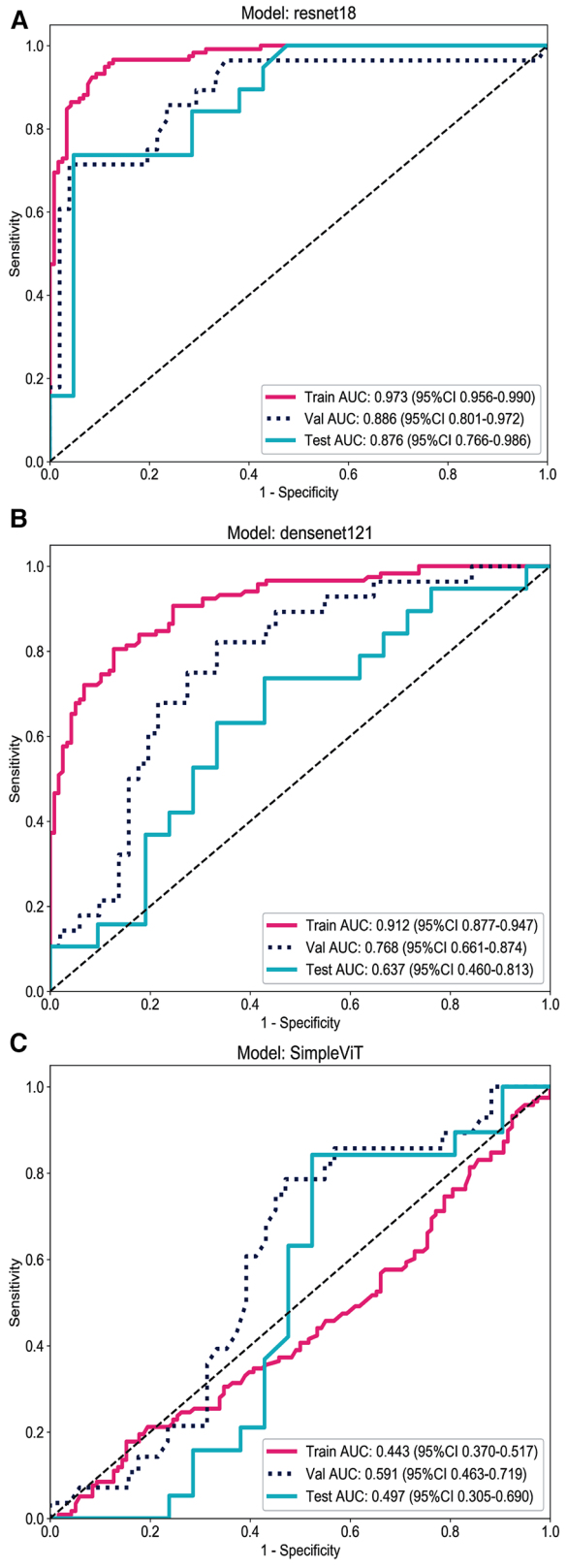

FIGURE 1
Comparison of the AUC curves for the three models across the training, validation, and testing datasets. (A) Resnet18. (B) Densenet121. (C) SimpleViT.

both the Densenet121 and SimpleViT models across training (Figure 2), testing (Figure 3), and validation sets (Figure 4).

As shown in Figure 2A, on the training set, the Decision Curve Analysis (DCA) performance of the Resnet18 model consistently outperforms the "treat none" strategy. Moreover, at most threshold values, the model's curve exceeds the "treat all"

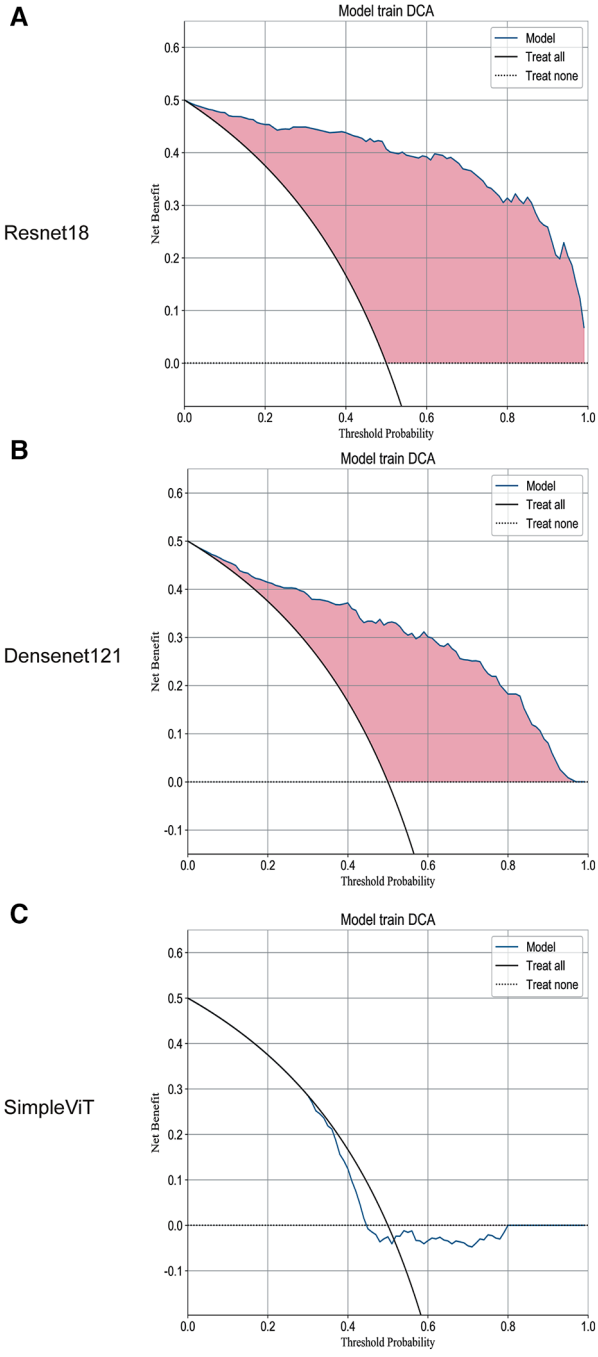

FIGURE 2
The DCA curves of the three models on the training set. (A) Resnet18. (B) Densenet121. (C) SimpleViT.

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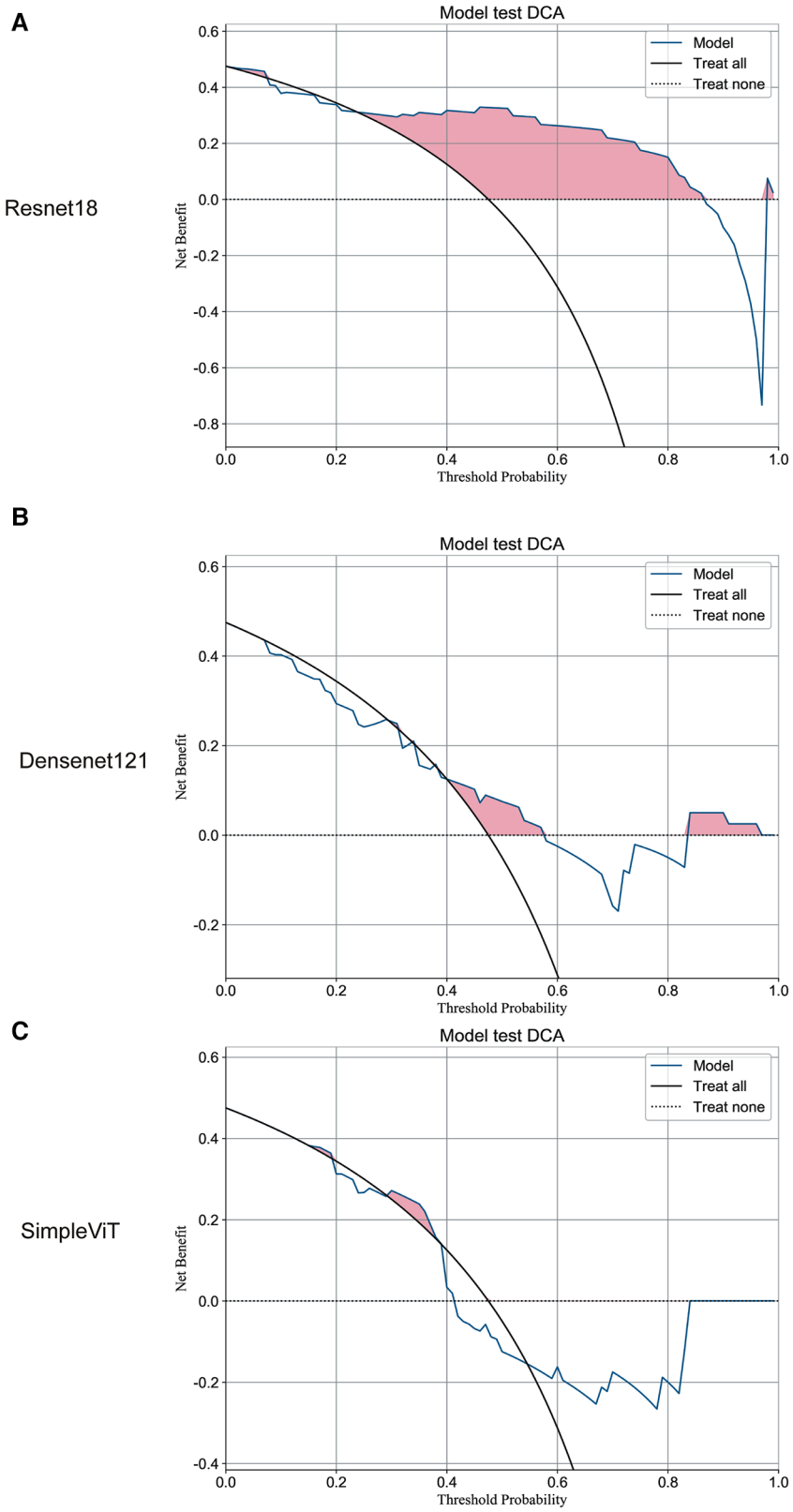

FIGURE 3
The DCA curves of the three models on the test set. (**A**) Resnet18. (**B**) Densenet121. (**C**) SimpleViT.

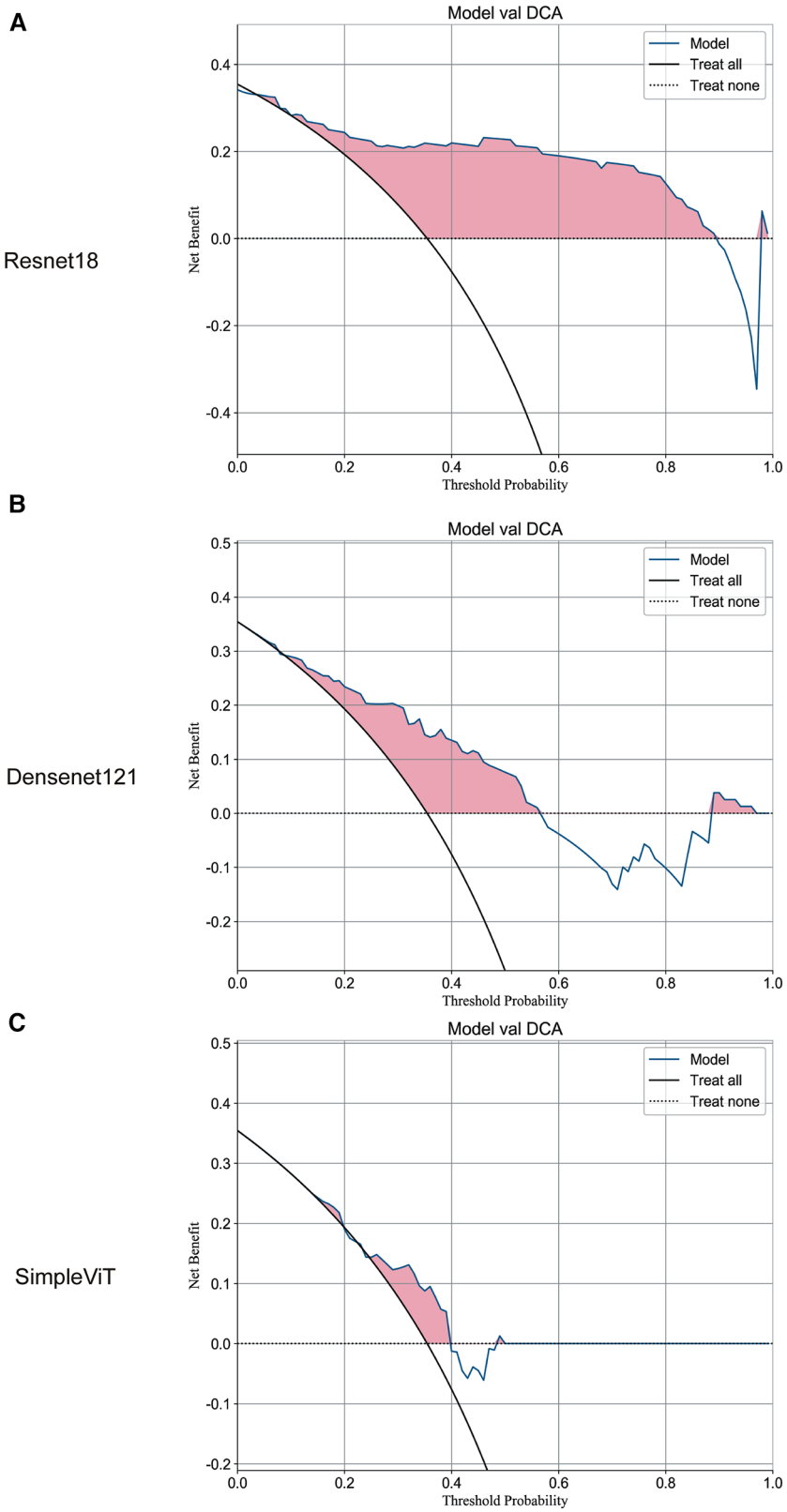

FIGURE 4
The DCA curves of the three models on the validation set. (**A**) Resnet18. (**B**) Densenet121. (**C**) SimpleViT.

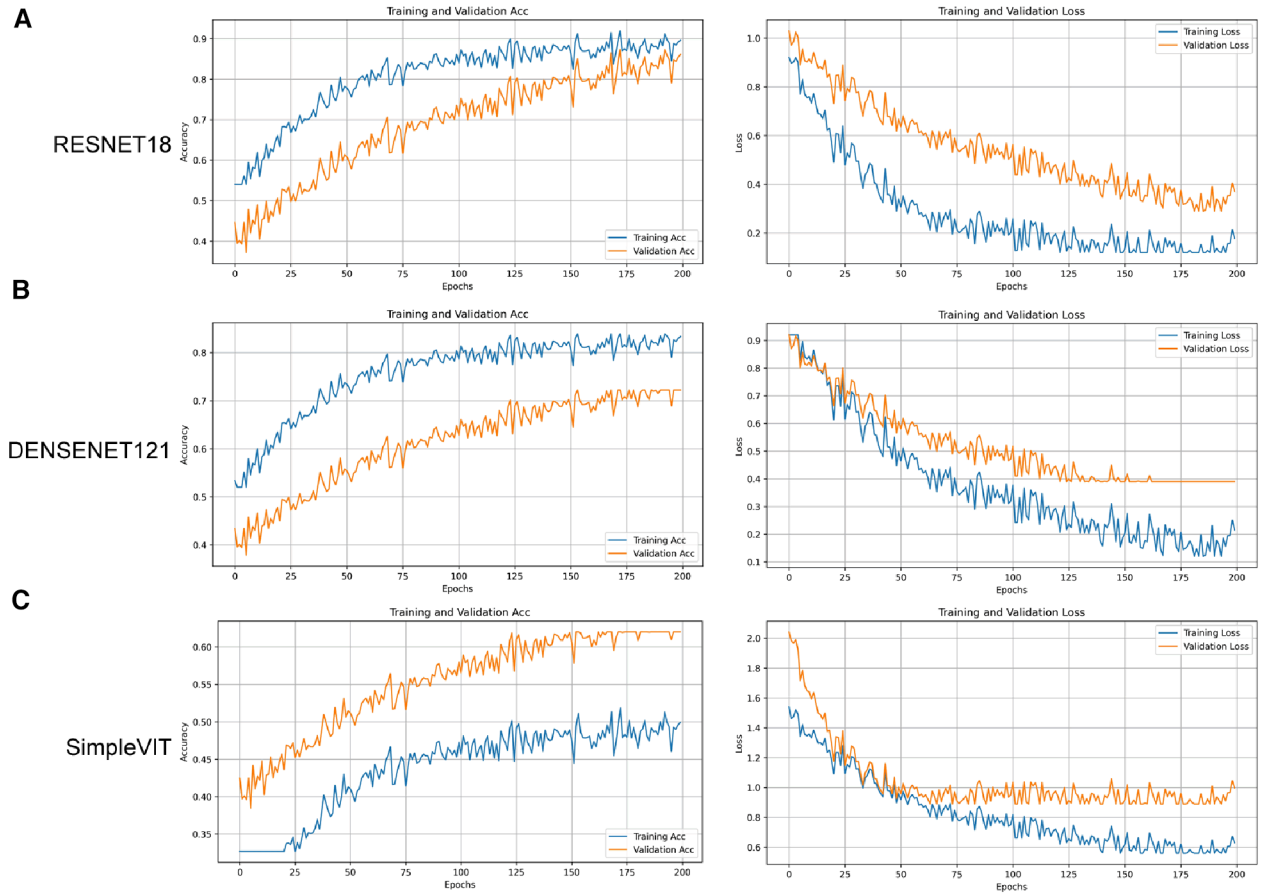

FIGURE 5
The accuracy and loss curves for the three models on the training and validation sets. (**A**) Resnet18. (**B**) Densenet121. (**C**) SimpleViT.

approach, suggesting that this model could assist clinicians in making accurate decisions about whether to proceed with surgical interventions in children diagnosed with NEC.

As illustrated in Figure 5A, compared to Densenet121 (Figure 5B) and SimpleViT (Figure 5C), the Resnet18 model demonstrates good performance on the training set and exhibits a positive learning and generalization trend on the validation set, although the latter's rise is not as steady as on the training set. With the number of training iterations increasing, the loss curves for both the training and validation sets demonstrate a declining trend, indicating that the model is progressively enhancing its predictive accuracy while minimizing loss as much as possible.

Overall, the Resnet18 model exhibits excellent performance on the training set and maintains good performance on the test set, despite an expected decrease in effectiveness as the model transitions from familiar training data to previously unseen data. However, it is noteworthy that the AUC value for the test set indicates the model's potential for providing robust diagnostic or predictive capabilities in practical applications.

Table 1 displays a comparative analysis of various performance metrics for three models - Densenet121, Resnet18, and SimpleViT —across training, validation, and test datasets. These metrics include accuracy (Acc), area under the curve (AUC), 95% confidence interval (95% CI), sensitivity, specificity, positive and negative predictive values (PPV and NPV), precision, recall, F1 score, and decision threshold. The Resnet18 model exhibited robust performance with high accuracy and AUC, indicating strong generalizability.

Furthermore, through 2D-Grad-CAM analysis applied to the final convolutional layer of the model (Supplementary Material Figures S1–S3), heatmaps highlighting focal areas were generated. This study provides visual insigts into the model's capability to detect intestinal lesions. Notably, the Resnet18 model exhibited significant alignment and activation in the intestinal regions, emphasizing its interpretative accuracy in medical imaging diagnosis.

Discussion

Previous studies, such as the one by Gao et al. (16), developed a complex multimodal model based on radiomic features and the SENet network model to predict surgical necessity in acute NEC cases. However, this did not include NEC cases requiring surgical intervention after treatment. In other aspects, many studies have described several potential biomarkers, mainly isolated from serum, stool, and urine samples, to differentiate between non-surgical and

TABLE 1 Comparison of the performance of five deep learning models.

Model Name	Acc	AUC	95% CI	SENS	SPE	PPV	NPV	Precision	Recall	F1	Threshold	Cohort
Densenet121	0.839	0.912	0.877–0.948	0.805	0.873	0.864	0.817	0.864	0.805	0.833	0.519	TRAIN
	0.722	0.768	0.661–0.874	0.821	0.667	0.575	0.872	0.575	0.821	0.676	0.313	Val
	0.65	0.637	0.460–0.813	0.737	0.571	0.609	0.706	0.609	0.737	0.667	0.313	TEST
Resnet18	0.919	0.973	0.956–0.990	0.924	0.915	0.916	0.923	0.916	0.924	0.92	0.494	TRAIN
	0.873	0.886	0.801–0.972	0.714	0.961	0.909	0.86	0.909	0.714	0.8	0.513	Val
	0.85	0.876	0.766–0.986	0.737	0.952	0.933	0.8	0.933	0.737	0.824	0.513	TEST
SimpleViT	0.513	0.443	0.370–0.517	0.178	0.855	0.538	0.508	0.538	0.178	0.268	0.56	TRAIN
	0.62	0.591	0.463–0.719	0.786	0.529	0.478	0.818	0.478	0.786	0.595	0.36	Val
	0.65	0.497	0.305–0.691	0.842	0.5	0.593	0.769	0.593	0.842	0.696	0.36	TEST
Resnet50	0.924	0.907	0.861–0.954	0.907	0.941	0.939	0.91	0.939	0.907	0.922	0.501	TRAIN
	0.65	0.622	0.435–0.808	0.842	0.476	0.593	0.769	0.593	0.842	0.696	0.379	VAL
	0.722	0.661	0.533–0.789	0.321	0.941	0.75	0.716	0.75	0.321	0.45	0.481	TEST
Resnet101	0.919	0.973	0.957–0.990	0.915	0.924	0.923	0.916	0.923	0.915	0.919	0.498	TRAIN
	0.675	0.638	0.456–0.820	0.842	0.524	0.615	0.786	0.615	0.842	0.711	0.142	VAL
	0.595	0.587	0.460–0.714	0.857	0.451	0.462	0.852	0.462	0.857	0.6	0.128	TEST

surgical NEC. Cakir et al. (24) described the predictive value of endothelial cell-specific molecules and interleukin-33, which gradually increase in patients undergoing surgery. However, obtaining these indicators is time-consuming and expensive, often necessitating surgical intervention in patients before detection, showing a clear lag compared to bedside chest and abdominal x-rays. In ultrasonography diagnosis, Chen QinYao et al. (9) described the role of focal or strong echo effusion in surgical prediction. However, ultrasonography often depends on the level and subjective judgment of the ultrasonographer, lacking objectivity compared to x-ray examination and is greatly interfered by increased intestinal gas. Currently, bedside ultrasound or upright abdominal films are more commonly used in clinical practice for intestinal condition analysis, with few using abdominal CT scans for evaluation. However, in our study, we decided to use bedside chest and abdominal films to construct models. Performing upright abdominal films usually requires a DR photography room and is inconvenient for bedside operation. Bedside chest and abdominal films are convenient, low-cost, highly repeatable, and easy to master, providing advantages for diseases like NEC that may require multiple assessments within a day. Moreover, bedside chest and abdominal films, compared to ultrasound, provide more objective and comprehensive results. Also, compared to abdominal CT scans, bedside chest and abdominal films involve lower radiation doses, making them more feasible for generally unstable infants and having lower side effects. For the non-surgical group, the most significant imaging features of NEC can be obtained, and for the surgical group, bedside film images closest to the clinical physician's judgment standard are obtained. We constructed an auxiliary means for determining the treatment strategy for neonatal NEC using three deep learning models (Densenet121, Resnet18, SimpleVit) and analyzed and compared their efficacy. Table 1 indicates that the Resnet18 model outperforms the other two models in terms of DCA and AUC curves, as well as 2D-Grad-CAM. It exhibits high values in sensitivity, specificity, PPV, and NPV across training, validation, and test datasets. Furthermore, by fine-tuning hyperparameters, we achieved superior performance compared to the conventional Resnet18 model. Notably, the model demonstrates excellent generalization capability on the validation set. Hence, we believe this model could aid clinicians in deciding whether surgical intervention is necessary for NEC patients, thus preventing the risk of missing the optimal surgical window due to continued conservative treatment.

Limitations

It is a single-center study with a relatively small sample size. Moreover, assessing whether children require NEC surgery relies not only on x-ray examinations but also necessitates an analysis of the infant's basic vital signs and tolerance for surgical intervention and general anesthesia. In the clinical decision-making process, other clinical indicators such as complete blood count, coagulation tests, blood gas analysis, and electrolyte levels are indispensable. Looking ahead, we plan to collaborate with multiple centers to collect more bedside chest and abdominal x-ray images of infants with NEC, aiming to enlarge the scale of the training, validation, and test sets. We will also explore adjustments in fine-tuning methods to enhance accuracy, such as modifying the model's loss function, learning rate, employing different optimizers, and implementing early stopping mechanisms.

Conclusion

The Resnet18 deep learning model, constructed using bedside chest and abdominal imaging, effectively assists clinical physicians in determining whether infants with NEC require surgical intervention.

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 authors.

Ethics statement

The studies involving humans were approved by Institutional Ethics Committee of Children's Hospital of Soochow University. 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. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZW: Conceptualization, Data curation, Software, Writing – original draft. RZ: Writing – original draft, Formal Analysis, Validation. XL: Writing – original draft, Visualization. BW: Resources, Writing – review & editing. JW: 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.2024.1405780/full#supplementary-material

SUPPLEMENTARY FIGURE S1
The regions of interest activated in the training set by the 2D-Grad-CAM module during the prediction of supine abdominal plain films by three different models.

SUPPLEMENTARY FIGURE S2 AND S3
The attention areas in the prediction of the Resnet18 model for supine abdominal radiographs of surgical versus non-surgical NEC within the test group activated by the 2D-Grad-CAM module.

SUPPLEMENTARY FIGURE S4
The calibration curves for each model of RESNET18, DENSENET121 and SimpleVIT.

SUPPLEMENTARY FIGURE S5
Comparison of the performance of the ResNet50 and ResNet101 models.

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EDITED BY
Minesh Khashu,
University Hospitals Dorset NHS Foundation Trust, United Kingdom

REVIEWED BY
Helen B. Stolp,
Royal Veterinary College (RVC), United Kingdom
Karel Allegaert,
KU Leuven, Belgium

*CORRESPONDENCE
Julie A. Wixey
✉ j.wixey@uq.edu.au

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The search for blood biomarkers that indicate risk of adverse neurodevelopmental outcomes in fetal growth restriction

Hannah Musco[1], Kate Beecher[1], Kirat K. Chand[1], Roslyn N. Boyd[2], Paul B. Colditz[1,3] and Julie A. Wixey[1]*

[1]UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia, [2]Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia, [3]Perinatal Research Centre, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia

Fetal growth restriction (FGR) impacts 5%–10% of pregnancies and is associated with increased risk of mortality and morbidity. Although adverse neurodevelopmental outcomes are observed in up to 50% of FGR infants, a diagnosis of FGR does not indicate the level of risk for an individual infant and these infants are not routinely followed up to assess neurodevelopmental outcomes. Identifying FGR infants at increased risk of adverse neurodevelopmental outcomes would greatly assist in providing appropriate support and interventions earlier, resulting in improved outcomes. However, current methods to detect brain injury around the time of birth lack the sensitivity required to detect the more subtle alterations associated with FGR. Blood biomarkers have this potential. This systematic review assessed the current literature on blood biomarkers for identifying FGR infants at increased risk of adverse neurodevelopmental outcomes at >12 months after birth. Four databases were searched from inception to 22 February 2024. Articles were assessed for meeting the inclusion criteria by two reviewers. The quality of the included article was assessed using Quality Assessment of Diagnostic Accuracy Studies-2. A summary of findings is presented as insufficient articles were identified for meta-analysis. Excluding duplicates, 1,368 records were screened with only 9 articles considered for full text review. Only one article met all the inclusion criteria. Quality assessment indicated low risk of bias. Both blood biomarkers investigated in this study, neuron specific enolase and S100B, demonstrated inverse relationships with neurodevelopmental assessments at 2 years. Four studies did not meet all the inclusion criteria yet identified promising findings for metabolites and cytokines which are discussed here. These findings support the need for further research and highlight the potential for blood biomarkers to predict adverse outcomes.

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KEYWORDS

fetal growth retardation, intrauterine growth restriction, small for gestational age, detection, newborn, brain

1 Introduction

Fetal growth restriction (FGR) is a major cause of increased risk of mortality and morbidity in infants occurring in 5%–10% of pregnancies with higher rates in low-income countries (1, 2). FGR is defined as ultrasound estimated fetal weight below 10th percentile with other factors included for diagnosis such as umbilical artery Doppler flow assessment, physiological determinants and neonatal features of malnutrition (3–5).

The causes of FGR are complex and can arise from several potential sources including maternal (hypertension, diabetes, preeclampsia, malnutrition, maternal age) (6), placental (placental dysfunction leading to poor blood supply and nutrient transfer) (7), and fetal (multiple pregnancy, congenital infections, genetics) (6). Placental insufficiency is the most common cause where a reduction in supply of oxygen and nutrients to the developing fetus results in a chronic hypoxic environment impacting normal growth and development of the fetus.

The chronic hypoxic environment that FGR fetuses are exposed to *in utero* particularly affects brain development. Lower grey matter and white matter complexity are major neuropathophysiological features of FGR which are shown to persist after birth (8). Changes in white matter microstructure are observed at 8–10 years of age in FGR compared to normally grown (NG) children (9). Adverse long-term neurological outcomes are reported in 24%–53% of FGR infants (10, 11), including language delays, learning and behavioral problems and cerebral palsy (CP) (12–14). Yet, the ability to identify FGR neonates at risk of adverse neurodevelopmental outcomes is lacking. Unlike for neonatal hypoxic-ischemic encephalopathy (HIE) where severity of injury is assessed using the Sarnat Grading Scale, there is no defined criteria at birth to score injury in FGR babies. Therefore, the likelihood to predict which newborn may have adverse outcomes is not clear and therefore interventions and support systems are commonly not implemented until developmental delays become evident years later. Due to evidence of positive impacts on CP infants with early physiotherapy intervention after birth (15), it is crucial to determine effective and efficient methods to identify FGR infants at risk of long-term adverse neurodevelopmental outcomes.

Studies have investigated the reliability of cranial ultrasounds, magnetic resonance imaging (MRI) and electroencephalography (EEG) to provide an indication of risk of adverse neurodevelopmental outcomes for FGR infants (16, 17). All three methods however, require further evidence for confirming the sensitivity of predicting long-term adverse neurodevelopmental outcomes in FGR. Cranial ultrasounds can identify brain structure abnormalities such as brain volume neuropathologies including intracranial hemorrhages and hydrocephalus (18). Although MRIs can detect more subtle structural changes such as white matter injury which has associations with cognitive and motor outcomes, the costs, resources and expertise required do not make it an ideal method for widespread implementation (19, 20). EEG studies have shown promise in identifying FGR infants at risk of adverse neurodevelopmental outcomes, however studies to date have utilized only visual interpretation of EEGs which relies on operator proficiency (17), rather than objective quantitative analysis.

Due to the limitations of these current methods for measuring subtle brain alterations, the search for sensitive predictors of long-term adverse neurological outcomes is ongoing. Blood biomarkers have the potential to provide an objective indication of risk of adverse brain outcomes. The diagnostic and prognostic utility of blood biomarkers to detect adverse brain outcomes is currently being investigated in adult and neonatal neurological disease states. There is evidence to suggest that alterations in the brain due to injury or disease are reflected in the blood. For example, alterations in proteins have been detected in blood samples from amyotrophic lateral sclerosis patients that distinguish these patients from healthy controls and other brain conditions (21–23). Furthermore, alterations in proteins present in blood of traumatic brain injury patients are correlated with adverse brain outcomes (24–26). Interest in blood biomarkers has grown with several recent studies examining blood biomarkers in FGR neonates. This systematic review examines the current literature to identify potential blood biomarkers that indicate risk of long-term adverse neurodevelopmental outcomes in FGR neonates with the ultimate goal to enable earlier interventions. We hypothesize blood biomarkers may indicate risk of adverse neurodevelopmental outcomes in FGR infants shortly after birth.

2 Methods

2.1 Search strategy

This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) November 2022 (ID: CRD42022369242) (27) and designed in accordance with the PRISMA Guidelines.

A comprehensive search was undertaken of online databases Pubmed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science and Excerpta Medica Database (EMBASE) from inception to 22 February 2024. A PICO (patient/population, intervention, comparison and outcomes) search strategy was implemented using Medical Subject Headings (MeSH) and keywords for the target population of "fetal growth restriction infants" with outcomes of "brain injury" or "neurological outcomes". Additional search terms (listed in Appendix A) were added to identify studies with "blood biomarkers". The search was limited to "humans" and only articles with professional English translations available were considered. Likelihood of language bias was considered to be minimal (28, 29).

2.2 Inclusion/exclusion criteria

No restrictions on language were used when conducting searches. Studies were eligible for inclusion if they were conducted in humans and in which all the following criteria were met:

- The participant population was defined as infants born <10th percentile for gestational age and at least one other clinical indication used for diagnosis of FGR such as umbilical artery Doppler assessment, physiological determinants and neonatal features of malnutrition as described in the current literature (3–5).
- The same protocol was conducted in a cohort of NG infants (birthweight >10th percentile) with no other clinical indications of FGR, low birthweight, malnutrition or major congenital abnormalities.
- An applicable, valid, reliable and standardised reference test was used to identify cognitive and/or motor delays at least 12 months after birth such as Bayley Scales of Infant and Toddler Development (BSITD) or school age outcomes.

The inclusion criteria for long-term adverse neurodevelopmental outcomes were intended to ensure that identified articles provided long-term follow-up rather than identifying brain abnormalities at birth. This was crucial to achieve the aim of this review, given that current brain injury detection methods such as cranial ultrasounds, MRIs or EEGs do not detect the subtle brain alterations associated with FGR adverse outcomes as discussed above. Studies were excluded if they were commentaries, cross sectional or descriptive studies or single case reports.

2.3 Data extraction and quality assessment

The search strategy was jointly devised by HM, KB and RB. Titles and abstracts were extracted and screened by HM and KB, supervised by JAW. The full text of all articles deemed potentially eligible were reviewed and assessed by HM and KB for conformity to all inclusion criteria. Conflicting viewpoints were discussed until consensus was reached or resolved by JAW.

A single study that met the inclusion criteria was extracted for further assessment. The quality, risk of bias and applicability of patient selection of the study was assessed using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) by HM and KB (30). Insufficient articles met the inclusion criteria for meta-analysis to be conducted.

3 Results

Excluding duplicates, 1,368 records were retrieved across the four databases searched (Figure 1). Only nine studies remained for full-text review after the initial title and abstract screening (Figure 1). Five of these studies did not include a control group of NG infants (31–35). These would have also been excluded for other reasons such as not meeting FGR definition (very low birth weight, preterm birth only), not assessing neurodevelopmental outcomes, or that no blood biomarkers were assessed. One study was excluded as it did not include neurodevelopmental assessments (36) and another was excluded as it reported only the presence of brain injury for the FGR cohort (37). Finally, one study was a twin study but was excluded as it did not separate the FGR twins from the normally grown pair for comparison (38).

This resulted in only one remaining study to be included for analysis.

To broaden our perspective, we considered whether any additional papers would be included if we altered our inclusion criteria to include small for gestational age (SGA) and FGR. Small for gestational age (SGA) differs from FGR in that it is solely defined by birthweight <10th percentile (3–5). We observed, however, that the studies included for full text review that included SGA cohorts either did not have a cohort of NG infants as controls or did not conduct a neurodevelopmental assessment >12 months of age for the NG cohort (31–37). Therefore, even when broadening the inclusion criteria to include SGA infants, our search of the current literature still only yielded one study that met all inclusion criteria.

Thirty-one FGR and 25 non-FGR or NG neonates were recruited for this study (39). FGR neonates were recruited consecutively, and NG neonates were gestational age-matched (±7 days) to the FGR neonates. FGR was confirmed after birth if birthweight <3rd percentile or, <10th percentile with abnormal Doppler study or abnormal cerebroplacental ratio. Mean gestational age at delivery was not statistically significantly different between NG and FGR neonates (262 days [standard deviation (SD) = 21] and 257 days (SD = 15) respectively). Gender differences were not reported. Birthweight and birthweight percentile were much lower in the FGR cohort compared to NG neonates as expected. Incidence of nulliparity, preeclampsia and severe preeclampsia were all significantly higher in the FGR cohort.

Both fetal umbilical arterial and venous blood samples were collected at the time of delivery and supernatant stored at −80°C (39). Serum S100B protein and neuron specific enolase (NSE) assays were performed to measure the protein levels in both sample types. These formed the four individual index tests examined in this study. At 2 years of age, developmental function was assessed using BSITD third edition (BSITD III), conducted as per the test manual.

3.1 Methodological quality of included study with QUADAS-2

3.1.1 Participant selection

The included study was considered to have a low risk of bias for the selection of participants. FGR singleton pregnancies were consecutively enrolled in the study with age-matched controls (39). Reasons for exclusion from the study included maternal illicit drug use, maternal endocrine pathologies, fetal infection, fetal malformations, genetic abnormalities, failure to follow clinical protocols or delivery in a hospital not included in the study. It was important to exclude cases where there may have been adverse neurodevelopmental outcomes due to other causes and therefore, these reasons for exclusion were reasonable.

There was also low concern regarding the applicability of the study. Included FGR participants were confirmed using three definitions of FGR consistent with Australian clinical standards and the inclusion and exclusion criteria matched the aims of this review.

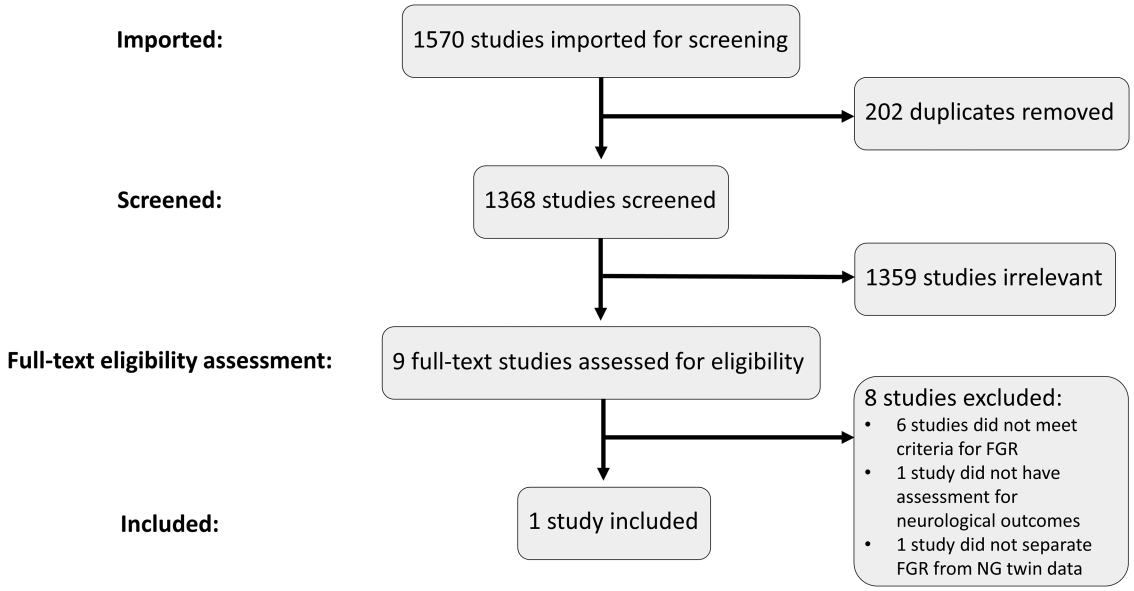

FIGURE 1
PRISMA flowchart and selection process. Studies were imported into Covidence to conduct the screening and eligibility assessment processes. Duplicates were removed, leaving 1,368 studies to be screened. Relevant studies were included for full-text review where the eligibility criteria were assessed. Only one study met all the inclusion criteria and was included for further analysis.

3.1.2 Index tests

Mazarico, Llurba (39) included four index tests: S100B and NSE levels each measured in maternal venous blood and fetal umbilical arterial blood. All these tests were rated as low risk of bias as the measurement of S100B and NSE in the blood samples were conducted objectively. Concerns regarding the applicability of these tests was also considered to be low. Concentrations of S100B and NSE in both maternal venous blood and fetal umbilical arterial blood were compared with the results of the neurodevelopmental assessment conducted at 2 years corrected age to identify potential relationships between results of these tests.

3.1.3 Reference standard

BSITD III was the reference standard used by Mazarico, Llurba (39) to determine neurodevelopmental outcomes for the study participants. As a formal assessment tool to identify developmental delays in early childhood (40), BSITD III is regularly used in the literature to assess development at 2 years of age. As is standard procedure, BSITD III was performed by a trained psychologist without knowledge of the study group and the perinatal outcomes for each participant. Some aspects of the BSITD III involved parent-report questionnaires which are also standard for conducting the BSITD III. Considering this, the reference test used was considered to have a low risk of bias and there were low concerns regarding the applicability of the study.

3.1.4 Flow and timing

There were also low concerns for the risk of bias for the flow and timing of the study. All patients received the same reference standard and were included in the analysis. Although there was a delay of 2 years before BSITD III was conducted, this was expected and consistent with the design of this study.

3.2 Relationships between S100B or NSE concentrations and adverse neurodevelopmental outcomes

Table 1 summarizes the findings from Mazarico, Llurba (39). Each subtest of BSITD III was investigated for associations with NSE or S100B levels in the blood samples collected. For FGR infants, there was a statistically significant inverse relationship

TABLE 1 Summary of significant relationships of investigated blood biomarkers from Mazarico, Llurba (39) in identified participants that are associated with neurodevelopmental outcomes at 2 years of age.

Biomarker	Sample	Cohort	Statistically significant inverse relationship with
S100B	Maternal serum	All participants	–
		FGR	Adaptive behaviour test
		Non-FGR	–
	Umbilical cord blood	All participants	Cognitive test and expressive communication subtest.
		FGR	–
		Non-FGR	Language composite score values.
NSE	Maternal serum	All participants	–
		FGR	–
		Non-FGR	–
	Umbilical cord blood	All participants	Cognitive test, fine motor subtest and social-emotional test.
		FGR	–
		Non-FGR	Fine motor subtest and social-emotional test.

between concentration of S100B in maternal serum and the adaptive behavior test. However, statistically significant inverse relationships were also observed for NG infants between the concentration of S100B in cord blood and the language composite score values. For NG infants, the concentration of NSE in cord blood was also in a statistically significant inverse relationship with each of the results of the fine motor subtest and the social-emotional test.

Mazarico, Llurba (39) found no differences between the FGR and NG groups for the results of any subtests of BSITD III. This indicated that outcomes were similar across groups. Across all infants, the concentration of S100B in cord blood displayed a statistically significant inverse relationship with the results of each the cognitive and expressive communication tests (39). Statistically significant inverse relationships were also observed for all infants between NSE concentrations in cord blood and the results for each of the cognitive test, fine motor subtest and social-emotional test (39).

4 Discussion

This is the first systematic review to our knowledge of potential blood biomarkers for identifying risk of adverse neurodevelopmental outcomes in FGR. Only one study was identified as relevant to this systematic review despite ensuring our search terms were sufficiently broad to account for differences in terminology in the literature. This systematic review has the scientific merit of our search strategy returning key articles to inform a scientifically robust examination of the topic. If inclusion criteria were broadened more articles may be included, but this would negatively impact on scientific quality and impact as meta-analysis could not be conducted.

This search of the literature highlighted a number of gaps, limitations and differences in terminology that exist. Firstly, the search terms used were relatively broad to ensure these captured all potential publications investigating blood biomarkers for detecting risk of adverse neurodevelopmental outcomes in FGR infants. For example, some studies use "intrauterine growth restriction" (IUGR) to describe FGR (39), while other studies report SGA but also include cohorts that matched our definition of FGR (37). Another example of this was sufficiently capturing a variety of possible descriptions for "adverse neurodevelopmental outcomes". Some articles investigated "neural injury" (39), while others investigated "brain injury" (34), or "white matter damage" (35). Although a number of different search terms were used as alternatives to broaden the search query, only nine publications were included in the full-text review, with only one meeting all inclusion criteria.

Only two blood biomarkers were considered in the identified study (39) which was deemed high quality using QUADAS-2. These results indicate the potential blood biomarkers have for indicating risk of adverse neurodevelopmental outcomes for FGR infants. However, as eight studies were excluded from this systematic review for multiple reasons, as mentioned above, this demonstrates the clinical literature lacks rigor. Preclinical studies are extremely important to answer research hypotheses as they can be undertaken in controlled environments. However, changing the approach of this review to include preclinical literature is not feasible as there are no studies to our knowledge that investigate blood biomarkers of brain injury in animal models of FGR. This review identifies the need for future studies to further investigate blood biomarkers for risk of adverse neurodevelopmental outcomes in FGR infants.

Neurodevelopmental outcomes measured at 2 years were not statistically significantly different between NG and FGR infants in the identified study (39). This finding does not align with the majority of studies demonstrating significant adverse long-term neurodevelopmental outcomes observed in FGR compared with NG infants (10–14). This may be due to the selection process for the NG group. What has been described here as the NG control group for Mazarico, Llurba (39) is more appropriately described in the study as a non-FGR group. Although this group is not classified as FGR, these infants have comorbidities such as 8% from preeclamptic pregnancies, 16% with respiratory distress syndrome, 28% neonatal morbidity and 32% neonatal admission (compared to 24%, 25.8%, 32.2% and 58% for FGR respectively) (39). The results indicate that the blood levels of NSE and S100B may indicate risk of adverse neurodevelopmental outcomes for all infants. This is an interesting and important finding, but also suggests a significant limitation of the study, that the non-FGR group also potentially has comparable rates of adverse neurodevelopmental outcomes and may not be a true representation of NG infants. Furthermore, a recent systematic review demonstrates the potential for NSE and S100B as biomarkers of injury in the newborn. They showed levels of both biomarkers correlate with unfavorable outcomes in HIE newborns (41). Although the paper concluded more studies are required to determine the sensitivity and specificity of these biomarkers, this further demonstrates the potential for these two biomarkers to predict adverse outcomes.

Four studies were excluded from the systematic review due to not meeting all the selection criteria, however some of their findings were of particular interest and may suggest other blood biomarkers to examine in future long-term studies.

The first of these studies considered correlations between cord blood gas and outcomes at 6–12 months in infants with low birthweight (31). Although the best single predictor for mental development index was pH of infant arterial blood gas, the best single predictor for psychomotor development index was gestational age (31). These findings demonstrate the need for research into blood biomarkers as indicators of risk of adverse outcomes to be broadened as current measures such as cord blood gases provide only limited insight.

Another study excluded after full-text review compared blood biomarker levels in FGR infants with brain injury to infants without brain injury on postnatal days 1–5 (34). Although increases in interleukin (IL)-6, IL-8, IL-10 and glial fibrillary acidic protein (GFAP) were observed in FGR infants with brain injury (34), it is not clear whether similar increases would be observed in cases of more subtle brain injury in FGR infants that are not currently detectable at birth.

A third study excluded from full text review identified increases in levels of NSE and ischemia-modified albumin (IMA) for SGA infants with brain abnormalities compared to SGA infants without brain abnormalities (37). These brain abnormalities were identified using cranial ultrasounds 12 h after birth (37). Although this finding is interesting, like the previous studies highlighted, it also does not

provide evidence on whether these proteins indicate risk for adverse long-term outcomes in FGR infants.

Finally, a twin study where one twin was FGR and the other >25th percentile for birthweight, was ultimately excluded due to the NG sibling's data being combined with the FGR sibling (38). Correlations were identified between maternal metabolite levels of creatine, L-serine, L-arginine, and L-histidine with communication, first walking time, gross and fine motor function, and problem solving (38). With these findings indicating correlations between maternal metabolite levels and outcomes at 2 years of age even when FGR only impacts one twin, this demonstrates the potential for biomarkers to provide an indication of risk of adverse outcomes at birth.

The current literature identifies inverse relationships between blood biomarkers, NSE and S100B, measured at birth and neurodevelopmental outcomes at two years of age (39). This systematic review highlights the need for more research to determine blood biomarkers that indicate risk of adverse neurodevelopmental outcomes in FGR infants. Future studies assessing outcomes at school age would also be beneficial as cognitive and motor impairments are commonly observed at this age range, but unfortunately no FGR blood biomarker studies have assessed school age outcomes. Although there are many challenges for future research in this area, identifying blood biomarkers that indicate risk of adverse neurodevelopmental outcomes for FGR infants has the potential to vastly improve the lives of these infants, as up to 50% of FGR infants are reported to have adverse neurodevelopmental outcomes (10, 11). With notable improvements observed in infants with CP when interventions are implemented earlier (15), it is crucial to investigate effective and efficient methods to identify FGR infants at risk of long-term adverse neurodevelopmental outcomes in order to implement earlier support and interventions. This will enable these infants to have the best possible long-term neurodevelopmental outcomes.

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.

Author contributions

HM: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. KB: Conceptualization, Investigation, Methodology, Writing – review & editing. KC: Conceptualization, Investigation, Writing – review & editing. RB: Methodology, Writing – review & editing. PC: Conceptualization, Supervision, Writing – review & editing. JW: Conceptualization, Investigation, 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

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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Pranav Jani,
Western Sydney Local Health District, Australia
Rajesh Maheshwari,
NSW Government, Australia
Darjan Kardum,
General Hospital Zadar, Croatia

*CORRESPONDENCE
Kamal Ali
alika@ngha.med.sa

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Rectal and axillary admission temperature in preterm infants less than 32 weeks' gestation, a prospective study

Shaimaa Halabi[1,2], Rana Almuqati[1], Amenah Al Essa[1], Manal Althubaiti[1], Musab Alshareef[1], Radha Mahlangu[1], Abdulaziz Homedi[1], Faisal Alsehli[1,3], Saif Alsaif[1,2,3] and Kamal Ali[1,2,3]*

[1]Neonatal Intensive Care Department, King Abdulaziz Medical City-Riyadh, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia, [2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, [3]King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Objectives: The purpose of this research was to evaluate the differences between rectal and axillary temperature measurements in preterm infants who were born less than 32 weeks' gestation using digital thermometers upon their admission to the Neonatal Intensive Care Unit (NICU).

Methods: Prospective, observational, single centre study. Rectal and axillary temperatures measurements were performed using a digital thermometer. The study examined various maternal and neonatal factors to describe the study group, including the use of prenatal corticosteroids, the occurrence of maternal diabetes and hypertension, a history of maternal prolonged rupture of membranes (PROM), maternal chorioamnionitis, the mode of delivery, along with the neonate's gender, birth weight, and gestational age. The Pearson correlation coefficient (R) was calculated to ascertain the linear relationship between the temperatures taken at the rectal and axillary sites. The concordance between the two sets of temperature data was analyzed using the Bland-Altman method.

Results: Eighty infants with a mean gestational age of 28.4 weeks (SD = 2.9) and a mean birth weight of 1,229 g (SD = 456) were included in the study. The mean axillary temperature was 36.4 °C (SD = 0.7), which was lower than the mean rectal temperature of 36.6 °C (SD = 0.6) ($p = 0.012$). Rectal temperatures surpassed axillary measurements in 59% of instances, while the reverse was observed in 21% of cases. Rectal and axillary temperatures had a strong correlation (Pearson correlation coefficient of 0.915, $p < 0.001$). Bland-Altman plot showed a small mean difference of 0.1C between the two temperatures measurements but the limits of agreement were wide (+0.7 to −0.6 °C). For hypothermic infants, the mean difference between rectal and axillary temperatures was 0.27 °C, with a wide limit of agreement ranging from −0.5 °C to +1 °C. Conversely, for normothermic infants, the mean difference was smaller at 0.1 °C, with a narrower limit of agreement from −0.4 °C to +0.6 °C.

Conclusions: While there is a good correlation between axillary and rectal temperatures, the wider limits of agreement indicate variability, particularly in hypothermic infants. For a more accurate assessment of core body temperature in hypothermic infants, clinicians should consider using rectal measurements to ensure effective thermal regulation and better clinical outcomes.

KEYWORDS

preterm, temperature, axillary, rectal, correlation

Abbreviations

NICU, neonatal intensive care unit; DR, delivery room; OT, operating theatre; AH, admission hypothermia; AT, axillary temperature; RT, rectal temperature.

Introduction

Based on the World Health Organization (WHO) practical guide on thermal protection of the newborn published in 1997, the temperature ranges for hypothermia and normothermia in neonates are as follows: Mild hypothermia is defined as a temperature between 36.0 °C and 36.4 °C, moderate hypothermia between 32.0 °C and 35.9 °C, and severe hypothermia below 32.0 °C. Normothermia is defined as a temperature between 36.5 °C and 37.5 °C. Preterm infants are particularly prone to rapid heat loss following birth. Despite efforts to mitigate heat loss during stabilization in the delivery room (DR), a significant number of preterm newborns still present with abnormal temperatures upon admission to the neonatal intensive care unit (NICU) (1, 2).

Previous research has indicated that that hypothermia at admission is linked to a higher likelihood of mortality and various complications in newborns (3–8).

There is no definitive standard for measuring newborn's body temperature, but ideally, clinicians should measure rectal temperature (RT) to accurately reflect the body's core temperature, particularly the hypothalamic temperature (9). Previous studies using glass and mercury thermometers have highlighted potential complications associated with measuring rectal temperature in infants (10, 11). To prevent these complications, axillary temperature measurements are commonly used as a surrogate measure of the core body temperature. Measuring the temperature from the axilla is easier to access and is less invasive compared to the rectum.

Inconsistent results have been noted in studies assessing the agreement between rectal and axillary temperatures taken with digital thermometers in newborns, infants and children. A meta-analysis that reviewed 20 studies involving 3,201 term infants and children found notable discrepancies in temperature measurements (12). The overall mean difference between rectal and axillary temperatures was 0.85 °C, with a variation range from −0.19 °C to 1.90 °C, showing a wide degree of variability (12). For newborns specifically, this variability was smaller, with a mean difference of 0.17 °C, which varied from −0.15 °C to 0.50 °C (12).

However, much of the existing research on rectal and axillary temperature correlation is centered on comparing rectal and axillary temperature measurements in stable, normothermic infants who are past the admission period—the first hour after birth—at various times during their stay in NICU. Additionally, the majority of previous studies only compared the AT and RT measurements in term or late preterm infants. Therefore, we focused on extremely and very preterm infants <32 weeks of gestational age to determine whether AT and RT measurements are also comparable in this group of patients. Furthermore, a notable gap exists in understanding this correlation specifically among newborn very preterm infants upon admission post-stabilization in the delivery room. This population often presents unique challenges due to deviations from normothermia and a lack of clinical stability. Consequently, there is a pressing need to investigate the correlation between rectal and axillary temperatures in this cohort.

The purpose of this research was to evaluate the differences between rectal and axillary temperature measurements in preterm infants less than 32 weeks' gestation upon admission to the NICU.

Methods

Between the 27th of September 2023 and the 31st of March 2024, a prospective observational study was carried out in the NICU at The King Abdulaziz Medical City (KAMC), Riyadh, Kingdom of Saudi Arabia. We included premature infants who were less than 32 weeks gestational age at birth. Outborn infants and those with birth defects that made it impossible to measure temperature via the axilla or the rectum were excluded.

King Abdullah International Medical Research Centre (KAIMRC) ethics committee approved the project with IRB number: NRC23R/336/04. Informed consent was obtained retrospectively in cases of emergent deliveries where antenatal consent could not be obtained. This deferred consent process allowed us to enroll patients and collect data while ensuring that parents were approached for consent at the earliest appropriate opportunity.

Temperature in the operating theatre (OT) and the DR was kept at between 23 and 23.5 °C. Directly following birth, infants were promptly positioned in a plastic covering and a hat was applied to cover the head. The plastic bag used in our study is NeoHelp™ by Vygon. NeoHelp™ is made of transparent polyethylene, which allows for visual monitoring of the infant while maintaining a warm environment. The portable incubator (Babyleo TN500; Drager) utilized for transferring the infants between the DR/OT and the NICU was preset to a stable temperature of 36 °C. To ensure optimum warmth, the NICU's incubators were conditioned with moisture and heat before each delivery with the humidity level set at 80%. The NICU is directly opposite the DR and OT.

Upon the infants' entry into the NICU, after initial medical care and taking body size measurements, their admission temperatures were recorded within the first hour after birth.

Temperature measurements of both the rectum and axilla were taken using the "Safety 1st 3-in-1 Nursery Thermometer," which is approved for rectal and axillary use in children and infants. The Thermometer is manufactured by Dorel Juvenile. The measurement temperature range for this thermometer is 32.2–43.2 °C. It has a measurement accuracy of ±0.1 °C for temperatures between 35 and 42 °C and ±0.2 °C for temperatures below 35 °C and above 42 °C. The operational environment for the thermometer is between 10 and 40 °C, and the storage environment is between −25 °C and 60 °C.The manufacturer states that this thermometer is calibrated at the time of its production, and adhering to the provided instructions ensures that the measurement accuracy remains intact. It is a digital thermometer that beeps when the reading is complete. It has a flexible tip which is comfortable for infants during a rectal reading and features an over-insertion gauge for safety during rectal use. The 3-in-1 Nursery Thermometer includes both a protective storage case and a long battery life. It provides accurate reading in 30 s (°F/C) and has the feature to recall last reading.

Eight medical staff were involved in the study and undertook training on temperature measurement using the digital thermometer on the two sites. This helped to ensure the validity of the rectal and axillary temperature measurements in infants

included in the study. In every case, rectal temperature was recorded first. Members of the research team were instructed to turn on the thermometer and wait for a signal before accessing the incubator through the portholes. They were then to gently insert the thermometer's tip up to 1 cm deep into the rectum. The device continuously displayed the temperature until a second signal (eight beeps) indicated that the peak temperature was achieved, usually within about 30 s. For axillary temperature, the thermometer was placed under the arm, ensuring the tip contacted the skin, following the previously outlined procedure. The same thermometer was used for all measurements and was cleaned with an alcohol wipe between each use to maintain hygiene and accuracy.

The study examined various maternal and neonatal factors to describe the study group, including maternal prenatal corticosteroid administration, the occurrence of both pre-pregnancy diabetes mellitus (DM) and gestational diabetes mellitus (GDM), hypertension (both pre pregnancy and pregnancy induced), a history of prolonged rupture of membranes (PROM) in the mother, history of chorioamnionitis, the mode of delivery, along with the neonate's gender, birth weight, and gestational age. In our study, chorioamnionitis was defined clinically based on the presence of maternal fever (≥38.0 °C) and one or more of the following criteria: uterine tenderness, maternal or fetal tachycardia, foul-smelling amniotic fluid, or purulent vaginal discharge, as per the guidelines recommended by the American College of Obstetricians and Gynecologists (13). In our study, antenatal steroid administration was reported for any administration of steroids, including both partial and full courses. At our center, dexamethasone is used as the corticosteroid of choice.

Statistical analysis

The statistical evaluation of the data was conducted using the SPSS version 26.0 software. For this study, a power analysis factoring in the projected differences in rectal and axillary admission temperatures and the standard deviations from existing literature (14) indicated that a sample size of 80 infants would be sufficient. With a targeted power level of 80% and a significance level set at 0.05, this number of participants was anticipated to allow for the detection of statistically significant differences in temperature measurements between the two methods in infants born at less than 32 weeks' gestation.

Normality test was done using the Kolmogorov-Smirnov test. Continuous variables that displayed a normal distribution, were presented as the average (mean) with the standard deviation (SD). On the other hand, variables not adhering to a normal distribution were expressed using the median and the interquartile range (IQR). The comparison of rectal and axillary temperature readings utilized the student's paired t-test, with a *p*-value threshold of less than 0.05 set for determining statistical significance. Variables that were categorical in nature were represented as frequencies and percentages. The Pearson correlation coefficient (R) was calculated to ascertain the linear relationship between the temperature taken at the rectal and axillary sites, and this correlation was illustrated through a scatterplot. The concordance between the two sets of temperature data was analyzed using the Bland-Altman method, which involved plotting the difference between the axillary and rectal readings against their average value. The consistency range was defined by the mean difference plus or minus two standard deviations, establishing the bounds of agreement (15).

Results

In this study, we included eighty infants with a mean gestational age of 28.4 weeks (SD = 2.9) and a mean birth weight of 1,229 grams (SD = 456). The majority of the infants (59%) were male, and (62.5%) were delivered via caesarean section. Antenatal steroid therapy was administered in 74% of the cases. Maternal health conditions were documented: 25% of the mothers had diabetes, 12.5% had hypertension, 38.8% experienced prolonged rupture of membranes (PROM) lasting more than 18 h, and chorioamnionitis was present in 8.8% of the cases (Table 1).

Table 2 presents the temperature data for both mothers and infants participating in the study. The ambient temperature in the DR/OT averaged 23.2 °C (SD = 0.2), while maternal axillary temperature at the time of birth was 36.8 °C (SD = 0.3). In line with hypothermia prevention protocols, all neonates were promptly covered in plastic wrap and fitted with head covers post-delivery. The infants were admitted to the NICU within 17 min (SD = 9) of birth. Upon NICU admission, the mean axillary temperature registered at 36.4 °C (SD = 0.7), which was

TABLE 1 Maternal and infants' characteristics.

Gestational age (weeks) (Mean ± SD)	28.4 (2.9)
Birthweight (grams) (Mean ± SD)	1,229 (456)
Gender (male)	47/80 (59%)
Antenatal steroids	59/80 (74%)
Delivery by Caesarean section	50/80 (62.5%)
Maternal hypertension	10/80 (12.5%)
Maternal diabetes	20/80 (25%)
Maternal Prolonged Rupture of Membranes (PROM) > 18 h	31/80 (38.8%)
Maternal chorioamnionitis	7/80 (8.8%)

TABLE 2 Maternal and infant's temperatures characteristics.

Maternal axillary temperature °C (Mean ± SD)	36.8 (0.3) °C
DR/OT temperature °C (Mean ± SD)	23.2 (0.2) °C
Use of plastic bag (NeoHelp™)	80/80 (100%)
Use of head cover	80/80 (100%)
Time from birth to admission (minutes) (Mean ± SD)	17 (9)
Time from birth to admission (minutes) for (DR) deliveries (Mean ± SD)	17 (9)
Time from birth to admission (minutes) (OT) (Mean ± SD)	18 (8)
Infant's axillary temperature °C (Mean ± SD)	36.4 (0.7)
Infants' rectal temperature °C (Mean ± SD)	36.6 (0.6)
Rectal temperature > axillary	47/80 (59%)
Rectal temperature < axillary	17/80 (21%)
Rectal temperature = axillary	16/80 (20%)

DR = Delivery Room. OT = Operating Theatre.

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significantly lower than the mean rectal temperature which was 36.6 °C (SD = 0.6) ($p = 0.012$). The range of axillary temperature was 5.2 °C (33.2–38.4 °C), whereas the range for rectal temperature was 4.5 °C (33.9–38.4 °C). Rectal temperature surpassed axillary measurements in 59% of instances, while the reverse—axillary readings higher than rectal—was observed in 21% of cases. In 20% of the occurrences, both temperature readings were analogous. No rectal injuries were reported among the patients in our cohort.

This scatter plot (Figure 1) depicts the correlation between rectal and axillary admission temperature in our cohort. The data points represent individual temperature pairs measured upon admission to the NICU, with rectal temperature along the x-axis and axillary temperature along the y-axis. Our analysis of the correlation between rectal and axillary admission temperatures in our cohort yielded a Pearson correlation coefficient of 0.915, which is highly significant ($p < 0.001$) (Table 3). This strong positive correlation is illustrated in the scatter plot, where the close clustering of data points around the line of best fit indicates a consistent linear relationship between the rectal and axillary temperature (Figure 1).

In evaluating the clinical agreement between rectal and axillary temperature measurements in preterm infants, a Bland-Altman plot was employed. This plot revealed a mean difference, or bias, of 0.1 °C, suggesting a slight tendency for axillary temperatures to measure marginally lower than rectal temperatures. Clinically, this minimal bias may be considered negligible; however, the scope of agreement requires careful consideration. The limits of agreement, calculated as the mean difference plus and minus 1.96 times the standard deviation of the differences, range from +0.7 to −0.6 °C (Figure 2). This range is relatively wide, particularly in the context of the narrow temperature range that is critical in neonatal care.

We have analyzed the rates of hypothermia on admission to the NICU (<36.5 °C) in our cohort and found that 23 out of 80 infants (29%) were hypothermic upon admission. Additionally, we examined the limits of agreement between the two temperature measurements for both hypothermic and normothermic infants and found notable differences. For infants who were hypothermic on admission to the NICU ($n = 23$), the mean difference between the two temperature measurements was 0.27 °C, with limits of agreement ranging from −0.5 °C to +1 °C (Figure 3). This indicates a wider range of discrepancy between the temperature measurements for hypothermic infants. In contrast, for infants with normal admission temperatures ($n = 57$), the mean difference was smaller at 0.1 °C, with a narrower limit of agreement ranging from −0.4 °C to +0.6 °C (Figure 4).

TABLE 3 Correlation of rectal and axillary admission temperature.

		Axillary temperature	Rectal temperature
Axillary temperature	Pearson correlation	1	0.915**
	Sig. (2-tailed)		<0.001
	N	80	80
Rectal temperature	Pearson correlation	0.915**	1
	Sig. (2-tailed)	<0.001	
	N	80	80

**Correlation is significant at the 0.01 level (2-tailed).

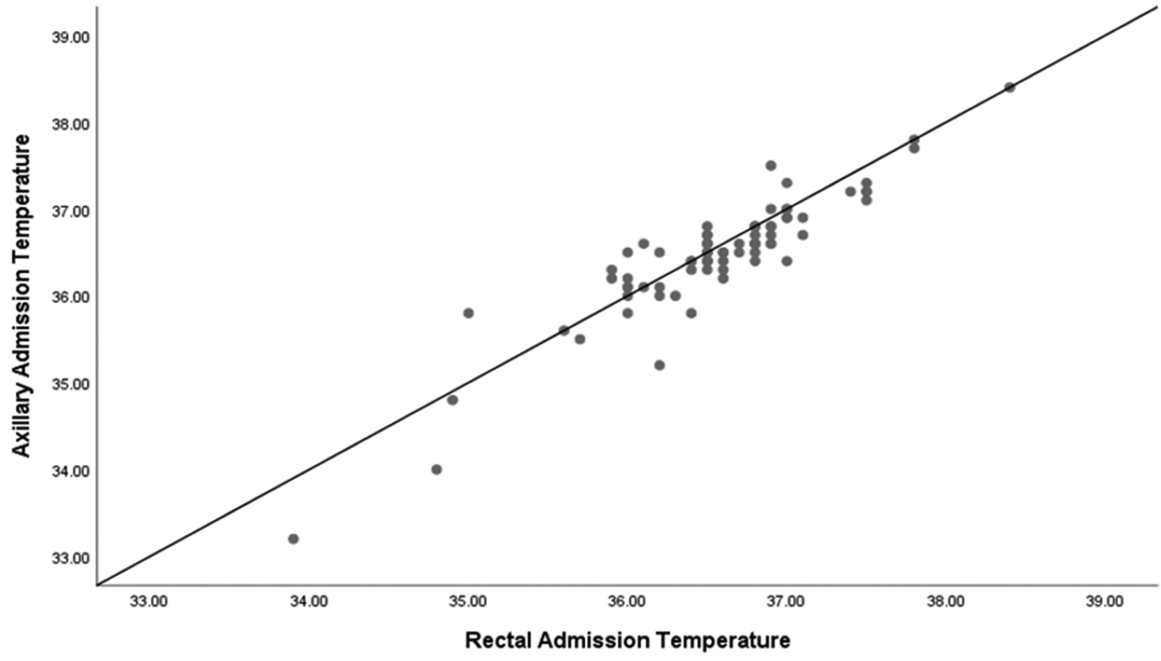

FIGURE 1
Scatter plot of rectal and axillary admission temperature.

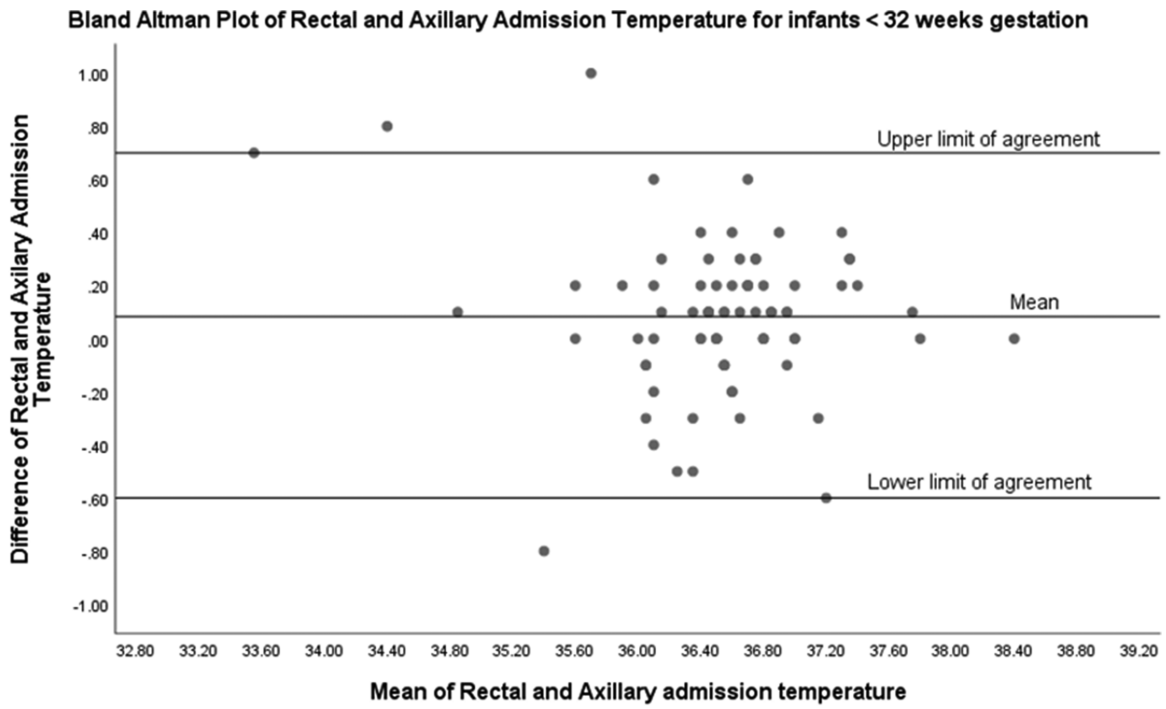

FIGURE 2
Bland-Altman plot of rectal and axillary temperature (n = 80).

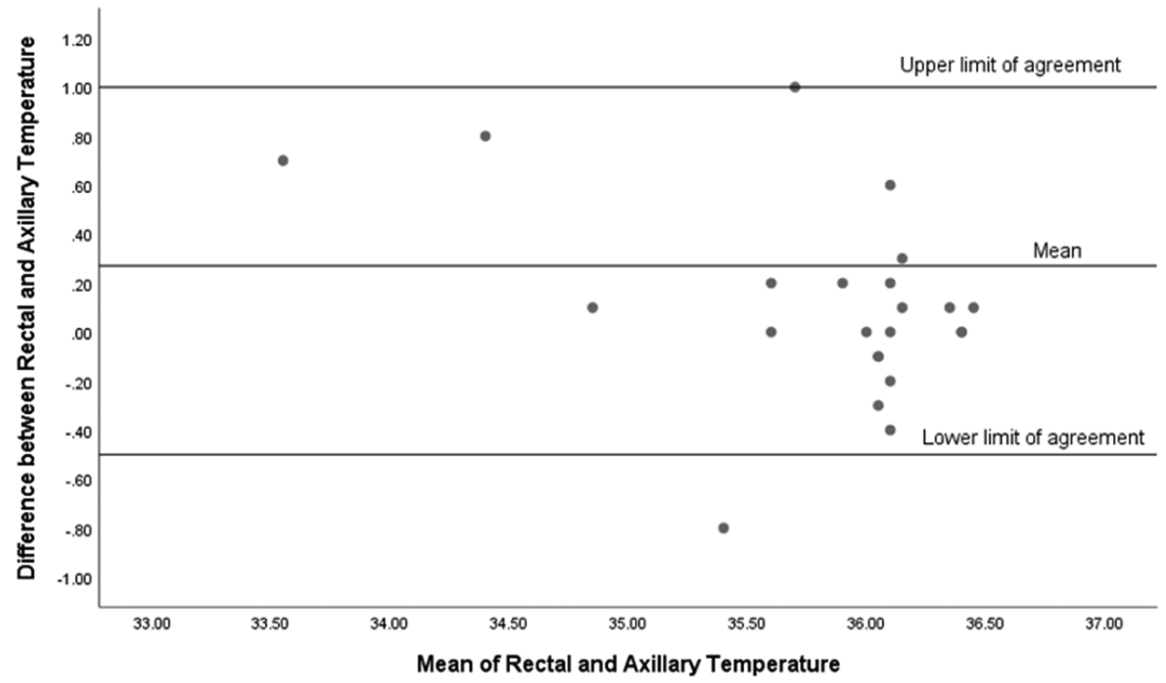

FIGURE 3
Bland-Altman plot for infants with admission temperature <36.5 °C (n = 23).

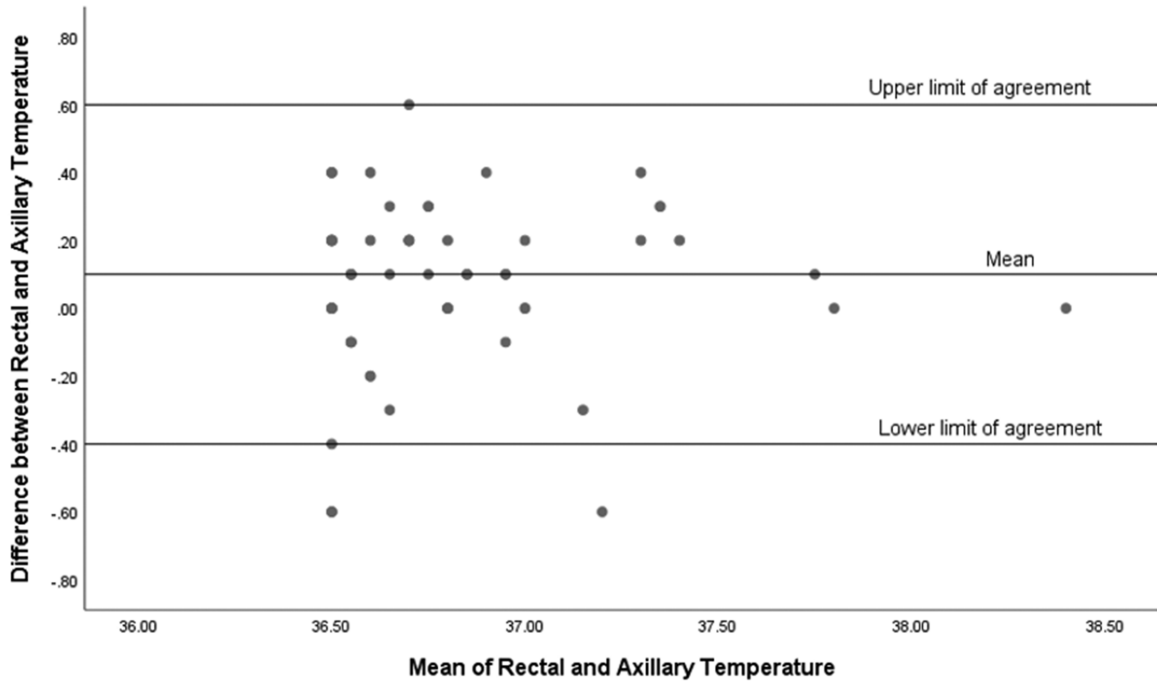

FIGURE 4
Bland-Altman plot for infants with admission temperature >36.5 °C (n = 57).

Discussion

In this prospective study, we observed a strong correlation between rectal and axillary temperature measurements in preterm infants who were born <32 weeks' gestation. Additionally, we found a high incidence of hypothermia on admission in these infants, with 29% being hypothermic upon arrival at the NICU. Despite the strong correlation between rectal and axillary temperatures, rectal temperatures were consistently higher than axillary temperatures, raising important considerations for clinical practice. Nevertheless, the limits of agreement between these two measurement methods were wide, particularly in infants who were hypothermic upon admission. This discrepancy highlights the potential challenges in relying solely on axillary temperatures for clinical decisions in the NICU.

In our study, the infants were predominantly delivered via cesarean section, had a mean gestational age of 28.4 weeks and received immediate interventions to prevent hypothermia in the delivery room as per the Newborn Resuscitation Program (NRP) (16).

We have shown that rectal temperatures in our cohort were higher than the axillary temperatures. Despite the strong correlation observed in the scatter plot analysis, the Bland-Altman analysis provided additional insight into the clinical applicability of using axillary temperature as a surrogate for rectal temperature. Our Bland-Altman plot for all infants in our cohort revealed that although the mean difference between rectal and axillary temperature measurements was small (0.1 °C), indicating good initial agreement between the two methods, the limits of agreement were wide (−0.6 °C to +0.7 °C). This discrepancy was even more pronounced in hypothermic infants. For hypothermic infants, the mean difference between rectal and axillary temperatures was 0.27 °C, with a wide limit of agreement ranging from −0.5 °C to +1 °C. This significant discrepancy suggests that axillary temperatures may not reliably reflect core body temperatures in hypothermic infants, potentially leading to suboptimal clinical decisions. Conversely, for normothermic infants, the mean difference was smaller at 0.1 °C, with a narrower limit of agreement from −0.4 °C to +0.6 °C, indicating a more consistent correlation between the two measurement methods. Therefore, while axillary temperature measurements may be informative for population-level assessments due to their correlation with rectal temperatures, our results advise caution when applying these findings to individual neonates. These findings emphasize the importance of selecting the appropriate method for temperature measurement in the NICU. While axillary temperature measurements are less invasive and generally correlate well with rectal temperatures in normothermic infants, their reliability decreases in hypothermic infants. Therefore, clinicians should consider using rectal temperature measurements for a more accurate assessment of core body temperature in hypothermic infants to ensure effective thermal regulation and better clinical outcomes.

The average discrepancy noted between rectal and axillary temperature readings of 0.1 °C. stands in contrast to the larger differences between rectal and axillary temperatures documented in earlier studies, where mean differences were observed at 0.17 °C (12), 0.27 °C (14), 0.16 °C (17), and significantly, a 0.7 °C difference (18). A plausible reason for our study showing

a narrower margin could be the uniformity of our sample group, which consisted solely of preterm infants less than 32 weeks' gestation, and the fact that temperature measurements were conducted concurrently at admission to NICU within a narrow time window of one hour. Other studies have incorporated a broader and more varied demographic, such as one investigation that looked at infants aged up to six months in both hospital and home environments (18), while another recorded temperatures at various intervals during the infants' stay in the NICU (17). Additionally, some studies have combined data from both term and preterm infants in their analysis (12, 14). In one particular study that performed a subgroup analysis on preterm infants, the data suggested that the alignment between rectal and axillary temperatures tends to be more consistent in preterm infants compared to those who are term (17).

More importantly, there is a scarcity of data concerning the correlation of rectal and axillary temperatures of extremely and very preterm infants at the time of their NICU admission. In a similar study to ours published recently (19), the authors found the mean difference between the rectal and axillary temperatures to be the same as ours (0.1 °C). However, the limits of agreement were even wider than ours (−1.4 °C-+1.5 °C). This suggests a tighter agreement in our measurements, yet it still underscores the potential clinical implications when utilizing axillary temperatures as proxies for rectal measurements in this patient population. We speculate that differences in the demographic characteristics of the study populations, such as age, weight, and clinical conditions, might have played a role in the different level of agreement between the two studies. Additionally, the types of thermometers used in the two studies were different, affecting the accuracy and consistency of the measurements. Finally, environmental conditions during temperature measurements, such as room temperature and humidity, could have influenced the results.

A notable advantage of our investigation is the provision of prospective data on a comparably uniform and sizeable cohort of extremely and very preterm infants, all assessed at the same temporal juncture. We recorded the rectal and axillary temperatures sequentially with the same thermometer for each baby, without any intervening medical procedures to modify the infant's body heat, making it improbable that body temperature fluctuations contributed to the observed differences in readings. Nevertheless, our study is not without its limitations. Despite utilizing a uniform thermometer for recording both rectal and axillary temperatures, the measurements were taken by various nurses and doctors, each with different levels of expertise. Nonetheless, the consistency of the thermometers and adherence to standard clinical procedures and manufacturer guidelines ensure a level of standardization. Still, numerous potential issues can affect the accuracy of temperature readings. The precision of axillary temperature can be influenced by factors such as the proper positioning of the axilla and local blood circulation. Similarly, the accuracy of rectal temperature readings might be impacted by how deeply the thermometer is inserted and whether there is stool in the rectum. Finally, this study is limited by its single-center design and relatively small sample size, which may restrict the generalizability of our findings. Future studies should aim to include multiple centers to enhance the robustness and applicability of the results.

Occasionally, there's hesitancy in performing rectal temperature checks on newborns due to the perception of it being an invasive procedure, historically linked to rare instances of rectal perforation. However, the incidence of injury from such temperature assessments is noted to be exceedingly low (18), with most reported cases of injury pertaining to the now-out of use mercury-in-glass thermometers. Contemporary practice has shifted to using plastic, digital thermometers that are designed with slender, smooth probes that produce results in just 30 s, diminishing the likelihood of breakage and injury.

Our current practice for measuring temperature in preterm infants at admission involves using axillary temperature measurements due to their non-invasive nature and ease of use. Although our study provides valuable insights, these findings are not yet sufficient to change our practice. Further validation through larger multicenter trials is necessary to establish robust evidence that could potentially influence clinical guidelines.

Conclusion

Given the critical importance of accurate thermal regulation in preterm infants, our study highlights the need for cautious interpretation of axillary temperature measurements upon admission to the NICU. While we found a strong correlation between rectal and axillary temperatures, the limits of agreement were wide, particularly in hypothermic infants. Therefore, clinicians should be aware of these discrepancies and consider using rectal temperature measurements, especially in infants with hypothermia, for more accurate assessment of core body temperature. This approach will help ensure more reliable data for critical care decisions, ultimately improving outcomes for premature infants.

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 King Abdullah International Medical Research Centre (KAIRMC). 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

SH: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Validation,

Writing – original draft, Writing – review & editing. RA: Data curation, Project administration, Resources, Writing – original draft, Writing – review & editing. AA: Data curation, Methodology, Resources, Writing – original draft, Writing – review & editing. MaA: Data curation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. MuA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. RM: Data curation, Writing – original draft, Writing – review & editing. AH: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. FA: Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing. SA: Writing – review & editing, Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft. KA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, 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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EDITED BY
Minesh Khashu,
University Hospitals Dorset NHS Foundation Trust, United Kingdom

REVIEWED BY
Lingkong Zeng,
Huazhong University of Science and Technology, China
Karel Allegaert,
KU Leuven, Belgium

*CORRESPONDENCE
Xianghong Li
lixianghong0329@126.com
Hong Jiang
jianghong@qdu.edu.cn

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

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The association between serum 25-hydroxyvitamin D levels and retinopathy of prematurity in preterm infants

Xiangyun Yin[1†], Shimin Xu[2†], Xuefei Zhang[3], Liangliang Li[1], Hongmin Xi[1], Lili Ma[1], Mengya Sun[1], Ping Yang[1], Xianghong Li[1*] and Hong Jiang[1*]

[1]Department of Neonatology, The Affiliated Hospital of Qingdao University, Qingdao, China, [2]Department of Neonatology, Beijing Jingdu Children's Hospital, Beijing, China, [3]Qingdao University, Qingdao, China

Objective: This study aimed to investigate the correlation between serum 25-hydroxyvitamin D (25(OH)D) levels and retinopathy of prematurity (ROP) in premature infants one month after birth.
Methods: Preterm infants (gestational age <32 weeks) admitted to the Affiliated Hospital of Qingdao University from 2017 to 2022 were divided into ROP and non-ROP groups based on ROP occurrence any stage. Serum 25(OH)D levels and clinical data were compared between the two groups at 1 month after birth, and the relationship between vitamin D levels and ROP was analyzed.
Results: Among the 217 premature infants included, 55 (25.35%) were in the ROP group, and 162 (74.65%) were in the non-ROP group. The ROP group had lower gestational age and birth weight, longer invasive ventilation (IV), non-invasive ventilation (NIV), and oxygen therapy times compared to the non-ROP group. Apgar scores, cesarean delivery, and antenatal steroids ratios were lower in the ROP group, while sepsis and pulmonary surfactant utilization ratios were higher (all $p < 0.05$). Significant differences in serum 25-(OH)D levels were observed among children in the non-ROP group (14.20 ± 5.07 ng/ml), ROP treated group (7.891 ± 1.878 ng/ml), and untreated group (12.168 ± 4.354 ng/ml) ($p < 0.001$). Multivariate regression analysis identified antenatal steroids as protective factors and lower birth weight, serum 25-(OH)D levels, long-term invasive mechanical ventilation, and sepsis as independent risk factors for ROP in premature infants.
Conclusion: Vitamin D, lower birth weight, long-term invasive mechanical ventilation, and sepsis were associated with incidence of ROP in preterm infants. Vitamin D was associated with the severity of ROP, emphasizing the importance of prudent vitamin D supplementation and regular monitoring of serum 25-(OH)D levels.

KEYWORDS

retinopathy of prematurity, serum 25-hydroxyvitamin D, lower birth weight infants, preterm infant, sepsis

1 Introduction

Retinopathy of prematurity (ROP) is characterized by abnormal proliferation of retinal blood vessels in the eyes of premature infants. The incidence and severity of ROP increase with decreasing gestational age and birth weight, posing a significant threat to infant vision. Severe cases may lead to retinal detachment and subsequent blindness (1–4).

ROP is linked to elevated levels of vascular endothelial growth factor (VEGF) caused by local hypoxia, promoting aberrant formation of blood vessels in newborns. After birth, premature infants experience a deficiency in the supply of IGF-1 from the placenta and lack autonomous production, thereby impacting the development of retinal blood vessels. Key factors contributing to ROP include premature birth, low birth weight, oxygen therapy, anemia, blood transfusions, sepsis, metabolic acidosis, respiratory distress syndrome (RDS), apnea, and maternal pregnancy complications (5, 6). As our understanding of ultra-premature infants advances, early identification of high-risk factors for ROP becomes crucial for prevention and treatment, ultimately reducing the incidence of blindness and improving the quality of life for premature infants (7).

Vitamin D, a biologically active fat-soluble vitamin synthesized endogenously, not only regulates calcium and phosphorus metabolism but also exhibits antioxidant and anti-inflammatory effects. Additionally, it plays a role in anti-angiogenesis, cell growth, and differentiation. Eye tissues contain vitamin D receptors and 1-hydroxylase, indicating a local regulatory role (8). Given that placental transfer of vitamin D mainly occurs during the third trimester, vitamin D deficiency is a concern, particularly in premature infants with a gestational age <32 weeks (9, 10). However, there is limited research on the association between vitamin D and ROP. Some studies suggested that lower 25(OH)D levels in premature infants with a gestational age <32 weeks after birth might be related to ROP (11–13).

This study aims to collect 25(OH)D levels in premature infants with a gestational age <32 weeks at 1 month after birth and retrospectively analyze clinical data to explore the relationship between serum 25(OH)D levels and ROP. The findings provide valuable insights for the clinical prevention and treatment of ROP in premature infants.

2 Patients and methods

2.1 Preterm infants

A retrospective study was conducted on all preterm infants with a gestational age <32 weeks admitted to the intensive care unit at the Affiliated Hospital of Qingdao University during 2017–2022. All infants in the hospital signed the written consent "clinical samples to carry out scientific research" by parents.

Inclusion criteria: (1) Preterm infants with a gestational age <32 weeks. (2) Premature infants admitted to the hospital within 24 h after birth, with a hospitalization duration exceeding 4 weeks. (3) Infants whose condition improves or is cured upon discharge.

Exclusion criteria: (1) Specific congenital eye diseases, such as retinoblastoma, congenital cataract, glaucoma, etc. (2) Infants with genetic metabolic diseases and congenital developmental malformations. (3) Cases involving death during hospitalization, incomplete clinical data, or family members opting for treatment discontinuation. (4) Individuals with incomplete information.

Based on the occurrence of retinopathy of prematurity (ROP), participants were divided into the ROP group and non-ROP group. Within the ROP group, two subgroups were identified based on whether ranibizumab or laser treatment was administered: treated ROP group and untreated group. The study received approval from the Affiliated hospital of Qingdao University ethics committee (QYFY WZLL 28884).

2.2 Methods

2.2.1 Vitamin D supplementation method

Enteral feeding should be initiated once the condition of the included children stabilizes. Refer to the "Recommendations for the Prevention and Treatment of Vitamin D Deficiency and Vitamin D Deficiency Rickets" (14) for vitamin D supplementation guidance. For preterm infants with a gestational age <32 weeks, prioritize breast milk when establishing enteral feeding. Breast milk fortifier (Similac Human Milk Fortifier, POWDER) is added when milk intake reaches 80–100 ml/kg. If breast milk is insufficient, formula milk is provided. Daily supplements include 1 Vitamin AD Soft Capsules (DYNE PHARMA, vitamin D 500 IU) and vitamin D3 400 IU per day. Parenteral nutrition for all premature infants follows the 2013 Chinese Clinical Application Guidelines for Neonatal Nutritional Support (15), with the vitamin D content of fat-soluble vitamins in intravenous nutrition at 400 IU/10 ml (neonatal dosage is 1 ml/kg).

2.2.2 ROP screening

Follow the "China Retinopathy of Prematurity Screening Guidelines (2014)" (16). Qualified ophthalmologists use indirect ophthalmoscopy or RetCam fundus cameras to screen infants with a gestational age of 32 weeks or a birth weight of 2,000 g. Premature and low birth weight infants undergo ROP screening, with the first screening performed at 4–6 weeks after birth or 31–32 weeks after menstruation, until corrected the gestational age to 44 weeks, retinal blood vessels should grow until the jagged edge. Indications for early treatment of ROP (17) involve the use of anti-VEGF drug ranibizumab or laser therapy.

2.2.3 Data collection methods: collect data on infants and their mothers through electronic medical records

General information includes sex, gestational age, birth weight, mode of delivery, Apgar scores at 1 and 5 min.

Clinical data encompass oxygen therapy time, invasive ventilation time, non-invasive ventilation time, serum 25-(OH)D level at 1 month after birth, pulmonary surfactant (PS) treatment and breastfeeding time.

Perinatal factors include preeclampsia, gestational diabetes mellitus, and antenatal steroids.

Major complications are defined as follows: Bronchopulmonary dysplasia (BPD), Patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and sepsis.

Use of invasive ventilation, non-invasive ventilation, PS, and antenatal steroids aligns with the "European Consensus Guidelines for the Management of Neonatal Respiratory Distress Syndrome (2019 Edition)" (18).

Oxygen therapy time is calculated by summing mechanical ventilation time, hood oxygen inhalation time, and nasal cannula oxygen inhalation time.

3 Statistical methods

SPSS 29.0 statistical software was utilized for comprehensive data analysis, while GraphPad Prism 10 software facilitated graphical representation. For measurement data conforming to a normal distribution, mean ± standard deviation ($x \pm s$) was employed. Group comparisons were conducted using independent samples *t*-test and single-factor ANOVA. In cases where measurement data deviated from normal distribution, the results are presented as median (interquartile range) M (Q1, Q3), and the Mann–Whitney *U* rank sum test was applied for between-group comparisons.

Count data was expressed as case (percentage) *n* (%), and the χ^2-test or Fisher's exact probability method was employed for group comparisons. Single-factor analysis helped identify statistically significant influencing factors as independent variables, with ROP occurrence serving as the dependent variable in the logistic regression model for multi-factor analysis. A significance threshold of $p < 0.05$ was considered indicative of statistically significant differences.

4 Results

4.1 Demographic information

Throughout the study period, 217 premature infants with a gestational age <32 weeks met the inclusion criteria at our hospital. This cohort comprised 162 infants (74.65%) in the non-ROP group and 55 infants (25.35%) in the ROP group. Specifically, among the ROP group, 13 infants underwent treatment with ranibizumab (treated ROP group), constituting 23.6% (13/55), while 42 infants remained untreated, representing 76.4% (42/55).

4.2 Single factor analysis of ROP

4.2.1 Analysis of perinatal factors

In the ROP group, the gestational age, birth weight, Apgar score, rate of cesarean section, and antenatal steroid usage were all notably lower than those observed in the non-ROP group. These differences reached statistical significance ($p < 0.05$). In contrast, when comparing sex, gestational diabetes mellitus, and preeclampsia between the two groups, no statistically significant differences were identified ($p > 0.05$) (refer to Table 1).

TABLE 1 Comparison of perinatal factors between the two groups.

	non-ROPgroup (162)	ROP group (55)	Statistical value	*p*-value
Sex			0.357	0.55
Female[a]	72 (44.4)	27 (49.1)		
Male[a]	90 (55.6)	28 (50.9)		
GA (d)[b]	212 (204,219)	196 (186,206)	−6.701	<0.001
BW (g)[b]	1,300 (1,100,1,550)	970 (850,1,130)	−6.722	<0.001
Cesarean delivery[a]	132 (81.5)	34 (61.8)	8.83	0.003
Apgar 1 min[b]	8 (7,9)	6 (5,8)	−4.923	<0.001
Apgar 5 min[b]	9 (8,10)	8 (7,9)	−4.661	<0.001
GDM[a]	28 (17.3)	7 (12.7)	0.63	0.427
Preeclampsia[a]	60 (37.0)	13 (23.6)	3.303	0.069
Antenatal steroids[a]	113 (69.8)	19 (34.5)	21.361	<0.001

GA, gestational age; BW, birth weight; GDM, gestational diabetes mellitus.
[a]Is represented by example (%).
[b]Is represented by M (Q1, Q3), and the statistical value is *Z* value or X^2 value.

4.2.2 Clinical data analysis

The serum 25-(OH)D level in the ROP group was observed to be lower than that in the non-ROP group. Additionally, the ROP group exhibited significantly higher values in terms of invasive ventilation time, non-invasive ventilation time, oxygen therapy time, sepsis incidence, and pulmonary surfactant (PS) treatment compared to the non-ROP group, with all differences proving statistically significant ($p < 0.05$). In contrast, there were no statistically significant differences noted in the occurrences of Patent Ductus Arteriosus (PDA), Bronchopulmonary Dysplasia (BPD), and Necrotizing Enterocolitis (NEC) between the two groups ($p > 0.05$) (refer to Table 2).

4.2.3 Multifactor analysis of ROP risk factors

Multivariate logistic regression analysis was employed on variables that exhibited statistical significance in the univariate analysis. The outcomes revealed that antenatal steroids serve as a protective factor for ROP in premature infants. Conversely, lower vitamin D, lower birth weight, prolonged invasive mechanical ventilation time, and sepsis were identified as independent risk

TABLE 2 Comparison of clinical data between the two groups.

	non-ROP group (162)	ROPgroup (55)	Statistical value	*p*-value
25- (OH) D (ng/ml)[a]	14.20 ± 5.07	11.16 ± 4.31	3.982	<0.001
IV time (d)[b]	0 (0,0)	1 (0,11)	−6.634	<0.001
NIV time (d)[b]	11.5 (7,31)	31 (12,53)	−4.017	<0.001
Days with oxygen (d)[b]	7, (19,47.25)	35 (53,79)	−5.818	<0.001
PDA[c]	65 (40.1)	24 (43.6)	0.209	0.647
BPD[c]	53 (32.7)	22 (40.0)	0.963	0.326
Sepsis[c]	15 (9.3)	19 (34.5)	19.869	<0.001
PS[c]	50 (30.9)	34 (61.8)	16.582	<0.001
NEC[c]	17 (10.5)	9 (16.4)	1.341	0.247
DOB (d)[b]	51.5 (15,68.13)	38.5 (9,61)	−1.644	0.1

IV, invasive ventilation; NIV, non-invasive ventilation; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; PS, pulmonary surfactant; NEC, necrotizing enterocolitis; DOB, days of breastfeeding.
[a]Is expressed as $x \pm s$.
[b]Is expressed as M (Q1, Q3), and the statistical value is *t*, *Z* or X^2 value.
[c]Is expressed as example (%).

TABLE 3 Logistic regression analysis of risk factors for retinopathy of prematurity.

Influence factor	*B*	Wald value	*p*-value	OR value	95% CI
Level of 25- (OH) D	−0.105	4.471	0.034	0.901	0.818–0.992
BW	−0.003	7.91	0.005	0.997	0.994–0.999
Sepsis	1.102	4.131	0.042	3.011	1.04–8.717
Antenatal steroids	−1.821	14.846	<0.001	0.162	0.064–0.409
IV time	0.109	6.733	0.009	1.115	1.027–1.211

factors for the development of retinopathy of prematurity (ROP) in preterm infants (refer to Table 3).

4.2.4 Comparison of serum 25-(Oh)D levels among non-ROP, treated ROP, and untreated ROP groups and correlation analysis with ROP severity

Significant differences in serum 25-(OH)D levels were observed among the three groups of children ($p < 0.001$). Specifically, the treated ROP group exhibited the lowest serum 25-(OH)D levels (see Figure 1).

5 Discussion

ROP is one of the leading causes of blindness in preterm infants. The development of fetal retinal blood vessels initiates from the optic disc at approximately 16 weeks of gestation and progresses towards the periphery. By about 32 weeks of gestation, these vessels reach the lateral peripheral part. Notably, the temporal retinal blood vessels do not achieve full maturity until the fetus reaches full term. The immaturity of retinal blood vessels is more pronounced in infants with younger gestational ages, correlating with an increased likelihood of ROP development. In this study, the incidence of ROP in premature infants with a gestational age <32 weeks was found to be 25.35%, a figure that aligns closely with the results reported in both domestic and foreign studies (16, 19–21).

The etiology and pathogenesis of Retinopathy of Prematurity (ROP) involve the intricate interplay of multiple factors. Notably, preterm birth and low body weight stand out as foundational contributors to the development of ROP (19, 21). Cytokines that play a crucial role in promoting retinal development are relatively scarce in early pregnancy and do not witness a significant increase until the later stages of pregnancy. Among these cytokines, insulin-like growth factor-1 (IGF-1) emerges as a key regulator of the vascular endothelial system, playing a pivotal role in the occurrence and progression of ROP (22, 23). After birth, premature infants experience a deficiency in the supply of IGF-1 from the placenta and lack autonomous production, thereby impacting the development of retinal blood vessels. The findings of this study corroborate these insights, revealing that children in the ROP group had lower gestational ages and birth weights compared to those in the non-ROP group. It is evident that low birth weight serves as a high-risk factor for the onset of ROP.

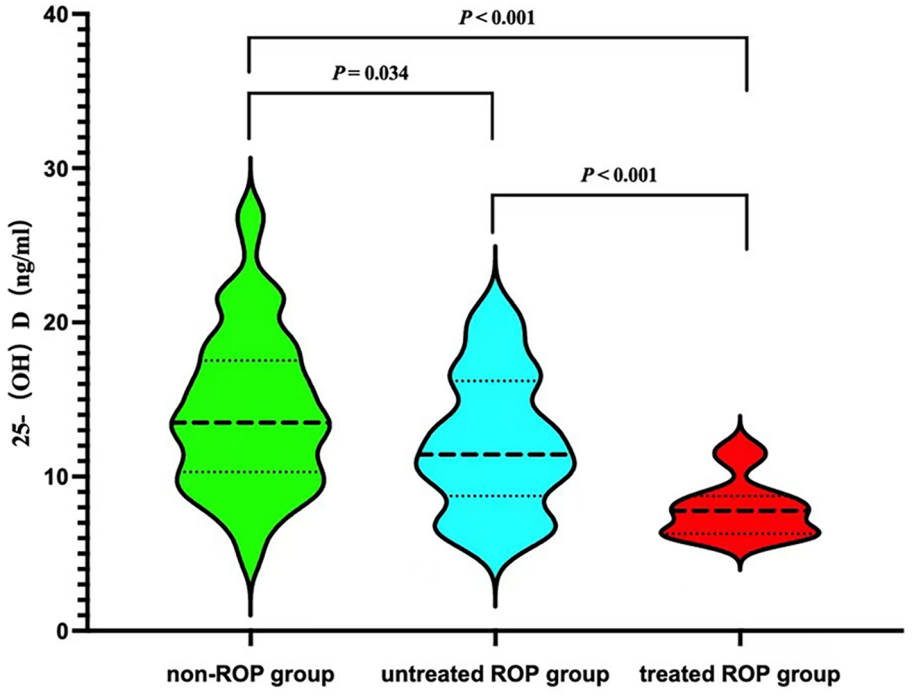

FIGURE 1
Comparison 25- (OH) D levels among three groups.

Due to the underdeveloped respiratory system and nervous system of premature infants, they often experience frequent apnea or neonatal respiratory distress syndrome, necessitating high-concentration oxygen therapy for survival. The immature retinal blood vessels in these infants are highly sensitive to oxygen, and exposure to high concentrations can lead to vasoconstriction and, in severe cases, occlusion, resulting in relative hypoxia in the retina. The intricate interplay of various active factors under these conditions promotes the generation of numerous new blood vessels, culminating in the development of Retinopathy of Prematurity (ROP) (24, 25). The findings of this study align with these mechanisms, indicating that children with ROP had higher durations of invasive mechanical ventilation, non-invasive mechanical ventilation, and oxygen therapy compared to those without ROP. Notably, invasive ventilation time emerged as an independent risk factor for the occurrence of ROP. de las Rivas Ramírez et al. retrospectively collected ROP data from preterm infants treated in Regional University Hospital of Málaga, in the multivariate analysis, weight and mechanical ventilation duration, and late-onset sepsis were independently associated with the development of ROP (26).

This study identifies sepsis as a significant risk factor for Retinopathy of Prematurity (ROP). Sepsis poses an increased risk for ROP, with inflammatory factors playing a pivotal role in this association (27, 28). During infections, premature infants release substantial amounts of cytokines, including IL-6 and TNF-α. These cytokines can inflict damage on endothelial cells or disrupt vascular function, subsequently stimulating retinal vascular endothelial cells to produce vascular endothelial growth factor (VEGF), thereby contributing to the onset of ROP (29–31). Infections in premature infants may also induce hemodynamic changes, influencing retinal blood perfusion and resulting in heightened retinal ischemia, ultimately leading to the development of ROP.

Antenatal steroids emerge as protective factors against Retinopathy of Prematurity (ROP), effectively reducing the risk of its occurrence (32, 33). Notably, this study revealed a notably low rate of antenatal steroid administration in the ROP group, standing at only 34.5%. The "European Guidelines for the Management of Neonatal Respiratory Distress Syndrome" advocate for the administration of antenatal steroids to all pregnant women with a gestational age of less than 34 weeks and those at risk for preterm birth. The administration of glucocorticoids aids in promoting fetal lung maturation, decreasing the postpartum oxygen requirement, and consequently mitigating the risk of ROP. Additionally, antenatal steroids exhibit inhibitory effects on the production of oxidative stress and inflammatory factors, indirectly contributing to the prevention of ROP.

Vitamin D undergoes hydroxylation in the human liver to form 25-(OH)D. This metabolite, characterized by a stable structure and a long half-life, serves as the optimal indicator for assessing the nutritional status of vitamin D (34). Studies by Alsalem et al. (8) have identified the presence of vitamin D receptors and hydroxylase in ocular cells, including corneal epithelial and retinal cells. These cells have the capacity to convert vitamin D from an inactive form to its active form. Given that intrauterine placental transport of vitamin D predominantly occurs in the third trimester, vitamin D deficiency is prevalent among premature infants. Despite routine vitamin D supplementation, our study reveals an overall deficiency in 25-(OH)D levels among premature infants in our hospital. The serum 25-(OH)D concentration in the ROP group at one month is significantly lower than that in the non-ROP group, exhibiting a consistent pattern, and that had significant difference between treated group and untreated group. A study conducted in Iran (35) found an association between low vitamin D levels in premature infants on the first day after birth and ROP. The severity of ROP increased with greater vitamin D deficiency. Another study from India (36) demonstrated persistent vitamin D deficiency in premature infants with ROP at 4 weeks after birth compared to those without ROP. The current understanding of the pathogenesis of vitamin D in retinopathy encompasses several aspects: Antioxidant effect: Vitamin D's antioxidant properties mitigate oxidative stress damage to the retina and optic nerve by preserving mitochondrial function and neutralizing free radicals (37). Anti-inflammatory and immunomodulatory effects: Studies have demonstrated that vitamin D can modulate T cell subset proportions in retinopathy, inhibit inflammatory response signaling pathways, and decrease inflammatory cell infiltration, thereby reducing damage to the retina and optic nerve (38, 39). Anti-angiogenic effect: Deregulation of vascular endothelial growth factor (VEGF) levels leads to (ROP). VIT-D binding domains are present in the promoter regions of VEGF, thus, VIT-D supplementation might aid in restoring VEGF levels, especially in pathologic conditions secondary to low VEGF levels (40). Jamali et al. (41) have demonstrated that vitamin D's inhibitory effect on retinal neovascularization is dependent on the expression of vitamin D receptors. Experimental studies in a mouse model of oxygen-induced ischemic retinopathy revealed that mice treated with calcitriol exhibited a significant decrease in VEGF expression, retinal neovascularization, and blood-retinal barrier permeability (42, 43). Investigation of serum vitamin D levels is recommended, Early correction of vitamin D deficiency may lead to reduction of RoP in premature infants (35).

6 Conclusion

In conclusion, this study highlights that Vitamin D, lower birth weight, long-term invasive mechanical ventilation, and sepsis were associated with incidence of ROP in preterm infants.

Standardizing the administration of antenatal steroids, providing judicious vitamin D supplementation, and closely monitoring serum 25-(OH)D levels can be instrumental in mitigating the incidence and severity of ROP in this vulnerable population.

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 Medical Ethics Committee of the Affiliated Hospital of Qingdao University. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from primarily isolated as part of your previous study for which ethical approval was obtained. 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

XY: Conceptualization, Writing – original draft. SX: Formal Analysis, Methodology, Writing – review & editing. XZ: Data curation, Investigation, Writing – review & editing. LL: Investigation, Writing – review & editing. HX: Data curation, Writing – review & editing. LM: Investigation, Writing – review & editing. MS: Funding acquisition, Writing – review & editing. PY: Writing – review & editing. XL: Supervision, Visualization, Writing – review & editing. HJ: 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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EDITED BY
Minesh Khashu,
University Hospitals Dorset NHS Foundation Trust, United Kingdom

REVIEWED BY
Vera M. Zdravkovic,
University Children's Hospital, Serbia
Xin Ding,
Children's Hospital of Soochow University, China
Siyu Chen,
China Pharmaceutical University, China

*CORRESPONDENCE
Hong Zhong
zhonghong_321@njmu.edu.cn
Xianwei Cui
xwcui@njmu.edu.cn
Chenbo Ji
chenboji@njmu.edu.cn

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

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Metabolic profiles in gestational diabetes mellitus can reveal novel biomarkers for prediction of adverse neonatal outcomes

Xiaoxiao Yin[1,2†], Tingting Yu[1†], Dongmei Jiang[1,2†], Chunjian Shan[1], Jiaai Xia[1], Min Su[3], Min Zhang[1], Ling Chen[1], Hong Zhong[1*], Xianwei Cui[1*] and Chenbo Ji[1,2*]

[1]Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital, Nanjing, Jiangsu, China, [2]School of Nursing, Nanjing Medical University, Nanjing, Jiangsu, China, [3]Department of Obstetrics and Gynecology, Affiliated Hospital of Nantong University, Nantong, China

Background: Gestational diabetes mellitus (GDM) significantly affects the fetal metabolic environment, elevating risks of neonatal hypoglycemia and macrosomia. Metabolomics offers promising avenues for early prediction and diagnosis of GDM and associated adverse offspring outcomes.
Methods: This study analyzed serum samples from pregnant women diagnosed with GDM at 24 to 28 weeks of gestation using untargeted metabolomics. We monitored the health outcomes of their offspring to explore the correlation between initial serum metabolite profiles and subsequent health outcomes, to uncover the predictive markers for hypoglycemia and macrosomia in these offspring.
Results: Out of 200 participants, 154 had normal newborns, 33 had offspring with hypoglycemia, and 19 had offspring with macrosomia. From 448 identified metabolites, 66 showed significant differences in cases of hypoglycemia, and 45 in macrosomia. A panel of serum metabolite biomarkers achieved Area Under the Curve (AUC) values of 0.8712 for predicting hypoglycemia and 0.9434 for macrosomia.
Conclusion: The study delineated metabolic disruptions in GDM during 24–28 weeks of gestation and pinpointed biomarkers capable of forecasting adverse neonatal outcomes. These findings could inform GDM management strategies and minimize the incidence of such outcomes.

KEYWORDS

GDM, hypoglycemia, macrosomia, metabolomics, prediction biomarkers

1 Introduction

Gestational diabetes mellitus (GDM), which is characterized by variations in glucose tolerance that first appear or are observed during pregnancy (1), accounts for 80%–90% of the cases of pregnancy-related hyperglycemia. A meta-analysis show that the global GDM prevalence was 14.2% by 2021 according to the IADPSG diagnostic criteria (2). The incidence of adverse pregnancy outcomes such as hypoglycemia, macrosomia, and hyperbilirubinemia in the offspring of women with GDM has been reported to be 1.16–2.02-fold higher than that in cases with normal glucose hemostasis (3, 4). Therefore, preventing or treating GDM and avoiding the occurrence of adverse pregnancy outcomes is clinically important.

Despite diet and exercise management during pregnancy, GDM is associated with a high risk of neonatal hypoglycemia and macrosomia. Ambient hyperinsulinemia plays a

crucial role in the development of fetal macrosomia and neonatal hypoglycemia (5). In severe cases, neonates with hypoglycemia may show feeding difficulties and brain damage, resulting in intellectual disability and permanent nerve damage (6). Similarly, macrosomia affects maternal and perinatal health and increases the risk of metabolic diseases such as obesity, diabetes, and hyperlipidemia in adulthood (7). Numerous studies have demonstrated that elevated fasting blood glucose (FBG) (8), glycated hemoglobin (HbA1c) (9), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) (10) levels are associated with adverse maternal and infant outcomes in cases of GDM. However, these clinical indicators are not sufficient to predict the risk of neonatal hypoglycemia and macrosomia.

Metabolomics has been recently used to predict and diagnose GDM (11, 12). The changes in metabolites directly reflect the activities or processes that have occurred or are currently occurring within an organism (13). Untargeted metabolomics can provide insights into the role of metabolites in physiological and pathological conditions (14, 15). Serum metabolomic studies have identified significant changes in metabolites such as iconic acid, glucosamine, and tetrahydrocortisone, making them potential biomarkers for early GDM diagnosis (16–18). Metabolomics has also been used to predict the risk of progression from GDM to type 2 diabetes mellitus in the early postpartum period (19), indicating that metabolite disorders occur before the diagnosis or progression of GDM and that analysis of the metabolic spectrum is a practical approach to discovering early biomarkers. Importantly, since GDM leads to metabolic disorders in women and affects the fetal metabolic environment, untargeted metabolomics is a useful technique for identifying early-stage metabolite predictors to avoid adverse neonatal outcomes in cases of GDM.

Therefore, in this study, we conducted untargeted metabolomics analyses using pregnancy samples of patients with GDM at 24 to 28 weeks and followed-up the neonatal outcomes to investigate the metabolic changes in cases of GDM with adverse neonatal outcomes and to predict the risk of neonatal hypoglycemia and macrosomia using serum metabolites.

2 Materials and methods

2.1 Study population and study design

For this study, we recruited women diagnosed with GDM based on the IADPSG criteria (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al.) at Nanjing Women and Children's Healthcare Hospital in 2022. According to the IADPSG criteria, GDM is diagnosed by FBG level $\geq$ 5.1 mmol/L, 1-h postprandial glucose level $\geq$ 10.0 mmol/L, or 2-h postprandial glucose level $\geq$ 8.5 mmol/L. The study included mothers aged 25–35 years who had natural and singleton pregnancies and underwent a 2-h 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. Their pre-pregnancy body mass index (BMI) ranged from 18.5 to 28 kg/m^2. The study participants were all Chinese. Mothers with abnormal glucose metabolism or diabetes mellitus before pregnancy, neurological dysfunction, cognitive disorders, cardiac issues, malignant tumors, pulmonary failure, renal diseases, or any other diseases were excluded. The study protocol was established in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Nanjing Women and Children's Healthcare Hospital (No: 2020KY-075). Participants volunteered to take part in the study and provided informed consent. Fasting serum samples were collected at the time of the OGTT and stored at −80°C for the subsequent metabolomics studies.

The participants' clinical data were also collected from 24 to 28 weeks of gestation, and their pregnancy outcomes were followed-up. Data for TC, TG, and HbA1c levels were missing in the group with no neonatal abnormalities, and the missing data rate was 0.5%. We adopted a multiple interpolation approach to impute the missing data. The study design is shown in Supplementary Figure S1. The study cohort was divided into three groups on the basis of the pregnancy outcomes. The Case N group included all cases with no neonatal abnormalities; the Case A group included cases showing neonatal hypoglycemia (blood glucose < 2.2 mmol/L within 48 h of birth); and the Case B group included cases showing neonatal macrosomia (birth weight $\geq$ 4,000 g). Patients who could not be traced due to various reasons and cases involving other neonatal diseases were excluded.

For creating the predictive models, we used shrinkage methods to estimate the sample size. Shrinkage methods deal with the problem of overfitting by reducing the variability in the developed model's predictions such that extreme prediction (20). The formula is as follows, where n is the sample size, $P = 5$ (number of alternative predictor variables), $S = 0.9$ (shrinkage factor), and $R^2CS = 0.2$ (Cox-Snell R^2, a conservative metric for evaluating the performance of the model). This approach indicated that a sample size of 198 cases was required for this study.

$$n = \frac{P}{(S-1)\ln\left(1-\frac{R^2_{CS}}{S}\right)}$$

Finally, 200 samples were collected and were sufficient to meet the sample size requirements and biological replication for untargeted metabolomics analysis (21–23).

2.2 Untargeted metabolomics analysis

2.2.1 Detection and identification of serum metabolites

Untargeted metabolomics analysis was conducted using a high-performance liquid chromatography-mass spectrometry (HPLC-MS) unit (Biotree Biomedical Technology Company, Shanghai). Quality control samples were prepared by pooling all samples to evaluate the stability of subsequent tests. To avoid systematic error, deviation values were filtered, and metabolite data with

≥50% missing values in a single group and ≥50% missing values in all groups were excluded. Then, the remaining missing values were filled by multiplying the minimum value by a random number between 0.1 and 0.5. Finally, metabolite identification was achieved through a spectral match using the Human Metabolome Database (HMDB) and Kyoto Encyclopedia of Genes and Genomes (KEGG).

2.2.2 Data processing

First, principal component analysis (PCA), an unsupervised analysis, was used to visualize the distribution and grouping of the samples. We generated all PCA plots using SIMCA software, with ellipses marking the 95% confidence intervals used to identify potential outliers in the dataset. Second, orthogonal projections to latent structures-discriminant analysis (OPLS-DA) was used to reflect the differences between groups and discriminate significantly changed metabolites. Finally, the value for the variable importance in the projection (VIP) of the first principal component in the OPLS-DA analysis was acquired to summarize the contribution of each variable to the model. Metabolites with VIP > 1 (by OPLS-DA) and $P < 0.05$ (by Student's *t*-test) were considered to show significant changes (24).

2.3 Pathway analysis

A public database was used for pathway enrichment analysis with KEGG and MetaboAnalyst 5.0. Based on the enrichment results of the differential metabolites in KEGG metabolic pathways, the differential abundance score was obtained by calculating the ratio of the difference between the number of annotated upregulated differential metabolites and the number of downregulated differential metabolites in a specific pathway to the number of all metabolites in this pathway, which could reflect the overall change of all the different metabolites in a pathway. To further screen the pathways and find the critical pathways showing the highest correlation with the differential metabolites, we performed enrichment and topological analyses of these pathways.

2.4 Predictive analytics

The sample for this study was an unbalanced dataset. We used the Synthetic Minority Oversampling Technique (SMOTE) to balance it (25). SMOTE was performed using the "UBL" package. New samples were added to the dataset by synthesizing them artificially based on k nearest-neighbor sampling with the value of k set to 5. The sample size of the dataset for the Case A (hypoglycemia) and Case B (macrosomia) groups was increased to 151 and 152 cases respectively. In this study, the "randomForest" package was used to analyze the sample dataset. The random forest (RF) algorithm is a state-of-the-art machine learning method used to develop predictive models. It can be used for predictor variables of various sizes or distributions and is suitable for application in high-dimensional environments where the number of predictor variables may be greater than the number of observations. In addition, this method can emphasize the relevance of each predictor variable through the use of so-called variable significance measures. Therefore, this method is well-suited for analyzing complex data, such as omics data (26). The dataset was divided into training and validation sets in a 7:3 ratio through random sampling. The mean Gini index reduction in clinical factors and differential metabolites was calculated to identify the five variables that had the most significant impact on adverse maternal and infant outcomes in patients with GDM. These five variables were then used to construct a risk-prediction model. The performance of the prediction model was evaluated using the area under the receiver operating characteristic curve (AUC) metric. Both of the above packages are from RStudio 4.2.2.

3 Results

3.1 Clinical characteristics of the participants

This study enrolled 200 pregnant women with GDM at 24–28 weeks of gestation, including 154 cases with no neonatal abnormalities (Case N), 33 cases of neonatal hypoglycemia (Case A), and 19 cases of neonatal macrosomia (Case B). The clinical characteristics are summarized in Table 1. The three groups showed no significant differences in prenatal and sociodemographic characteristics (age, BMI, gravidity, and parity). The clinical indicators in the Case A group (gestational week in OGTT, systolic blood pressure, diastolic blood pressure, and FBG, 2-h blood glucose, HDL-C, LDL-C, TG, and TC levels) showed no significant differences from those in the Case N group. However, at 24–28 weeks of gestation, the HbA1c level in the Case B group was considerably higher than that in the Case N group ($P = 0.005$), but it was still within the clinical normal reference range. Each of these 14 clinical characteristics were included in the subsequent predictive analyses. In the assessment of pregnancy outcomes, neonates from the Case A and Case B groups showed significantly lower blood glucose levels ($P < 0.001$, $P = 0.005$) and higher birth weights ($P < 0.001$, $P < 0.001$), respectively, than the corresponding values in the Case N group. In terms of the sex of the neonates, the number of males was slightly higher than that of females in the Case N group; the male/female ratio was balanced in the Case A group; and the number of male neonates was significantly greater than that of female neonates in the Case B group. Baseline data showed no significant differences in clinical characteristics between GDM patients with and without neonatal adverse outcomes at 24–28 weeks of gestation, which suggested that only focusing on clinical indicators could not predict the occurrence of adverse neonatal outcomes.

3.2 Serum metabolomics profile of GDM with adverse pregnancy outcomes

To explore the metabolite variations in pregnancy that corresponded to adverse pregnancy outcomes, we performed untargeted metabolomics analysis using serum samples obtained

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TABLE 1 Clinical characteristics of pregnant women with GDM.

Clinical characteristics	Case N	Case A	Case B	Case N vs. Case A *P*-values	Case N vs. Case B *P*-values
Prenatal and sociodemographic characteristics					
Age (years)	29.42 ± 2.79	29.36 ± 2.56	29.47 ± 2.97	0.912	0.940
Pre-pregnancy BMI (kg/m^2)	20.94 ± 1.84	21.12 ± 1.66	21.52 ± 1.36	0.611	0.188
Gravidity, *n*	1.62 ± 0.86	1.58 ± 1.15	1.84 ± 1.26	0.816	0.312
Parity, *n*	0.29 ± 0.49	0.27 ± 0.45	0.32 ± 0.58	0.89	0.807
Clinical indicators at 24–28 weeks of gestation					
Gestational week(OGTT)	25.90 ± 0.73	25.86 ± 0.65	25.87 ± 0.70	0.773	0.889
SBP (mmHg)	108.62 ± 9.96	107.48 ± 11.31	111.21 ± 11.02	0.562	0.293
DBP (mmHg)	69.37 ± 7.66	69.55 ± 8.64	68.47 ± 8.04	0.907	0.633
FBG (mmol L $^{-1}$)	4.62 ± 0.41	4.57 ± 0.36	4.74 ± 0.43	0.457	0.245
2hBG (mmol L $^{-1}$)	8.67 ± 1.17	8.97 ± 1.19	8.29 ± 1.19	0.188	0.180
HbA1c, %	4.99 ± 0.20	4.98 ± 0.26	5.13 ± 0.27[b]	0.985	0.005
HDL-C (mmol/L)	2.30 ± 0.37	2.34 ± 0.42	2.14 ± 0.34	0.620	0.075
LDL-C (mmol/L)	2.92 ± 0.59	2.93 ± 0.72	3.01 ± 0.78	0.942	0.542
TG (mmol/L)	2.14 ± 0.66	2.14 ± 0.64	2.31 ± 0.62	0.995	0.280
TC (mmol/L)	5.98 ± 0.82	6.02 ± 0.94	5.98 ± 1.15	0.815	0.988
Offspring outcome index					
Blood glucose (mmol/L)	3.48 ± 0.89	1.90 ± 0.40[a]	2.87 ± 0.80[b]	<0.001	<0.001
Birth weight (kg)	3.27 ± 0.31	3.57 ± 0.42[a]	4.18 ± 0.22[b]	<0.001	<0.001
Sex					
Male	89 (57.79%)	16 (48.48%)	13 (68.42%)	–	–
Female	65 (42.21%)	17 (51.52%)	6 (31.58%)	–	–

Data are presented as mean (SD) or *n* (%). Student's *t*-test was used for continuous variables (mean, SD). The *P*-values corrected by Bonferroni correction. Case A, hypoglycemia; Case B, macrosomia. SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; 2hBG, 2 h value of OGTT; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; TG, triglyceride; TC cholesterol.

[a]*P*-values <0.0167 for Case A vs. Control.

[b]*P*-values <0.0167 for Case B vs. Control.

at 24–28 weeks of gestation from mothers with GDM in the Case N, A, and B groups. PCA and OPLS-DA analysis were used to summarize the variations and visualize the distribution in all samples. The PCA model showed that most samples were placed inside the 95% confidence interval (Figures 1A,B), whereas a supervised OPLS-DA analysis visibly distinguished the Case A and Case B groups from the Case N group (Figures 1C,D), indicating significant differences in the metabolomics profiles of GDM cases showing adverse pregnancy outcomes. Moreover, all groups were well-clustered, indicating that the differences in metabolic profiles between the Case N group and the Case A and Case B groups were significant.

A total of 26,661 peaks were obtained, and 21,874 peaks were retained after preprocessing and eliminating invalid data (Supplementary Table S1). On the basis of the VIP values calculated by OPLS-DA (VIP > 1) and Student's *t*-test ($P < 0.05$), Case A and Case B groups showed 2,696 and 760 changed features in comparison with the Case N group, respectively (Supplementary Table S2). Specifically, as shown in the volcano diagram, 1,964 features were upregulated and 732 features were downregulated in the Case A group (Figure 1E), while 317 features were upregulated and 443 features were downregulated in the Case B group (Figure 1F). These results together indicated that the metabolite expression patterns of GDM patients at 24–28 weeks of gestation showed significant changes before the occurrence of neonatal hypoglycemia or macrosomia.

3.3 Classification of metabolite changes in GDM with neonatal hypoglycemia or macrosomia

After matching with the Human Metabolome Database (HMDB), a total of 448 metabolites were identified. The secondary and tertiary classifications of the metabolites identified in the Case A group were shown in Figure 2A; the metabolites identified were mainly lipids and lipid-like molecules (24.24%), organic acids and derivatives (24.24%), and organoheterocyclic compounds (24.24%). The metabolites identified in the Case B group were mainly lipids and lipid-like molecules (35.56%) and organic acids and derivatives (26.67%), similar to the Case A group (Figure 2B). Among these metabolites, 66 were differential metabolites in Case A, of which 29 were upregulated and 37 were downregulated in comparison with the Case N group. Among the differential metabolites screened, carbohydrate metabolites were all downregulated (Figure 2C). We further screened 45 differentially expressed metabolites in the Case B group, of which 14 metabolites were upregulated and 31 were downregulated, with lipids showing a downward trend. In contrast, amino acids showed an upward trend (Figure 2D). Among these differentially expressed metabolites, eight were altered in both Case A and Case B groups, including Acetylleucine (VIP = 2.348, $P < 0.001$; VIP = 3.983, $P < 0.001$), Arecaidine (VIP = 1.702, $P = 0.024$; VIP = 1.193, $P < 0.001$), Diatretin 2 (VIP = 2.346, $P < 0.001$; VIP = 4.129, $P < 0.001$), N-Acetylglutamine (VIP = 2.399, $P < 0.001$; VIP = 4.010, $P < 0.001$), N-Acetylhistidine

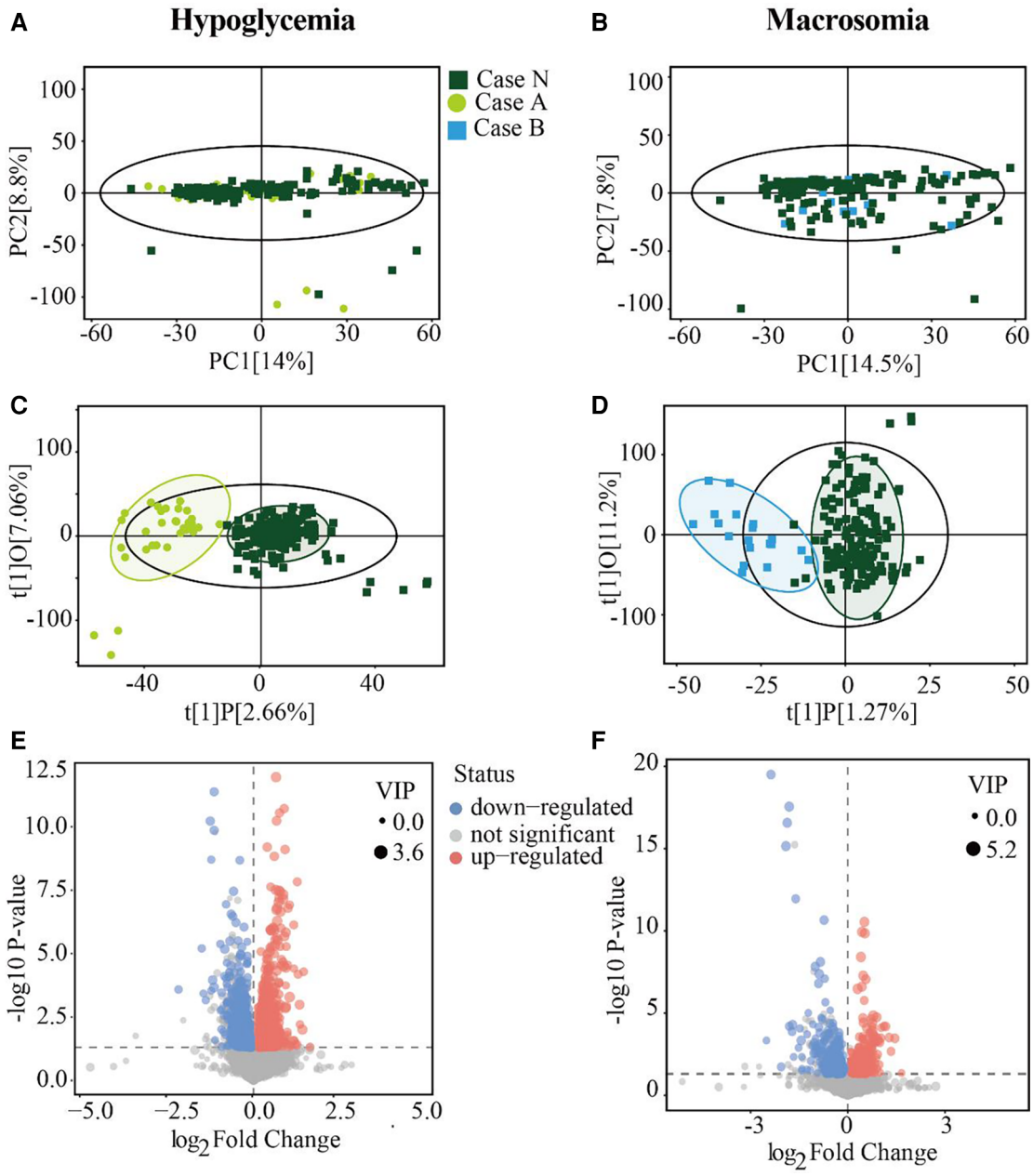

FIGURE 1
Serum metabolites differ between the GDM and case groups. (A,B) PCA score plots for Case N vs. Case A groups and Case N vs. Case B groups. (C,D) Score scatter plots of the OPLS-DA model for Case N vs. Case A groups and Case N vs. Case B groups respectively. (E and F) Volcano plot showing -log 10 (*P*-value) vs. log 2 (fold-change) for all metabolites. Areas of 95% confidence were highlighted in circles. PCA, principal component analysis; OPLS-DA, orthogonal projections to latent structures-discriminate analysis.

(VIP = 1.976, $P < 0.001$; VIP = 3.406, $P < 0.001$), N-Acryloylglycine (VIP = 1.195, $P = 0.003$; VIP = 1.546, $P = 0.042$), N-Acetyl-L-phenylalanine (VIP = 2.634, $P < 0.001$; VIP = 2.197, $P = 0.011$), and Vinylacetylglycine (VIP = 2.260, $P < 0.001$; VIP = 3.248, $P = 0.007$).

3.4 Pathway analysis based on metabolomics

Pathway enrichment analysis was performed to identify the metabolite pathways associated with altered metabolite levels (Supplementary Table S3). In the Case A group, 10 of the pathways involving the differential metabolites showed significant changes. Figure 3A shows that five pathways were downregulated and three pathways were upregulated. Thus, metabolite disturbances could disrupt the overall metabolic status of GDM patients through metabolic pathways. In the Case B group, 11 pathways showed significant changes, of which only the glycerophospholipid metabolism pathway was upregulated (Figure 3B). Enrichment and topological analysis showed that the critical pathway showing the highest correlation with the

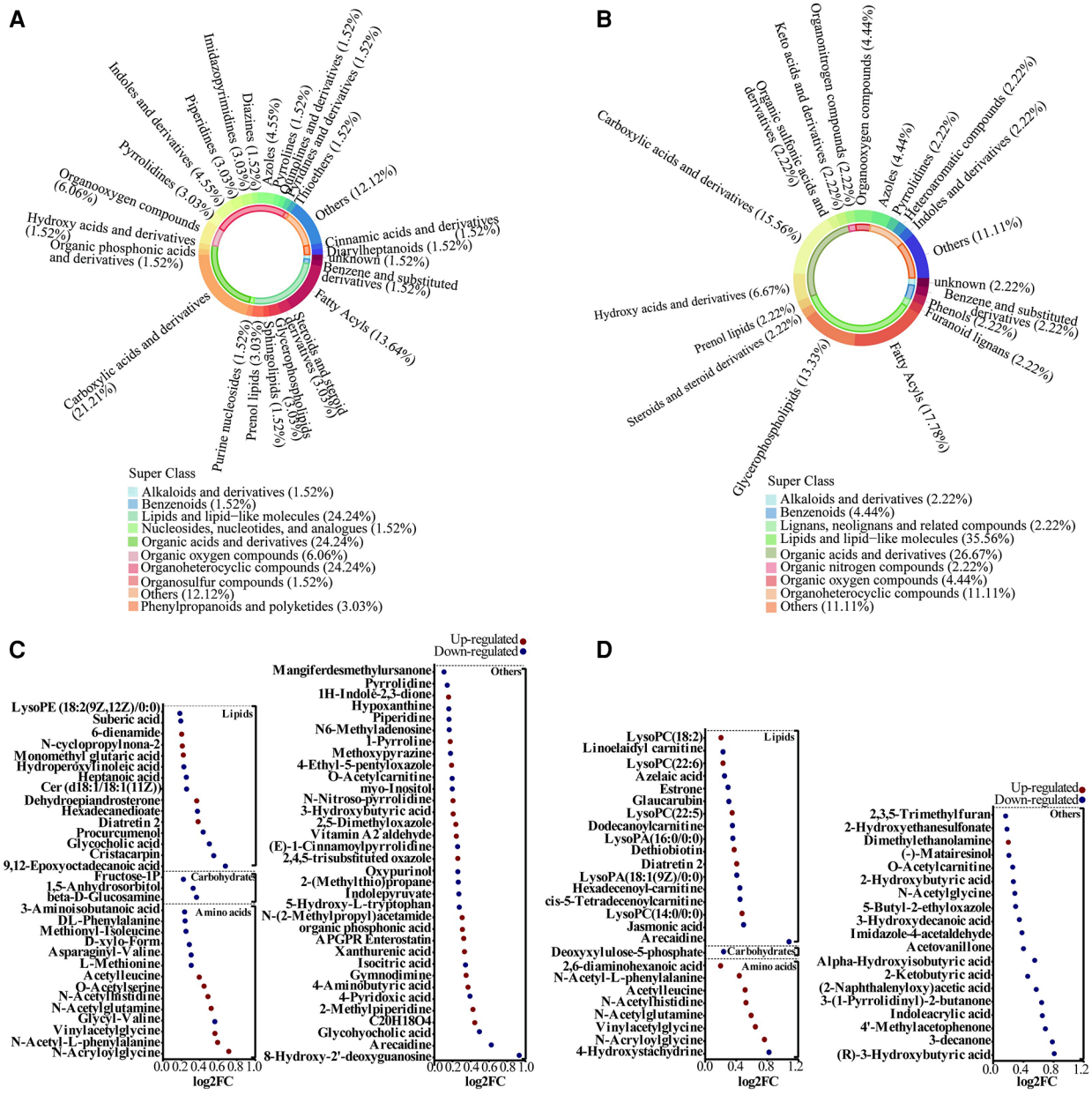

FIGURE 2
Alterations in metabolites species associated with adverse offspring outcomes. (A,B) Metabolite classification for Case A and Case B groups. (C,D) Bubble plot showing the differentially altered metabolites in Case A and Case B groups. Red indicates up-regulation and blue denotes down-regulation.

differential metabolites was the cycle (TCA cycle) in the Case A group (Figure 3C) and biotin metabolism in the Case B group (Figure 3D). Thus, these may be the main pathways underlying metabolic changes in patients with GDM.

3.5 Metabolites with good prediction capacity for neonatal hypoglycemia and macrosomia

The 66 screened serum metabolites for the Case A group and the 14 clinical factors were further characterized using RF analysis. The RF analysis identified *N*-acetylglutamine, *N*-acetyl-l-phenylalanine, *N*-acetylhistidine, acetylleucine, and diatretin 2 as the five metabolites showing the most significant reductions in the mean Gini index (Figure 4A). The datasets of the neonatal hypoglycemia and control groups were randomly divided into training and test sets. An RF-based risk-prediction model using the five metabolites listed above was constructed; the model's error rate was minimized when mtry = 6 and was stabilized when ntree = 800. The RF model achieved the lowest error rate at mtry = 6 and ntree = 800, and showed an AUC of 0.8712 in the test set (Figure 4B), indicating that the selected serum metabolites had good prediction performance.

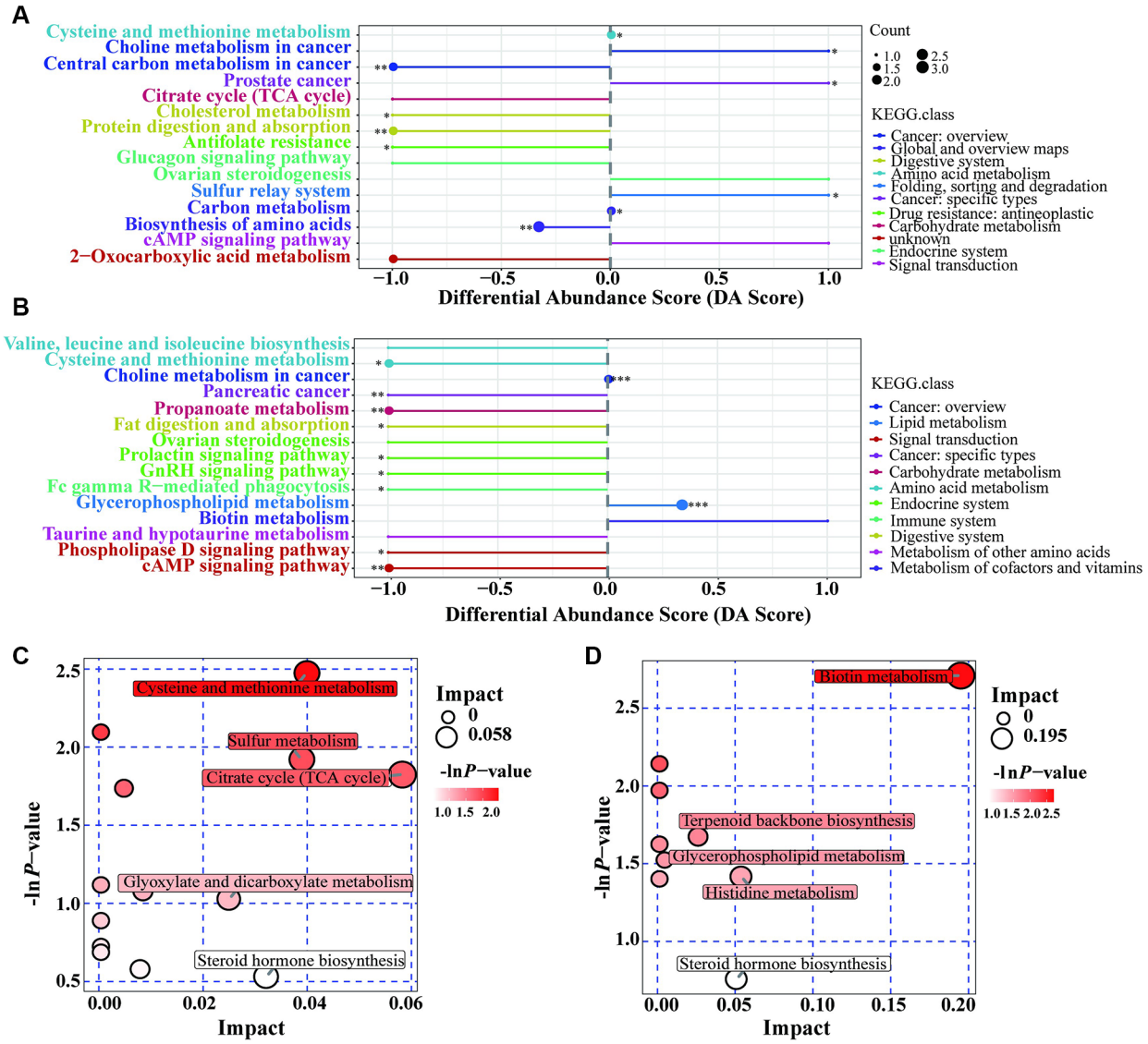

FIGURE 3
Pathway analysis based on metabolomics. (A): Differential abundance score for Case A vs. Case N; (B): Differential abundance score for Case B vs. Case N; (C): Pathway analysis for g Case A vs. Case N; (D): Pathway analysis for g Case B vs. Case N. DA Score: Ratio of the difference between the number of up-regulated and down-regulated differential metabolites annotated on a pathway to the number of all metabolites on the pathway; Impact: Impact factors obtained through topological analysis.

Similarly, the 45 screened serum metabolites for the Case B group and the 14 clinical factors were also characterized using RF. The five most essential characteristics identified in the RF analysis were diatretin 2, acetylleucine, *N*-acetylglutamine, *N*-acetylhistidine, and arecaidine levels (Figure 4C), all of which were serum metabolite levels. The model achieved the lowest error rate when mtry = 2, and the error rate stabilized when ntree = 700. The AUC for the test set was 0.9434 (Figure 4D), indicating that the model had good prediction accuracy.

These findings indicated that metabolites were suitable biomarkers of neonatal hypoglycemia and macrosomia.

4 Discussion

The number of GDM patients has more than doubled since the formulation of the diagnostic criteria for GDM by the IADPSG and their widespread adoption worldwide (27). The criteria formulated by the IADPSG are based on the relationship between hyperglycemia and adverse pregnancy outcomes (28), making them suitable for managing most GDM patients and reducing the incidence of adverse maternal and infant effects. While these standards imply a more rigorous approach to managing the health of patients with GDM, a subset of GDM patients undergoing such management remain at a high risk of

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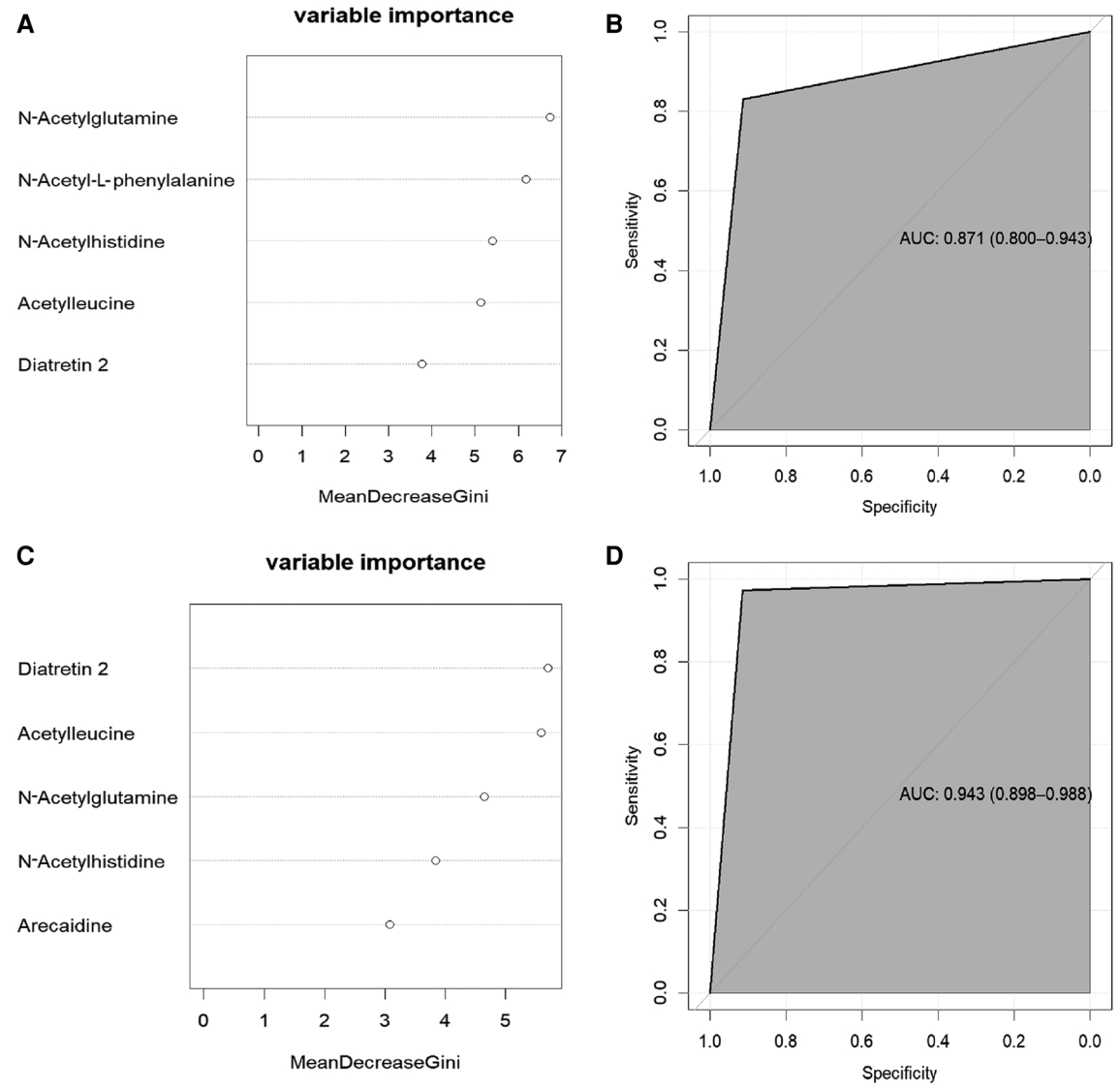

FIGURE 4
Prediction of adverse offspring outcome in women with GDM. **(A)**: the five metabolites with the greatest reduction in the mean Gini index in the Case A. **(B)**: In the random forest model, the signature with five variables provided the AUC 0.871 for predicting hypoglycaemia. The 95% confidence interval is 0.800-0.943.**(C)**: the five metabolites with the greatest reduction in the mean Gini index in the Case B. **(D)**: In the random forest model, the signature with five variables provided the AUC 0943 for predicting macrosomia. The 95% confidence interval is 0.898-0.988.

adverse infant outcomes such as hypoglycemia and macrosomia, which can combine and seriously threaten the near-and long-term health of the neonate (29, 30). Thus, early identification and appropriate management of high-risk GDM groups are of great practical significance in reducing adverse neonatal outcomes. This study conducted untargeted metabolomics analysis to examine the serum metabolic profile of GDM patients with different pregnancy outcomes. Biomarker panels using a combination of five metabolites in maternal serum obtained at 24–28 weeks of gestation accurately predicted neonatal hypoglycemia or macrosomia among pregnant women with GDM. Generally speaking, our findings could facilitate the identification of high-risk GDM populations with adverse neonatal outcomes. Following the diagnosis of GDM based on the IADPSG criteria, healthcare providers can implement tailored lifestyle interventions including diet and exercise, and the results of our study can make these management more targeted and efficient, which can better protection of maternal and child health.

Previous studies have shown that the incidence of neonatal hypoglycemia and macrosomia in the GDM population was 20%–35% and 4%–27.6%, respectively (30, 31). In our study, the incidence of neonatal hypoglycemia and macrosomia was low, which may be attributable to blood glucose management during pregnancy. Moreover, among the 200 neonates we followed-up, six had both neonatal hypoglycemia and macrosomia, indicating a potential link between these two adverse outcomes. A prospective study indicated that macrosomia is a risk factor for neonatal hypoglycemia (32). Giant fetuses are obviously exposed

to higher concentrations of free insulin in the uterus, which can cause a state of metabolic decompensation. As a result, adverse offspring outcomes in women with GDM are expected and may be concurrent.

The metabolic profile of GDM patients with hypoglycemia or macrosomia in their offspring showed significant changes at 24–28 weeks of gestation. Specifically, carbohydrate metabolites 1, 5-anhydroglucitol (1,5-AG), β-d-glucosamine, and 1-phosphate fructose were significantly downregulated in the Case A group. Previous studies have proposed that 1,5-AG is sensitive to urinary glucose excretion and can capture glucose variability that cannot be captured by HbA1c measurements (33, 34). Moreover, 1,5-AG has been recently identified included as an essential blood glucose parameter in the study of adverse pregnancy outcomes of diabetes (35, 36). Additionally, our findings indicated that amino acid levels were significantly upregulated in the Case B group, which may be a manifestation of maternal overnutrition. Previous studies have proven that aromatic amino acids, glutamic acid, glutamine, and other amino acids were related to the birth weight, which is also consistent with our research results (37, 38).

In our study, serum metabolites were good predictors of neonatal hypoglycemia and macrosomia. Although previous studies assessed a variety of adverse outcomes as outcome indicators, our study focused on neonatal hypoglycemia and macrosomia, which are more relevant for clinical application, thereby providing a direction for clinical management and prevention and showing more practical significance. In recent years, metabolomics has been increasingly used for the diagnosis and prognostication of GDM, indicating that metabolites play a crucial role in the development and pathogenesis of GDM (39, 40). This approach allows the identification of metabolic observations that can predict poor prognosis in the offspring of GDM patients. A previous study reported that the C-statistic for predicting GDM-related adverse pregnancy outcomes on the basis of social and demographic factors, obstetric and family history, and physical characteristics was less than 0.7 (41). However, in our study, the RF prediction model showed that the top five factors affecting hypoglycemia and macrosomia outcomes were all serum metabolites, and that a prediction model consisting of these five metabolites had AUCs of 0.8712 and 0.9434, respectively, which were superior to the AUCs of clinical indicators in predicting adverse pregnancy outcomes in the offspring of patients with GDM. The use of serum metabolites from weeks 24 to 28 of pregnancy to predict the likelihood of neonatal hypoglycemia and macrosomia in cases of GDM could assist healthcare professionals in implementing proactive measures to prevent these adverse outcomes. Since wearable electrochemical biosensors can be used to monitor metabolites and nutrients (42), in the future, wearable devices that detect serum metabolite levels may be useful for the clinical management of GDM patients to achieve accurate control through early identification of metabolic disorders.

Nevertheless, some limitations of this study require consideration. First, while all participants in this study received consistent diet and exercise counseling, constraints in follow-up prevented us from conducting detailed subject-specific studies of diet and exercise. Therefore, we could not assess the effect of diet and exercise on metabolism during pregnancy. Second, the small sample size of this study may have precluded the evaluation of the differential levels of some metabolites. Metabolites, especially those released at 24–28 weeks of gestation, need to be tested in larger, more diverse populations to assess their predictive value. Third, the range of samples collected in this study was limited, and more case specimens are needed for external verification. Therefore, the results should be interpreted with caution and the predictive potential of the prediction models requires further validation in additional large-sample prospective clinical studies. Last, the metabolomics measurement technique (HPLC-MS) used in this study did not allow for absolute quantitative analysis.

5 Conclusions

In summary, we profiled the serum metabolite composition in the context of GDM and further used changed metabolites to predict adverse outcomes in offspring. The high sensitivity of serum metabolites plays a vital role in predicting the risk ofadverse neonatal outcomes in GDM patients. It may be an auxiliary monitoring indicator for the management of GDM in the future.

Data availability statement

All data generated or analyzed during this study are included in this published article and its Supplementary Material. Raw data are not publicly available due to ethical restrictions, since they contain information that could compromise the privacy of research participants, but they are available from the corresponding author on reasonable request.

Ethics statement

The studies involving humans were approved by Human Ethics Committee of Nanjing Women and Children's Healthcare Hospital. 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

XY: Formal Analysis, Writing – original draft, Writing – review & editing. TY: Data curation, Writing – review & editing, Formal Analysis. DJ: Formal Analysis, Investigation, Writing – review & editing. CS: Resources, Writing – review & editing. JX: Resources, Writing – review & editing. MS: Data curation, Writing – review & editing. MZ: Data curation, Writing – review & editing. LC: Data curation, Writing – review & editing. HZ: Conceptualization, Project administration, Supervision, Writing – review & editing.

XC: Conceptualization, Project administration, Supervision, Writing – review & editing. CJ: Conceptualization, Funding acquisition, Project administration, 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.2024.1432113/full#supplementary-material

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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Jana Pressler,
University of Nebraska Medical Center, United States
Marisa Rodrigues,
Centro Hospitalar Universitário de São João (CHUSJ), Portugal

*CORRESPONDENCE
Francesca Catapano
francesca.catapano3@unibo.it

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A qualitative analysis of parents' experiences while their neonates with congenital heart disease require intensive care

Francesca Catapano[1]*, Rochelle Steinwurtzel[2], Elvira Parravicini[2] and Charlotte Wool[3]

[1]Department of Medical and Surgical Science, University of Bologna, Bologna, Italy, [2]Department of Neonatology, Columbia University Irving Medical Center, New York, NY, United States, [3]Stabler Department of Nursing, York College of Pennsylvania, York, PA, United States

Objective: To better understand the experience of parents with neonates with congenital heart diseases (CHD) admitted to a neonatal intensive care unit (NICU) in order to identify challenges faced by parents and discover support strategies helpful in positive coping.
Study design: Prospective cohort study of parents of neonates with CHD. Parents completed a questionnaire with open ended questions regarding their experience and feeling during the hospitalization within one week of the child discharge from the NICU. Krippendorff's content analysis was used to examine data.
Results: Sixty-four parents participated. Three themes were highlighted – Dialectical parental experiences, Suboptimal Parental Experiences and Positive Parental Experiences – describing the state of being and feelings that these parents face. Through this analysis, we were able to develop clinical considerations and identify coping strategies.
Conclusion: The understanding of parental experience and challenges when dealing with their child admitted in the NICU is crucial to identify coping strategies to promote adaptation and enhance the development of positive coping mechanisms.

KEYWORDS

neonatal intensive & critical care, content analysis, congenital heart defect (CHD), parents' experience, coping strategies

1 Introduction

Congenital heart disease (CHD) is the most frequent type of congenital anomaly accounting for nearly 1 percent of births annually in the United States (1); these may vary in degree of complexity, and depending on the type of malformation, the defect may require immediate medical and/or surgical intervention or a later treatment or sometimes, no treatment is needed, only follow-up is required. However, for most children born with CHD, lifelong monitoring will be required (1). Among other anomalies, CHD has the highest mortality rate, results in the longest hospital stay and subsequent frequent and prolonged hospital visits (2). These are the main explanations behind the unique and well-known psychological health pattern of parents of children with CHD (3). Despite the knowledge that all new parents can be subject to psychological distress (4), parents of babies admitted to the neonatal intensive care unit (NICU) are known to experience higher levels of stress and an altered parent-child relationships (5–9). Moreover, parents of infants with CHD admitted to Intensive Care

Units (10, 11) report experiencing anxiety, stress, and post-traumatic stress disorder present from diagnosis and persistent throughout the entire course of hospitalization (12) regardless of the severity of the heart condition itself (10, 13). Numerous studies have shown that the psychological profile, often referred to as the "emotional rollercoaster", of parents of children with CHD – depression, anxiety, somatization, hopelessness, guilt, fear, poor quality of life, hypervigilant – is a chronic state, which persists over time (12–16). Impaired parental mental health, if not properly treated, can negatively affect parents' ability to care for their children and can eventually result in long-term cognitive, health, and behavioral problems in offspring (10, 14, 17, 18). Given the incidence of CHD, psychological distress affects a relatively large number of parents, and can lead to deterioration of the parent-child relationship. However, it has been shown that this increasingly present and persistent challenge in the Neonatal Intensive Care Unit (NICU) can be lessened by the introduction of early palliative care (PC) (11, 19).

Early PC interventions can decrease parental stress, reducing some of the unmet needs of parents and of the whole family while increasing the comfort of the newborn (19–22) but still there is a need to identify specific challenges and coping support mechanisms for parents of neonates with CHD.

The aim of this study were to better understand the experience of parents with neonates affected by CHD and admitted to the NICU in order to identify challenges faced by parents and discover support strategies helpful in positive coping.

2 Material and methods

2.1 Design

The consolidated criteria for reporting qualitative studies (COREQ) checklist was referenced to promote complete and transparent reporting, with an aim to improve rigor and comprehensiveness of the data analysis. While COREQ is specific to interviews and focus groups, and our data were retrieved via a written survey, only select items from the COREQ checklist were addressed as applicable (23).

This is a prospective cohort study of mothers and fathers of neonates with congenital heart disease admitted to the NICU at Columbia University Irving Medical Center (CUIMC) from June 2017 to May 2018. Parents of neonates transferred from other institutions, who did not speak English, or whose neonate was diagnosed with a life-limiting condition or died during the admission were excluded from the study. Approval was obtained by the CUIMC Institutional Review Board (Protocol #AAAR3403).

Parents – both elements of the couple could participate – underwent written informed consent and those who wished to participate received a printed questionnaire asking for demographic information and three open ended questions within one week of infant discharge from the NICU. An initial global question was presented to encourage parents to express their overarching experiences: "*What is it like for you to have a child in the NICU?*" This item was followed with two additional questions as follows: "*What have been the hardest parts of this experience for you?*" and "*What has helped you cope with having a child in the NICU?*"

2.2 Procedure

Krippendorff's content analysis was used to examine data, which is a research technique for the objective and systematic description of the content communicated by participants. Content analysis is context sensitive, allowing the researchers to process data texts that are significant, meaningful, informative and representational to others (24, 25). A strength of content analysis is the opportunity to increase our understanding of phenomena, in this case experiences of parents who have a neonate with a CHD in the NICU. To start, each author worked independently to examine the qualitative content for each of the three research questions. A systematic approach was used in which all authors separately mapped patterns of co-occurring words to identify clusters of common meanings. Author CW then examined the manifest data and fully quantified and coded the textual materials. Figure 1 provides examples of the analyses processes from the original data, known as manifest content, to latent meaning of the data.

These steps were followed by a meeting of all authors in which individual results were compared. A total of three themes emerged and were agreed upon. Six categories were identified by the team members, all of which were identically matched. Authors RS and CW were responsible for cross-tabulating and reexamining the data. During this meeting two additional categories were identified [Mixed and sensory] and two of the originally identified categories were merged [Gratefulness merged into positive parental feelings]. Therefore, three themes and seven distinct categories were identified. The codes within each category were carefully reexamined and when appropriate, were moved to the respective category. The entire team then verified and confirmed the final organization of the data.

A goal of the research team was to create practical clinical applications for the reader if the data support it. As such, the qualitative analysis and responses to the question "What has helped you cope with having a child in the NICU?" will be examined in order to identify specific concerns and needs of parents.

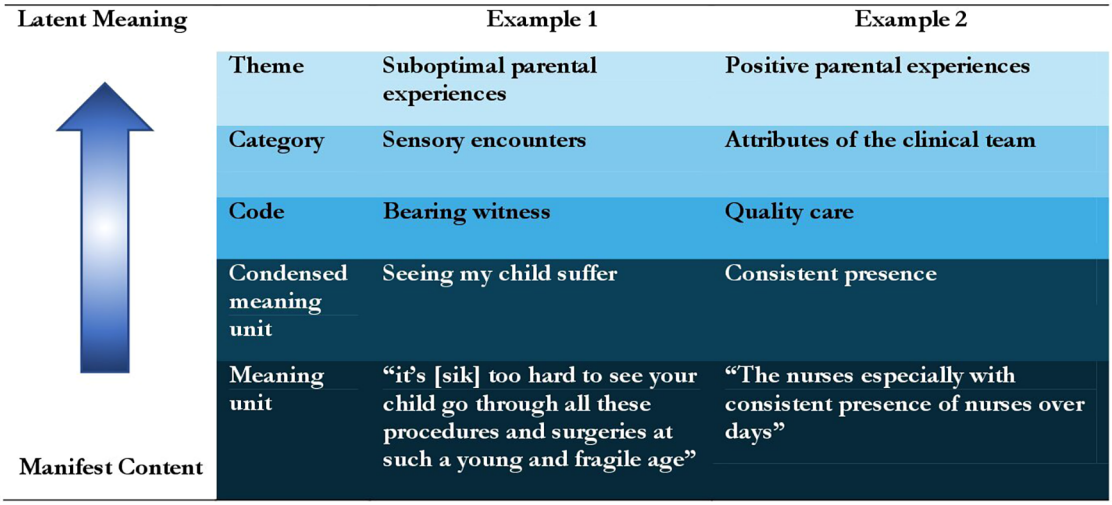
3 Results

3.1 Sample characterization

The parents of 44 neonates fulfilled the inclusion criteria. From that, 77 parents consented to participate, and, 64 (83%) submitted a written response. Demographic data are reported in Table 1 and the results are summarized in Table 2.

3.2 Theme 1 mixed emotions

Parents reported a variety of dialectical experiences when responding to "*What is it like for you to have a child in the*



	Example 1	Example 2
Theme	Suboptimal parental experiences	Positive parental experiences
Category	Sensory encounters	Attributes of the clinical team
Code	Bearing witness	Quality care
Condensed meaning unit	Seeing my child suffer	Consistent presence
Meaning unit	"it's [sik] too hard to see your child go through all these procedures and surgeries at such a young and fragile age"	"The nurses especially with consistent presence of nurses over days"

FIGURE 1
Examples of content analysis.

NICU?" And to "*What have been the hardest parts of this experience for you?"*. Parents face mixed emotions including happiness over small milestones, awareness and acceptance of their baby's clinical situation, stress, hope and uncertainty.

3.3 Category a. Synthesizing mixed experiences

3.3.1 Psychosocial stressors mixed with positive factors

The psychosocial stressors parents articulated were often paired with positive factors. Several parents noted how their infant's recovery process offset their negative emotions. One parent stated:

> *"It was quite an emotional rollercoaster. Hands down, the scariest situation I've ever been in. It was definitely a battle between staying strong and positive* vs. *being "realistic" and thinking of the worst. At the same time, it was incredible watching my baby improve/recover."*

and

> *"Mixed feelings. We are so thankful and happy that our baby made it this far. So, in some ways we are happy to be in a weird and stressful situation".*

3.3.2 Psychosocial stressors mixed with other variables

The psychosocial stressors parents articulated were often paired with other variables. Parents acknowledged their experiences as "*difficult*", "*stressful*", "*emotionally exhausting and traumatic*", while recognizing their infant was "*well taken care of*" and pointing out staff attributes, including clinicians' dedication, experience and knowledge.

> *"Definitely scary but overall given the circumstances, excellent experience. Felt reassured that we were getting world class care where everyone genuinely cared for the well being of the patient."*

A sense of practicality was also present as parents noted the need to have their infant in the NICU.

> *"It was a difficult situation. On one side of the equation, I know this was the best place for him to be. A place where he could be monitored and was in the hands of experienced nurses. Yet on the other side of the equation are feelings which caused me to worry."*

3.4 Theme 2 suboptimal parental experiences

Parents reported a variety of suboptimal experiences when responding to "*What have been the hardest parts of this experience for you?*" The data reported here are culled from this question as well as the first overarching question. Stressors stemmed from several feelings, including sensory encounters and the struggle to balance the demands of an infant in the NICU with other life responsibilities.

3.5 Category b. Parental stressors

3.5.1 Adverse parental feelings

Uncertainty and fear were mentioned by many parents as some of the hardest emotional experiences. Stress and worry were also commonly expressed along with other negatively charged words.

TABLE 1 Demographic data.

Parent demographics		*n* (%)
Gender	Mother	42 (67%)
	Father	22 (34%)
Age	<20	1 (1%)
	20–30	25 (39%)
	30–40	33 (52%)
	>40	5 (8%)
Education level[a]	Elementary	3 (5%)
	High School	8 (12%)
	College	28 (44%)
	Masters	17 (27%)
	Doctorate	7 (11%)
Marital status	Single	6 (9%)
	Married/Partnered	58 (91%)
First child	First child	25 (39%)
	Not first child	39 (61%)
Spirituality[a]	Not spiritual	17 (27%)
	Spiritual	44 (69%)
Religion[a]	Catholic	20 (31%)
	Protestant	10 (16%)
	Jewish	19 (30%)
	Muslim	7 (11%)
	Other	5 (8%)
Race[a]	Asian	3 (5%)
	African American	6 (9%)
	White	39 (61%)
	Other	6 (9%)
Neonates characteristics		
	Trasposition great vessels	10 (23%)
	Ebstein	1 (2%)
	Tetralogy of Fallot	5 (11%)
	Total anomalous pulmonary venous return	2 (5%)
	Coarctation	13 (30%)
	Arrhythmia	2 (4%)
	Single ventricle anatomy	11 (25%)
	Length of stay in days	
	Median	18
	25th/75th percentile	11/40

$N = 64$ for parents and $N = 44$ for neonates.
[a]Missing answers.

Examples of parental voice include the following: *"Horrible. Stressful. Traumatic, Very Traumatic;" "Stressful, Hurtful and painful not to go home with your baby;" "Fear of the unknown. Length of stay and prognosis for long term."* Exhaustion was also reported by parents.

3.5.2 Separation

Some parents (28%) stated the hardest part of their experience was not going home with their baby or leaving their baby behind in the NICU. The separation was described as "*heartbreaking*" and "*painful.*" Especially difficult for several parents was "*leaving at night*" and "*Being apart from my baby at night.*" Some hospital policies contributed to feelings of separation that led to dissatisfaction.

> *"Not being "allowed" in the room at times. Not being able to care for my baby at times due to NICU "rules". Having the baby be taken immediately at birth and not being able to see her four hours—seemed very unnecessary and was very upsetting."*

Some parents felt the NICU environment contributed to a sense of separation.

> *"Not being comfortable to visit, feeing like there no appropriate place to be peaceful with our baby."*

3.5.3 Feeling unable to parent

A difficult component of NICU admission is parents' limited ability to provide the comfort and care normally given to their infants. Parents yearned to introduce the new baby to its siblings, to feed, clothe and hold the baby. Being unable to parent contributed to suboptimal parental experiences.

> *"The hardest parts have been not being able to comfort my baby the way I wanted to throughout this experience…not being able to hold him nearly 2 whole weeks after birth. That was awful."*

and

> *"Feeling helpless and having to leave my baby in the NICU without my wife and I"*

and

> *"The hardest part by far was the inability to hold my child. I felt as if precious bonding time was being lost."*

Both mothers and fathers struggled with not being able to parent.

3.6 Category c. Sensory encounters

3.6.1 Bearing witness

The sights of the NICU were distressing to many parents who described their NICU experiences as primarily visual. Parents had difficulty "*watching our baby go through this*" or "*watching him endure things such as IVs and the chest tube.*" They noted bruises, needle marks and IVs, and verbalized seeing "*my swollen baby,*" "*my baby on ECMO,*" and my "*baby inhibited on CPAP.*" Some parents reported dreading the sights in the NICU such as the monitors, tubes, and wires. One parent stated "*Watching him endure things such as IVs an the chest tube*" was the hardest part of the NICU experience and another parent reported *"Terrible. Caused me to have panic attacks. Dreaded sights and sounds."* These sights and others, such as seeing their "*baby in pain*" were frequently reported as the hardest part of the NICU experience. The surgical experiences, both preoperative and postoperative, were also "*distressing to see.*" Furthermore, the sense of hearing also plays a crucial role; in fact, characteristic NICU noises such as monitor beeps have been reported to cause distress.

TABLE 2 Content analysis result.

Theme	Category	Code name & sample responses support the code
Theme 1 "Mixed emotions" *(n: 27)*	a. Synthesizing mixed experiences *(n: 27)*	i. Psychosocial stressors mixed with positive factors *(n: 17)* "It was quite an emotional roller coaster. Hands down, the scariest situation I've ever been in. It was definitely a battle between staying strong and positive vs. being "realistic" and thinking the worst. At the same time, it was incredible watching my baby improve/recover. A humbling experience"
		ii. Psychosocial stressors mixed with other variables *(n: 10)* "Unfortunate, yet needed to be done"
Theme 2 "Suboptimal parental experiences" *(n: 104)*	b. Parental stressors *(n: 72)*	i. Adverse parental feelings *(n: 42)* "Horrible. Stressful. Traumatic." "Fear of the unknown. Length of stay and prognosis for long term."
		ii. Separation *(n: 24)* "[Hardest part was] going home without my baby" "Heartbreaking not being with my baby 24/7"
		iii. Feeling unable to parent *(n: 6)* "Not being able to soothe my baby" "Inability to hold my child"
	c. Sensory encounters *(n: 19)*	i. Bearing witness *(n: 17)* "Watching our baby go through this" "Terrible. Caused me to have panic attacks. Dreaded sights and sounds"
		ii. Observing other babies *(n: 2)* "Seeing other babies who were sick"
	d. Concerns about balance *(n: 13)*	i. Balancing acts *(n: 13)* "Extremely difficult, helpless, sad, guilty to leave my baby, yet guilty being away from my older kids at home"
Theme 3 "Positive Parental experiences" *(n:118)*	e. Psychosocial *(n: 59)*	i. Positive parental feelings *(n: 16)* "Good because they were monitoring and checking her all the time"
		ii. Positive aspects of baby's progress *(n: 9)* "Incredible to watch [the] recovery"
		iii. Support systems *(n: 34)* "Family! So much support in every way" "Partner support" "The NICU team" "Faith"
	f. Attributes of the clinical team *(n: 56)*	i. Quality care *(n: 38)* "Knowing the nursing staff was exceptional, professional, compassionate, loving, and can take such good care of my baby" "Knowing that I was in the best hospital possible to provide exceptional care for my baby"
		ii. Team support strategies (source of Clinical Implications) *(n: 18)* "Regular updates and information" "Reached out, contacted us, asked if we needed any help" "Consistent presence of nurses over [multiple] days" "Allowed me to be here as often as I felt I wanted or needed to be" "Taught me different techniques and helpful practices" "Reassuring nurses and doctors"
	g. Coping strategies *(n: 3)*	i. Self directed *(n: 3)* "Support group" "Talking and writing about my feelings"

n refers to the number of times the code/category/theme was expressed in parental answers.

3.6.2 Observing other babies

Seeing other children in the NICU was also reported as one of the hardest things for parents. They commented on "*seeing other babies who were sick*" and the close proximity of their infant to other babies in the NICU. Hearing the noises from other infants' monitors was also described.

3.7 Category d. Concerns about balance

3.7.1 Balancing acts

Parents struggled with balancing an ill child with other responsibilities. Long commutes to the NICU, parking and money were some of the items parents had to balance. Some felt unable to provide adequate support to their partner as shown in this quote: "*Balancing home, NICU, work, supporting my wife.*" Many families had children at home and struggled with splitting their time and responsibilities. One parent mentioned several challenges, all fraught with guilt: "*Extremely difficult, helpless, sad, guilty to leave my baby, yet guilty being away from my older kids at home.*" Several families simply stated they had difficulty balancing among home life, relationship with their spouse, finance, and work.

3.8 Theme 3: positive parental experiences

The NICU experience included positive parental experiences. When responding to the question "*What has helped you cope*

with having a child in the NICU?" parents expressed many factors that positively influenced them. Support systems such as family, friends, and the clinical staff were frequently cited. Watching their infant heal and progress contributed to their coping. Parents also used self-help strategies to cope with their circumstances.

3.9 Category e. Psychosocial

3.9.1 Positive parental feelings

Parents voiced several positive feelings when they reflected on their NICU journey. They understood the necessity of a NICU admission, and some stated they were thankful, grateful and fortunate. One parent expressed happiness stating "*We are SO thankful and happy that our babies made it this far. So, in some ways we are happy to be in a weird and stressful situation."*

3.9.2 Positive aspects of baby's progress

The opportunity to see their child progress and heal contributed to coping and positivity. One parent stated their "*sick child was getting better*" while another reported that it was "*incredible to watch recovery.*" Several parents were grateful their child was given a "*chance to survive*".

3.9.3 Support systems

Parents relied on many different supportive relationships. Support from family and the nursing staff were most heavily mentioned (33% and 31% respectively). Spouses expressed appreciation for their partners. Parents voiced appreciation for supportive friends. Seventeen percent of respondents accessed their faith in God and prayer to help them cope.

3.10 Category f. Attributes of the clinical team

3.10.1 Quality care

Parents repeatedly expressed high regard for the clinical team members. Nurses, physicians, and other professionals were considered integral to the provision of quality care. Clinicians were described as "*amazing*", "*qualified*", "*experienced*", "*friendly*", and "*knowledgeable.*" Families felt a sense of relief their baby was in good hands and were "*confident in the team.*" One parent stated two quality attributes:

> *"1.) Knowing the nursing staff was exceptional, professional, compassionate, loving, and can take such good care of my baby 2.) Knowing that I was in the best hospital possible to provide exceptional care for my baby."*

Families benefitted from team members who provided comfort to them as parents and to their infant and expressed good care helped them to cope.

3.10.2 Team support strategies

Parents provided data that reflect the value of specific clinician behaviors, such as "*Consistent presence of nurses over [multiple] days*" and "*Reassuring nurses and doctors*".

3.11 Category g. Coping strategies

3.11.1 Self directed

Parents accessed several tools available to support their adaptation. While one parent preferred "*taking one moment at a time*" others preferred "*preparing in advance at pre-diagnosis*" and researching the condition. Parents found talking to other mothers, attending hospital support groups, and writing about their feelings useful. Some held a belief their baby would heal. Just being with and holding the baby were considered useful coping strategies.

Consideration for clinical practice in order to support parental coping are reported in Table 3.

4 Discussion

The main finding of our research is the identification of effective clinical coping strategies drawn from the experiences of parents with children undergoing hospitalization in the NICU due to Congenital Heart Disease (CHD). We have detailed these strategies for supporting parental coping in Table 3, along with qualitative data that underscores their effectiveness and considerations for clinical application. This achievement was made possible by conducting a thorough Krippendorff content analysis.

Theme 1 "Mixed emotions" refers to the different and opposing emotions that parents of CHD children face, consistent with other studies in this population (12–16). Our cohort of patients showed that their psychological asset is characterized by stress, fear, and anxiety. Alongside this vortex of negativity come the positive elements such as hope, acceptance, the joy of seeing their child fighting, getting better and making progress. Indeed, sometimes they expressed sadness and desperateness, other times they felt hopefulness and happiness: their emotions are not linear, they experience ups and down. This rollercoaster of emotions emphasizes how all parents of infants with CHD are at high risk for psychological distress (20, 26). We believe that in caring for these children and thus consequently for their parents, we cannot forget the psychological profile of these parents (27). We emphasize as the main clinical strategy associated to this first theme the continuous assessment of parental feelings and the support in the changing in hopes and dreams of parents. Indeed, health care professionals can have a significant impact on the care of these parents, embracing an individualized approach that supports the unique needs of families at different times (17, 28, 29), reassuring them and adapting care strategies according to either "Suboptimal Parental Experiences" (Theme 2) or to "Positive Parental Experiences" (Theme 3). These two themes identify the

TABLE 3 Strategies to support parental coping and considerations for clinical practice based on anwsers to question "what has helped you cope with having a child in the NICU?".

Strategies to support parental coping	Data from parental responses	Considerations for clinical practice
Knowledge and education	*"Knowing diagnosis and treatment options ahead of time prepared me for what I can expect my baby to be treated with how long processes will be."* *"Always took the time to explain to us what was going on."* *"Regular updates and information."* *"Reached out, contacted us, asked if we needed any help."* *"Taught me different techniques and helpful practices."*	• Assess parental knowledge prior to providing information. • Assess parental desire for knowledge – do they want every detail, or do they prefer small pieces of information over time? • Provide information in a timely fashion. • Consider contacting parents to offer support as appropriate. • Role model best practices. • Educate parents on evidence-based physical and developmental care for their infant.
Family presence in NICU	*"Being at daily rounds also helped immensely to fully understand what was going on and plan for the day."* *"Allowed me to be here as often as I felt I wanted or needed to be."*	• Invite parents into the clinical environment as partners on the care team. • Allow 24/7 parental involvement. • Provide a sleeping area for parents close to their infant.
Reassurance	*"Reassuring nurses and doctors."* *"Talked us down and told us everything is going to be alright."* *"Nurses telling me it is ok."* *"Positive smiling faces."* *"Helped cope with my son."*	• Assess parental feelings. • Cultivate an environment of encouragement. • Support the changing hopes and dreams of parents. • Offer emotional support and kind words. • Provide resources that support therapeutic coping mechanisms.
Focus on quality care	*"The quality of care provided."* *"Experienced staff."* *"Consistent presence of nurses over days."* *"Exceptional, professional, compassionate, loving, and can take such good care of my baby."* *"Help and support everyone gives here."* *"Knowing how caring and supportive the nurses were to him."*	• When able, schedule consistent caregivers. • Maintain professionalism coupled with genuine care. • Assure parents their infant is in experienced hands. • Early Palliative Care • Family Centered Care
Provision of resources	*Staff "to help with resources and dealing with the stress and strain."*	• Provide evidence-based, current resources to parents such as books, brochures, websites, and community supports. • Psychoeducational groups

two alternating psychological states that are characteristic of the psychological set-up described so far. Thus, Theme 1 is composed of an alternation of Theme 2 and Theme 3, which we will analyze in more detail below.

Theme 2 "Suboptimal Parenting Experiences" is characterized by negative parental feelings. Parental stress appears in our cohort to be mainly due to separation from their child and the subsequent feeling of being unable to parent, which is consistent with prior work (11, 19). Indeed, in this regard, parents emphasized as coping mechanisms the ability to be with their child as much as possible and the need to feel involved in health care decisions. We hold that it is necessary and of utmost importance the opportunity for parents to be with their babies 24/7 by providing a space where they can rest and at the same time be next to their newborn. It is critically important to build a relationship of trust with the care team so that parents feel that they are part of the health care decisions about their child's health, regardless of the infant's medical fragility. Establishing a solid relationship of trust (9) will facilitate a conversation with the healthcare team in order to explore the family's goals, hopes and concerns, allowing them to regain a sense of control. Fundamental is the implementation of early PC. PC is not only effective in treating conditions defined as life-limiting (30–32) or serious illnesses, such as CHD, but it is essential where survival is still a likely outcome (21). PC helps parents regain their sense of parenthood by bonding, holding, touching, feeding and taking care of their child (19, 33, 34). PC has also been shown to decrease anxiety in parents of newborns with CHD and it was also found that PC interventions helped parents with other children suggesting possible help in balancing all their responsibilities (20). Indeed, an additional category we identified in Theme 2 is the one that concerns loss of balance leading to a feeling of guilt, not only about the sick child, but also the siblings, the partner, the difficulty of managing these relationships, finances, and work. In correlation with this, what parents reported as most helpful was the presence of the partner, family members and friends (Theme 3 category support system); thus, our data shows that a family centered care approach is necessary (26, 33, 34).

The last category belonging to Theme 2 is sensory encounters, including the sight of their own child going through a serious and painful journey, the presence of other children suffering and the environment (sounds, monitrs etc) of the NICU. Negative sensory encounters can lead to trauma and post-traumatic stress syndrome (8, 35, 36). For this category, no coping skills were evidenced by the parents, and we consequently could not identify clinical strategies as the suffering described is part of the pathway of the conditions under consideration. Since most diagnoses of CHD are done prenatally, it maybe helpful explaining to the parents what their baby will look like during the NICU admission and at the time of surgery. Pictures can be shown along with explanation of the meaning of wires, tubes, and lines

that will be placed on the baby's body. Moreover, a prenatal tour of the NICU may help visualize the reality of the care and the hardware needed to help the baby during the admission.

Theme 3 "Positive parental experiences" is characterized by positive parental feelings arising from three main categories. In the psychosocial category, we identified the positive emotional parental feelings resulting from the acceptance and understanding of the need for hospitalization, their child's progress, and gratitude to the support system. In the support systems we identified the partner, family, faith, and healthcare team. As stated above family and partner are the most cited as coping mechanisms in our sample. The medical care team deserves further consideration as the quality of care reported by the parents interviewed enables the creation and maintenance of a trusting relationship, which is fundamental as reported at the beginning of the discussion. In addition, the key role of the team that was able to support the parents in this journey and help them face the hospitalization and care of their child, as reported in the literature (28, 37), emerged as one of the best coping support mechanisms. Other coping strategies identified in the analysis include self directed (Category g.i – Theme 3), such as journaling to express feelings, as well as participation in support and psychoeducational groups – these strategies have been demonstrated to enhance the quality of life of parents with CHD newborns (27).

Strengths of this study include the extensive sample size analyzed, particularly noteworthy for a qualitative analysis. The Krippendorff content analysis and the method used allows reproducibility of the results. Another strength is that all authors from the interdisciplinary team were involved in the analyses and had unanimous agreement in the categories and coding which limits the risk of bias.

There are some limitations. The study was conducted at a single tertiary care center therefore may not represent patient population of other centers. Similar limitation applies to the demographic distribution. Lastly, the exclusion of non-English speakers and an attrition rate of 17% in responses may result in missing a high-risk subgroups.

Understanding the parents' experience and the personal, economic, familial, professional, and social (multidimensional) challenges of having a child admitted to the NICU is crucial for identifying coping strategies.

Further studies are needed to develop interventions to alleviate parents' stress and anxiety and to prove their benefit.

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 IRB Columbia University Medical Center. 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

FC: Writing – original draft, Writing – review & editing. RS: Writing – original draft, Writing – review & editing. EP: Writing – original draft, Writing – review & editing. CW: Writing – original draft, Writing – review & editing.

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Publisher's note

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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Marwa Farag,
Alexandria University, Egypt
Mustafa Senol Akin,
Ankara Bilkent City Hospital University, Türkiye

*CORRESPONDENCE
Karambir Singh Gill
✉ drkaram.edu@gmail.com

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Correlation of anterior cerebral artery resistive index with early comorbidities in preterm neonates

Karambir Singh Gill*, Bhavna Gupta, Puneet A. Pooni and Siddharth Bhargava

Department of Pediatrics, Dayanand Medical College and Hospital, Ludhiana, India

Introduction: This study was undertaken to find the clinical correlation of resistive index (RI) in the anterior cerebral artery (ACA) of preterm neonates admitted to the Neonatal Intensive care unit (NICU) with comorbidities such as perinatal asphyxia, neonatal sepsis, and necrotizing enterocolitis (NEC).
Methods: An observational analytical study was conducted, including preterm neonates (<35 weeks) admitted to the NICU. Ultrasound cranium scans were performed on days 1–3 and 7 of life as per the study protocol. Baseline and clinical data of asphyxia, sepsis, and NEC were obtained. Images were acquired using a 4–8-MHz probe on a Sonosite M-turbo machine (Bothell, WA, USA). All statistical calculations were done using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) with the application of the Kolmogorov–Smirnov test and the Mann–Whitney test.
Results: During the study period, a total of 739 neonates were admitted. Of these, 73 neonates constituted the study group. Among the 73 patients, 33 were preterm neonates without comorbidities and 40 neonates had comorbidities such as perinatal asphyxia, sepsis, and NEC stage 2 and 3 (necrotizing enterocolitis). In the present study, the mean RI on day 3 of life was 0.76 ± 0.04 in neonates without comorbidities and 0.77 ± 0.04 in neonates with comorbidities, with a p-value of 0.247. On the 7th day of life, the mean RI was 0.82 ± 0.03 in both groups, with a p-value of 0.42.
Conclusion: We could not find any significant clinical correlation of RI in the ACA of preterm neonates <35 weeks of gestation with comorbidities.

KEYWORDS

RI, ACA, preterm, neonates, Doppler RI, Doppler

Introduction

Neonatal cranial ultrasound is a non-invasive, bedside-available modality useful for neonatologists in intensive care units. It is part of the point-of-care ultrasound performed by neonatologists, which helps in early diagnosis and timely management. In preterm neonates, there is an increased tendency for acquired brain injury during the perinatal period, which can lead to long-term neurodevelopmental consequences (1). Preterm neonates have pressure-passive circulation because of immature auto-regulation of cerebral circulation. Any hemodynamic instability in systemic perfusion directly affects cerebral perfusion (2). Changes in cerebral perfusion pressure play an important role in the pathogenesis of preterm brain injury (3). Many factors are responsible for altered cerebral hemodynamics in preterm babies, including sepsis, shock, perinatal

asphyxia, necrotizing enterocolitis (NEC), and respiratory failure requiring mechanical ventilation (4). Very few treatment options are available for preterm brain injury, so our focus is on the prevention of the same. Long-term consequences of preterm brain injury include neurodevelopmental (cerebral palsy), cardiovascular, endocrine, and metabolic disorders (5–7). Cerebral hemodynamic monitoring may help in the early detection of altered cerebral perfusion pressure and guide early intervention. Low cerebral oxygenation in preterms has been associated with poor neurodevelopmental outcomes (8).

Using bedside neonatal cranial ultrasound with color Doppler imaging, the resistive index (RI) of cerebral arteries can be calculated. This non-invasive modality is safe and can be performed at the bedside (9). Term neonates with birth asphyxia have a low resistive index. Ultrasound Doppler using anterior cerebral artery (ACA) RI can be used to diagnose perinatal asphyxia in resource-limited facilities (10). Preterm neonates with hemodynamically significant patent ductus arteriosus have a high resistive index (11, 12). The resistive index can be measured serially in the same vessel of a neonate for early detection of changes in cerebral hemodynamics associated with the onset of comorbidities. RI may vary depending on the nature of the vessel targeted for measurement (13). In our study, we compared the values of the resistive index in the anterior cerebral artery of healthy preterm neonates with those of preterm neonates who have comorbidities.

Aims and objectives

This study aimed to assess the clinical correlation of ACA RI with early comorbidities in preterm neonates admitted to Neonatal Intensive care unit (NICU)s.

Materials and methods

This prospective observational study was conducted in the Neonatal Intensive Care Unit of Dayanand Medical College and Hospital, Ludhiana (Punjab), over a period of 12 months from January to December 2022. As per the inclusion criteria, all inborn preterm babies with a birth gestation of ≤35 weeks admitted to the NICU were included in the study. As per the NRP (Neonatal Resuscitation Program) guidelines, 35 weeks is the cutoff for birth gestation to classify neonates into preterm and term for initial oxygen use during neonatal resuscitation at birth.

The exclusion criteria included the following: (a) birth gestation >35 weeks; (b) loss to follow-up; (c) congenital malformations; and (d) refusal to participate in the study by the parent/guardian.

Based on the incidence of preterm births and considering the level of significance at 5%, the sample size was calculated as 70. Informed consent was obtained on the consent/accent form from the parents of all study subjects, and the study was approved by the institutional ethics committee (IEC) DMCH under number DMCH/IEC/2023/209 in accordance with the Declaration of Helsinki. Mother's antenatal details, including age, gravida, parity status, past obstetric history, history of antenatal visits, antenatal complications, antenatal ultrasound findings, and antenatal Doppler images, were recorded as per a structured pro forma. Birth details, including birth gestation, birth weight, type of delivery, and Apgar score, were recorded to identify neonates with perinatal asphyxia.

During the postnatal stay in the NICU, babies were categorized into two groups: preterm neonates without comorbidities and those with comorbidities such as perinatal asphyxia, sepsis, and NEC. Perinatal asphyxia was defined as neonates who did not cry at birth as per the National Neonatal Perinatal Database (NNPD). Based on the Apgar score, moderate perinatal asphyxia was defined as an Apgar score of 4–6, while severe asphyxia was defined as no breathing or an Apgar score of 0–3 at 1 min of life. Sepsis was defined as symptomatic neonates with positive sepsis markers, with or without a positive blood culture. Necrotizing enterocolitis was defined as neonates with feed intolerance, abdominal distension, or intestinal perforation, classified as per Bell's staging. Postnatal details, including the need for continuous positive airway pressure (CPAP), surfactant, mechanical ventilation, inotropes, and primary diagnosis with outcome, were noted as per a structured pro forma.

All neonates underwent cranial ultrasound scanning along with color Doppler imaging as per the screening protocol. The first examination was done within 72 h of NICU admission, preferably at 24 h of life, followed by a second examination on days 7–10 of life. For babies with prolonged NICU stay, a day 14 scan was also conducted. Images were acquired in the sagittal plane through the anterior fontanel using a 4–8-MHz probe on a Sonosite M-turbo machine (Bothell, WA, USA). In the sagittal plane, the ACA was visualized using color flow mode, followed by pulsed wave Doppler flow assessment of blood flow in the ACA to calculate the RI. Three readings were taken for every scan. RI was calculated from Doppler waveforms of the ACA, with a caliper placed in the sagittal plane. Vmax and RI readings were obtained and noted.

The resistive index is a non-invasive method for assessment of cerebral blood flow (5). It is defined as follows (14):

$$\text{Resistive index} = \frac{\text{Peak systolic velocity} - \text{Diastolic velocity}}{\text{Peak systolic velocity}}$$

Data are described in terms of range, mean ± standard deviation (SD), median (IQR), frequencies (number of cases), and relative frequencies (percentages) as appropriate. The Kolmogorov–Smirnov test was used to determine whether the data were normally distributed. A comparison of quantitative variables between the study groups was performed using the Mann–Whitney *U*-test and the Kruskal–Wallis test for non-parametric data. For comparing categorical data, the chi-square (χ^2) test was performed, and the Fisher exact test was used when the expected frequency was less than 5. The receiver operator characteristic (ROC) curve was used to estimate the criterion value depending on the specificity and sensitivity, and the area

under the curve (AUC) was measured. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for the Social Science version 21.0 (SPSS) (SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

Characteristics of the study group

The study group characteristics are shown in Figure 1.

Results

During the study period, there were a total of 739 intramural and extramural admissions, with 493 being intramural admissions. Among these, 73 infants constituted the study group. Of these 73 patients, 33 were preterm neonates without comorbidities, while 40 neonates had other comorbidities such as perinatal asphyxia, sepsis, and NEC stage 2 and 3 (Table 1).

The most common reason for admission to NICU was respiratory distress syndrome (RDS), with 62 (85%) babies requiring CPAP and 17 (23%) requiring surfactant. Among the 73 patients, 16 (22%) neonates had perinatal asphyxia at birth and required neonatal resuscitation, while 12 (16%) were mechanically ventilated. Antenatal steroids were administered to 49 patients. Out of these 73 neonates, 11 were classified as small for gestational age (SGA). Apgar scores of less than 3 (severe perinatal asphyxia) at 1 min of age were recorded in 3 neonates, and moderate asphyxia was observed in 13 babies. There were 15 (20%) neonates with clinical sepsis and positive sepsis markers, with 11 (15%) requiring inotropes and 9 having NEC. Of the 11 babies with hypotensive shock requiring inotropic support, only 4 survived. Six preterm babies had both NEC and sepsis. Intraventricular hemorrhage (IVH) was seen in six babies, with IVH grade I in four and IVH grade II in two. Patent ductus arteriosus (PDA) was detected in 17 preterm babies, of which 7 were found to be hemodynamically significant and required medical management. Mean Hb was 16 (SD 2). Anemia (Hb <11 gm/dl) was seen in two babies at admission. As per the outcome, 66 (90.5%) babies were discharged, with a mean duration of NICU stay of 28 days (Table 2).

In this study, we calculated the mean RI on days 3 and 7 of life for preterm babies. Newborns without comorbidities were divided into various groups based on gestational age and weight. The mean RI was measured separately for each group on days 3 and 7 of life. For gestational age, the mean RI was 0.78 ± 0.03 ($\leq$28 weeks), 0.76 ± 0.04 ($28+1$ to 32 weeks), and 0.76 ± 0.04 ($32+1$ to 35 weeks) on day 3 of life and 0.82 ± 0.04 ($\leq$28 weeks), 0.82 ± 0.03 ($28+1$ to 32 weeks), and 0.83 ± 0.03 ($32+1$ to 35 weeks) on day 7 of life. For weight, the mean RI was 0.79 ± 0.04 ($\leq$1,000 g), 0.75 ± 0.05 (1,001–1,500 g), and 0.76 ± 0.04 (1,501–2,500 g) on day 3 of life and 0.85 ± 0.03 ($\leq$1,000 g), 0.81 ± 0.03 (1,001–1,500 g), and 0.82 ± 0.02 (1,501–2,500 g) on day 7 of life. The ACA RI on day 3 increased as gestational age decreased. Additionally, the ACA RI on days 3 and 7 was higher in babies

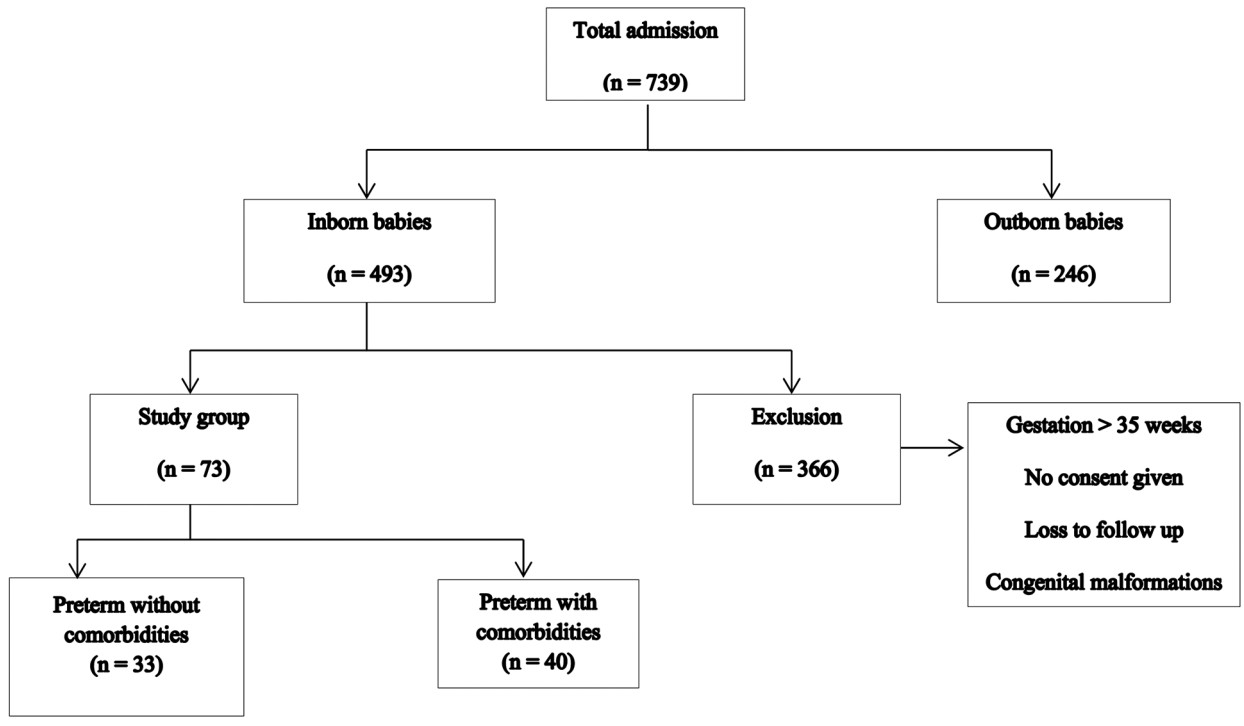

FIGURE 1
Characteristics of the study group.

TABLE 1 Maternal and neonatal demographics.

S. no.	Variables	Statistics, *n* (%)
1	Total subjects	73
2	Gestation	
	<28 weeks	12
	28–32 weeks	36
	32–35 weeks	25
3	Gender	
	Male	47 (64%)
	Female	26 (36%)
4	Antenatal steroids	49
5	SGA	11
6	Mode of delivery	
	LSCS	66
	Vaginal delivery	7
7	Mean gestation (range)	30 + 4 weeks (25–35 weeks)
8	Mean birth weight	1,383 g
9	Apgar score at 1 min	
	Less than 3	3
	4–6	13
	Apgar score at 5 min	
	Less than 3	2
	4–6	2
10	CPAP	62 (85%)
11	Surfactant	17 (23%)
12	Mechanical ventilation	12 (16%)
13	Inotropes	11 (15%)
14	Asphyxia	16 (22%)
15	Sepsis	15 (20%)
16	NEC	9 (12.3%)
17	Mean duration of NICU stay (range)	26 days (10–60 days)
18	Outcome	
	Discharged	66 (90.5%)
	Died	4 (5.5%)
	Discharged against medical advice	3 (4%)
19	Primary diagnosis	
	• RDS	22 (30%)
	• Perinatal asphyxia	16 (22%)
	• Sepsis	15 (20%)
	• NEC	9 (12.3%)
	Stage 2–5	
	Stage 3–4	
	• NEC + sepsis	6 (8.2%)
	• Others	6 (8.2%)

weighing less than 1 kg. As birth weight increased, the RI decreased, and this relationship was found to be statistically significant (Table 3).

In the present study, the mean RI on day 3 of life was 0.76 ± 0.04 in newborns without comorbidities and 0.77 ± 0.04 in newborns with comorbidities, with a *p*-value of 0.247. On day 10 of life, the mean RI was 0.83 ± 0.03 in both groups, with a *p*-value of 0.42. A ROC curve was created, which demonstrated a cutoff for ACA RI on day 3 of >0.82 for the prediction of mortality with an AUC of 0.645. For an ACA RI >0.82, the sensitivity is 43%, while the specificity is 88% (Table 4).

In our study, neonates with perinatal asphyxia had a mean RI of 0.76 ± 0.04 on day of life 3 (*p*-value 0.9) and 0.82 ± 0.04 on day 10 of life (*p*-value 0.9). Neonates with sepsis had a mean RI of 0.78 ± 0.04 on day 3 of life (*p*-value 0.9) and 0.82 ± 0.02 on day 10 of life (*p*-value 0.83). Neonates with NEC had a mean RI of 0.75 ± 0.04 on day 3 of life (*p*-value 0.9) and 0.82 ± 0.03 on day 10 of life (*p*-value 0.68) (Table 5).

The mean RI increased from 0.77 ± 0.04 on day 3 to 0.82 ± 0.03 on day 7, which is statistically significant. This indicated that RI increases with the increase in chronological age (Figure 2).

The mean RI on day 3 was 0.77 ± 0.04 in survivors and 0.79 ± 0.05 ($p = 0.208$) in non-survivors. The mean RI on day 7 was 0.82 ± 0.03 in survivors and 0.82 ± 0.03 in non-survivors ($p = 0.376$). Both the *p*-values were found to be non-significant.

Discussion

In preterm neonates, cerebral hemodynamic monitoring can be used as a preventive tool for acquired preterm brain injury (9). The resistive index of cerebral arteries can be used as a measure of cerebral hemodynamics (9). Risk factors for preterm brain injury cause altered cerebral perfusion pressure because of pressure-passive circulation, which is considered a major pathophysiological mechanism underlying brain injury (2). For timely detection of increased or decreased resistive index of cerebral arteries in preterm babies, we need to define reference values specific to the Indian context. Then, we need to compare the variability of RI values between healthy preterm neonates and those with comorbidities.

In this study, we observed that ACA RI values in healthy preterm neonates show a rising trend from day 3 to day 7 of life. Calvert et al. (11) assessed RI during the first 72 h of life for babies with gestations of 26–28 and 29–32 weeks. Their values contrast with our results. On the other hand, RI values assessed during the first 8 h of life by Pezzati et al. (15) correlate with our findings. RI values assessed by Romagnoli et al. (16) on days 1, 3, 7, 14, 21, and 28 of life for various gestational age groups did not show the same rising trend as observed in our study, but their values on day 3 of life correlate with our values.

In our study, the ACA RI on day 3 increased as gestational age decreased, but this observation was not statistically significant. The ACA RI on days 3 and 7 was higher in babies weighing less than 1 kg. As birth weight increased, the RI decreased, which was statistically significant ($p < 0.05$).

In a recent study, it was observed that the resistive index is higher in large arteries and lower in smaller arteries. Thus, for comparison purposes, we need to compare the RI of the same arteries across all babies. However, no difference was found between the RI values of left- and right-sided arteries of the same baby (12).

In this study, we examined the preterm babies to calculate ACA RI values as a marker for assessment of cerebral perfusion and compared the RI values in preterm babies without comorbidities with those in preterm babies with comorbidities such as asphyxia, sepsis, and NEC.

Term neonates with perinatal asphyxia have a low RI in the initial stages because of cerebral vasodilation and increased cerebral diastolic blood flow, but newborns with severe asphyxia have a high RI due to impaired auto-regulation and increased vascular resistance (17). Cranial ultrasound along with Doppler

TABLE 2 Values of the mean RI in the ACA.

	GA (weeks)	*n*	Mean	Std. deviation	Median	IQR	*F*	*p*-value
RI (3D)	<28	12	0.78	0.03	0.79	0.7425–0.82	2.928	0.231
	28.1–32	36	0.76	0.05	0.75	0.7325–0.78		
	32.1–35	25	0.76	0.04	0.76	0.73–0.79		
RI (7D)	<28	12	0.82	0.04	0.83	0.7775–0.84	0.381	0.826
	28.1–32	36	0.82	0.03	0.83	0.8025–0.84		
	32.1–35	25	0.83	0.03	0.82	0.8–0.85		
	Weight (kg)	*n*	Mean	Std. deviation	Median	IQR	*F*	*p*-value
RI (3D)	<1	21	0.79	0.04	0.79	0.75–0.82	11.52	0.003
	1–1.5	19	0.75	0.05	0.74	0.72–0.77		
	1.5–2.5	33	0.76	0.04	0.76	0.735–0.785		
RI (7D)	<1	21	0.84	0.03	0.83	0.815–0.86	7.626	0.022
	1–1.5	19	0.81	0.04	0.81	0.77–0.83		
	1.5–2.5	33	0.82	0.03	0.82	0.8–0.845		

TABLE 3 Variability of the mean RI with comorbidities.

		n	Mean	SD	Median	IQR	*Z*	*p*-value
RI (3D)	Neonates without comorbidities	33	0.76	0.04	0.75	0.73–0.785	−1.157	0.247
	Neonates with comorbidities	40	0.77	0.04	0.77	0.74–0.80		
RI (7D)	Neonates without comorbidities	33	0.83	0.03	0.83	0.805–0.85	−0.803	0.422
	Neonates with comorbidities	40	0.82	0.03	0.83	0.8–0.84		

TABLE 4 Variability of the mean RI with perinatal asphyxia, sepsis, and NEC.

		n	Mean	SD	Median	IQR	*F*	*p*-value	*p*-value
RI (3D)	NO	33	0.76	0.04	0.75	0.73–0.785	1.805	0.138	
	Asphyxia	16	0.76	0.04	0.76	0.74–0.79			0.998
	Sepsis	9	0.77	0.04	0.77	0.745–0.805			0.927
	NEC	9	0.75	0.03	0.75	0.735–0.77			0.994
	Sepsis + NEC	6	0.81	0.05	0.81	0.7625–0.85			0.108
RI (7D)	NO	33	0.83	0.03	0.83	0.805–0.85	0.625	0.646	
	Asphyxia	16	0.82	0.04	0.83	0.8–0.8475			0.973
	Sepsis	9	0.82	0.03	0.83	0.795–0.835			0.935
	NEC	9	0.81	0.03	0.81	0.795–0.83			0.828
	Sepsis + NEC	6	0.84	0.03	0.84	0.8–0.8725			0.965

NO, preterms without comorbidity.

TABLE 5 Mean RI on day 3 vs. day 7.

	RI (3D)	RI (7D)	*z*	*p*-value
Mean	0.77	0.82	−6.637	0.001
SD	0.04	0.03		
Median	0.76	0.83		
IQR	0.74–0.79	0.80–0.84		

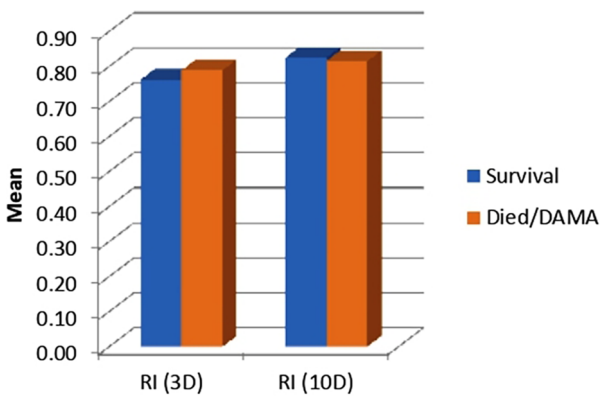

FIGURE 2
RI—survival vs. mortality group.

imaging has been proven as a useful modality to assess for cerebral perfusion and predict adverse outcomes newborns with perinatal asphyxia (18), but very little is known about its utility in preterm neonates with asphyxia.

Neonates with sepsis have impaired blood–brain barrier due to inflammation, leading to altered cerebral hemodynamics (19). Various studies have demonstrated the association of both increased and decreased cerebral blood flow in neonates with

sepsis. In a recent study, increased values of RI were demonstrated in the ACA of newborns with proven sepsis, indicating decreased cerebral blood flow with sepsis (19).

We observed that RI values have no statistically significant variation between healthy preterm neonates and preterm neonates with complications like perinatal asphyxia, sepsis, and NEC. Similar results were obtained in a systematic review by Camfferman et al. (20).

Superior vena cava flow, left ventricular output, and ACA Doppler measurements have been used to predict IVH in preterm babies (21).

In a study, the ACA RI was compared with cerebral oxygen saturation detected by near-infrared spectroscopy (NIRS) in preterm neonates born before 32 weeks of gestation, paving the way for future research (22–25).

The limitations of the study include the absence of MCA (middle cerebral artery) Doppler data, lack of blood gas analysis at the time of admission, and the absence of a detailed hemodynamic assessment along with Doppler evaluation. Individual values of peak systolic velocity (PSV) and end-diastolic velocity (EDV) can be assessed along with the RI for further evaluation of cerebral perfusion. Variables affecting Doppler flow measurements, including heart rate, temperature, and anemia, need more detailed assessment in all preterm babies, as these parameters affect cerebral blood flow velocity. Integration of NIRS with other cerebral perfusion parameters could further aid in the prevention of preterm brain injury.

Conclusion

Cerebral perfusion is important in the context of acquired preterm brain injury, and the resistive index serves as a marker for cerebral hemodynamics. However, we could not find any significant clinical correlation between ACA RI and early comorbidities in preterm neonates.

Data availability statement

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

Ethics statement

Informed consent was obtained on the consent/accent form from the parents of all study subjects, and the study was approved by the institutional Ethics Committee (IEC) DMCH under number DMCH/IEC/2023/209 in accordance with the declaration of Helsinki.

Author contributions

KG: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. BG: Formal Analysis, Methodology, Writing – review & editing. PP: Formal Analysis, Project administration, Supervision, Writing – review & editing. SB: Formal Analysis, 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.

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EDITED BY
Minesh Khashu,
University Hospitals Dorset NHS Foundation Trust, United Kingdom

REVIEWED BY
Rachana Singh,
Tufts University, United States
Brian Scottoline,
Oregon Health and Science University, United States
Roberto Murgas Torrazza,
Secretaría Nacional de Ciencia, Tecnología e Innovación, Panama

*CORRESPONDENCE
Venkatesh Sampath
✉ vsampath@cmh.edu

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Understanding necrotizing enterocolitis endotypes and acquired intestinal injury phenotypes from a historical and artificial intelligence perspective

Alain Cuna[1,2], Navin Kumar[3] and Venkatesh Sampath[1,2]*

[1]Division of Neonatology, Children's Mercy Kansas City, Kansas City, MO, United States, [2]School of Medicine, University of Missouri-Kansas City, Kansas City, MO, United States, [3]Division of Neonatology, Hurley Medical Center, Flint, MI, United States

Necrotizing enterocolitis (NEC) remains a devastating disease in preterm and term neonates. Despite significant progress made in understanding NEC pathogenesis over the last 50 years, the inability of current definitions to discriminate the various pathophysiological processes underlying NEC has led to an umbrella term that limits clinical and research progress. In this mini review, we provide a historical perspective on how NEC definitions and pathogenesis have evolved to our current understanding of NEC endotypes. We also discuss how artificial intelligence-based approaches are influencing our knowledge of risk-factors, classification and prognosis of NEC and other neonatal intestinal injury phenotypes.

KEYWORDS

necrotizing enterocolitis, machine learning, phenotype, endotype, prematurity, neonate

Introduction

Necrotizing enterocolitis (NEC) is a devastating disease in premature infants with an incidence of 5%–12% in very low birthweight infants (1–4). While less common than in preterm infants, recent studies have also identified risk-factors that predispose full-term neonates to NEC (5–8). Despite significant progress made in understanding NEC pathogenesis over the last 50 years, the inability of current definitions to discriminate the various pathophysiological processes underlying NEC has led to an umbrella term that limits clinical and research progress (9, 10). Further, the lack of precise clinical, biochemical and radiological tools to define NEC has hindered progress in delineating it from different conditions such as septic ileus (9). We propose that identifying endotypes of NEC based on pathophysiology, epidemiology and diagnostic tools will pave the way for precision approaches in preventing and treating NEC (11, 12). In this review, we provide a historical perspective on how NEC definitions and pathogenesis have evolved to our current understanding of NEC endotypes (Figure 1). We also discuss how artificial intelligence (AI)-based approaches are influencing our knowledge of risk-factors, classification and prognosis of NEC endotypes and other neonatal intestinal injury phenotypes.

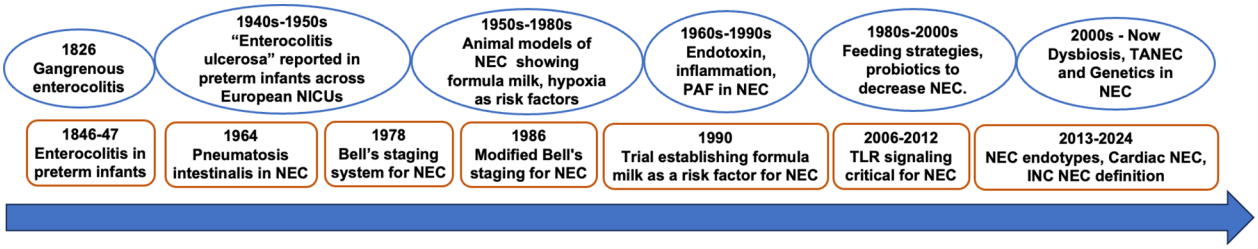

FIGURE 1
NEC – a brief history in time. INC, International Neonatal Consortium; PAF, platelet activating factor; TANEC, transfusion-associated NEC; TLR, Toll-Like Receptor.

NEC: diagnosis and definitions over time

The earliest report of an endotype resembling NEC could be Charles Billard's description 200 years ago from the Hôpital des Enfants Trouvés (13, 14). In his textbook, he describes "gangrenous enterocolitis" in neonates, characterized by abdominal distension, bloody stools, septicemia and death. Autopsy reports showed the ileum was particularly affected with erythema, swelling, ecchymosis, and friability (14). A systematic report of preterm NEC is found in Bednar's description of "entero-colitis" in 25 infants admitted to the Vienna hospital for foundlings between 1846 and 1847, 7 of whom were premature, with majority developing disease between 3 and 30 days of life. In 20 infants who died, autopsy showed evidence of necrosis, gangrene and hemorrhage, very similar to current descriptions of severe advanced NEC (15). In several neonatal intensive care units established across Europe to care for preterm infants between 1910 and 1940s, a NEC-like disease with pathological features including intestinal perforation in lethal cases is poignantly described (16, 17). Between 1948 and 1950, Schmidt and Kaiser et al. described "enterocolitis ulcerosa" in 85 mostly breast-fed preterm infants in Graz, Germany (18, 19). They accurately documented the ileocecal involvement, peritonitis, and perforation and speculated the role of a specific pathogen. Apart from the lack of corroborative radiological, cytological and bacteriology evidence, these physicians established the pathology of NEC and identified the at-risk preterm infant population. These studies did not delve into the pathophysiology of NEC, but hinted at infectious etiology, including viruses.

While pneumatosis intestinalis had been reported in NEC before, it was Berdon in 1964, who described the entire spectrum of what has become the *signe qua non* of NEC diagnosis (20–22). Bell et al. in 1978 proposed the first systematic classification of NEC, grading it from stage I to III based on clinical signs, biochemical markers, radiological signs and disease severity (23). This significant advance enabled consistency among clinicians and researchers to classify NEC more accurately than before, and also provided severity-based treatment guidelines. Around the time Bell et al. classified NEC, several investigators using animal and human studies suggested that hypoxia, formula feeding, speed of feed advancement and infection were risk factors for NEC in the late preterm population (24–26). Walsh and Kliegman in 1986 modified this classification to 6 categories with two subcategories for stage I, II and III (10). In their classical paper, they also summarized the existing thoughts on pathogenesis of NEC indicating the potential roles for direct intestinal infections, bacterial overgrowth, formula feeding, milk intolerance, ischemia, hypertonic enteral supplements in causing mucosal injury and inflammation in an immature gut (10). Interestingly, their summary hinted at multi-factorial causation and a broad spectrum of mechanisms underlying NEC evolution. While several other definitions including the Vermont Oxford Network, Centers of Disease Control and Prevention and the UK Neonatal Collaborative NEC Study group among others have defined NEC, Bell's staging and modified Bell's staging are still the most commonly accepted definitions for NEC (12). From mid-1980s to the current era, several investigators have unraveled the role of dysregulated Toll Like receptor 4 (TLR4) signaling, gut microbiome and dysbiosis, inflammatory mediators and genetic predisposition in NEC (1, 4, 27–35).

Recognizing the limitation of the Bell's criteria in not recognizing spontaneous ileal perforation (SIP), differentiating NEC in term infants vs. preterm infants, and standardizing definitions for research purposes, the International Neonatal Consortium NEC definition groups proposed to classify NEC based on gestational-age, timing of onset of disease, one of the two clinical signs (hematochezia and abdominal distension), and radiological evidence (9). These criteria demarcate NEC that develops in preterm infants from NEC in term infants, and also distinguishes SIP and septic ileus from NEC in preterm infants. While these criteria do address some of the short comings of the previous NEC definitions, it is agnostic with respect to the different pathogenic mechanisms and the resulting endotypes. In the subsequent paragraphs, we will briefly review current understanding of NEC and NEC-like intestinal injury endotypes in preterm and term infants focusing on differences in the pathogenic mechanisms, timing of onset, distinguishing features, and prognosis. A summary of different NEC endotypes is presented in Table 1.

Endotypes of NEC in preterm infants

Classical NEC

The most common endotype of NEC – coined "classical NEC" – occurs in preterm infants. The onset of presentation of classical NEC

TABLE 1 Summary of different endotypes of necrotizing enterocolitis.

	Clinical presentation	Age/Timing of presentation	Proposed mechanism of injury
Classical NEC	Sudden onset of feeding intolerance, abdominal distention, and bloody stools with systemic signs of illness	Preterm infants, typically occurring between 2 and 6 weeks after birth, around 28–32 weeks postmenstrual age	Deviant host-microbiota interactions in the immature gut triggering excessive intestinal inflammation. Other factors include genetic predisposition and formula-feeding.
Transfusion-associated NEC	Symptoms of classical NEC after packed red blood cell transfusion in otherwise stable preterm infant with established feeding	Preterm infants, within 48–72 h of receiving packed red blood cell transfusion	Ischemia-hypoxemia from chronic anemic state followed by reperfusion injury from transfusion; factors in transfused blood triggering excessive intestinal inflammation
Virus-associated NEC	Gastrointestinal symptoms such as emesis, diarrhea, feeding intolerance ± systemic signs such as fever, apnea, lethargy, or irritability	Preterm infants, occurring in clusters coinciding with peak seasons of viral transmission. Timing variable.	Direct invasion of virus into intestinal epithelial cells leading to intestinal injury and inflammation
Cardiac NEC	Signs of NEC occurring in infant with congenital heart disease, especially lesions with ductal-dependent systemic blood flow	Term infants, typically occurring in the first two weeks of life and/or post-surgical repair, but depends on feeding patterns	Mesenteric ischemia ± reperfusion injury in the setting of cardiac lesion that disrupts systemic perfusion
NEC associated with congenital intestinal anomalies	Signs of NEC occurring in infants with gastrointestinal anomalies such as gastroschisis and Hirschsprung's disease	Term and late-preterm infants, timing is highly variable, but typically in the first weeks of life and/or post-surgical repair	Structural and functional defects in the vasculature or mucosa related to underlying gastrointestinal anomaly that compromise circulation, barrier function and motility
NEC associated with impaired mesenteric blood flow	NEC associated with conditions that could impair mesenteric blood flow such as perinatal asphyxia or polycythemia	Term infants, typically occurring in the first week of life	Combination of mesenteric ischemia ± physiologic demands of feeding
Spontaneous intestinal perforation	Distinct entity from NEC presenting as abdominal distention, associated with exposure to hydrocortisone and indomethacin	Extremely preterm infants, typically occurring in the first 10 days of life with minimal or no feeds initiated	Focal intestinal necrosis of terminal ileum thought to be related to bowel wall ischemia or deficiency of muscularis propria
Cow milk protein allergy	Bloody stools with no systemic signs of illness that resolves with eliminating cow milk protein in diet	Term and preterm infants, occurring much later after several weeks of established feeds	Non-IgE mediated allergic reaction to cow milk protein resulting in intestinal inflammation

has an inverse relationship with gestational age (36), often occuring in the 28–32 week postmenstrual age with sudden onset of feeding intolerance, abdominal distention, and bloody stools that can rapidly progress towards intestinal perforation, peritonitis, and multi-organ dysfunction (4). The presence of pneumatosis intestinalis and/or portal venous gas on imaging is diagnostic of the disease, while free air heralds intestinal perforation requiring surgery (37). A gasless abdomen, or fixed, dilated loops – defined by persistent location and configuration for more than 24 h – are also a concerning imaging finding for NEC (38, 39).

While the pathogenesis of classical NEC is multifactorial, prematurity remains its single most important risk factor, with NEC incidence rising as gestational age and birth weight decrease. The immature preterm gut is structurally and functionally underdeveloped, with decreased mucosal integrity, reduced motility, and impaired barrier function. Preterm infants also possess an immature immune system that predisposes them to aberrant inflammatory responses. Experimental studies reveal excessive Toll-like receptor (TLR) activation as a key pathway that drives intestinal inflammation in NEC (40). The other major player in classical NEC pathogenesis is the gut microbiota. Dysbiosis – driven by formula-feeding, antibiotic exposure, and perinatal stress – can induce aberrant inflammation in the preterm gut causing mucosal injury, translocation of bacteria into the circulation and subsequent multi-organ dysfunction (1, 29). Conversely, factors that promote a healthy gut microbiome – such as breastmilk, avoidance of prolonged antibiotics, and probiotics – decreases the risk of NEC (41–44).

Despite these advances in our understanding, classical NEC remains a complex disease with significant morbidity and mortality risks. For instance, NEC continues to occur despite avoidance of formula-feeding, exclusive use of human breastmilk, probiotics, and judicious antibiotic stewardship. It remains a leading cause of mortality, especially in infants with extensive intestinal necrosis requiring surgery. Survivors of NEC are also at increased risk for complications including strictures, short gut syndrome, growth failure, and neurodevelopmental impairments.

Transfusion associated NEC (TANEC)

Another endotype of NEC in preterm infants is TANEC or transfusion related acute gut injury. TANEC often develops much later than classical NEC – after the 4th or 5th week of life – in otherwise stable preterm infants who have been established on enteral feeds for several weeks (45). Infants who develop TANEC have chronic anemia for several weeks, and symptoms of NEC often are evident within 48 h after packed red blood cell transfusion (45).

The exact pathogenesis of TANEC remains unknown. One proposed mechanism is that chronic anemia could mimic a state of ischemia-hypoxia in the mesenteric bed, and transfusion could trigger a reperfusion injury of previously ischemic intestinal tissue (46, 47). The generation of reactive oxygen species with reperfusion injury, combined with physiological demads of feeding, could be sufficient to cause mucosal damage and compromise the intestinal barrier, leading to TANEC. Based on

this pathophysiology, withholding feeds around transfusion has been adopted by some to prevent TANEC (48), although good-quality evidence supporting this practice remains lacking (49). Another proposed mechanism is that intestinal injury arises from hemolytic factors in the transfused blood. In an experimental model of TANEC, free hemoglobin and heme in packed red blood cells were shown to activate monocytes and macrophages in the intestine, triggering excessive TLR inflammation and NEC (50). Interestingly, the Transfusion of Prematurity trial did not show differences in NEC rates among extremely preterm infants randomized to high vs. low transfusion thresholds, and a secondary analyses showed no temporal relationship between red blood cell transfusion and NEC (51, 52).

TANEC poses significant morbidity and mortality risks for preterm infants. In one meta-analysis, TANEC had higher odds of mortality compared to classical NEC (53). In contrast, a study using the Canadian Neonatal Network database found no significant differences in mortality and morbidities between TANEC and classical NEC (54).

Viral infections and NEC

Gastroenteritis caused by viral pathogens can mimic NEC (55, 56). Rotavirus (57, 58), cytomegalovirus (59), norovirus (60), astrovirus (61, 62), and enterovirus have been implicated in neonatal gastroenteritis (63). As viral infections are typically not considered in the differential diagnosis of NEC, a high index of suspicion is required. A viral cause is suspected when NEC occurs in clusters, coinciding with peak seasons of viral transmission (55, 64, 65). While clinical presentation can vary, most cases present similarly as classical NEC with gastrointestinal symptoms such as abdominal distention, feeding intolerance, bilious emesis, and bloody stools. Some infants present with systemic signs such as fever, apnea, lethargy, or irritability (e.g., norovirus); while others present with extra-intestinal manifestations such as respiratory symptoms (e.g., enterovirus) or hepatic dysfunction (e.g., cytomegalovirus). Early recognition of viral NEC could limit the use of antibiotics and direct appropriate anti-viral treatment, such as ganciclovir for cytomegalovirus.

The pathogenesis of viral NEC includes direct invasion of virus into intestinal epithelial cells, leading to cellular injury, disruption of tight junctions, and loss of barrier function. Viral infection also triggers an inflammatory response which can mimic classical NEC. Nevertheless, viral NEC tends to have a more insidious onset and a less fulminant clinical course compared to classical NEC, which often presents with rapid progression.

Endotypes of NEC in term infants

Term infants can also develop NEC, although the incidence is much less than in preterm infants. NEC in term infants typically presents earlier than preterm NEC, with average age of onset in the 1st week of life (5, 66). Term NEC is also typically secondary to other underlying disease processes, most notably congenital heart disease (67).

Cardiac NEC

The incidence of NEC in term infants with congenital heart disease is about 2%–6%. The highest risk seems to occurr in conditions with ductal-dependent systemic blood flow such as hypoplastic left heart disease (68–70), although other lesions such as truncus arteriosus and common ventricle have been reported (71). Some studies suggest that the colon is significantly more involved in cardiac NEC (6), but others indicate the small intestine remains the primary location (72).

The pathophysiology of cardiac NEC is thought to be from mesenteric ischemia caused by anatomic lesions that disrupt systemic perfusion during diastole (73). Reperfusion injury following ischemia could also play a major role, particularly in infants who remain at increased risk for NEC even after surgical correction. Other mechanisms include hemodynamic changes while on cardiopulmonary bypass during surgery, or from medications such as vasopressin and opiates post-surgery (74–76). Because feeding can alter gastrointestinal perfusion and hemodynamics, there is often hesitancy to feed infants with cardiac disease, despite the absence of high-quality evidence (77).

Infants with cardiac NEC can have poor outcomes despite its occurrence predominantly in term infants. In one study, mortality rates were higher in infants with cardiac NEC compared to non-cardiac NEC (38% vs. 27%) (78). Prolonged hospital stay, mechanical ventilation, and parenteral nutrition were also noted (70, 71, 74). Although less common, NEC associated with severe congenital heart disease has also been reported in preterm infants, showing higher mortality compared to NEC in preterm infants without congenital heart disease (79).

Gastrointestinal anomalies and NEC

Term and late-preterm infants with gastrointestinal anomalies – such as intestinal atresia, malrotation with volvulus, Hirschsprung's disease, gastroschisis, and omphalocele – are also at increased risk of NEC (80–82). In particular, NEC has been reported to occur in up to 20% of infants with gastroschisis (81, 82). The pathogenesis of NEC in these conditions is related to structural and functional anomalies of the intestine including intestinal obstruction, dysmotility, and vascular compromise. The anatomical complexity of gastrointestinal anomalies can increase morbidity and mortality of these infants who also develop NEC, as the presence of gastrointestinal anomalies would typically require surgical repair of the underlying anatomical defect.

Other conditions associated with term NEC

Other conditions that could impair mesenteric blood flow or result in mesenteric ischemia – such as perinatal asphyxia, polycythemia, and septic shock – have been reported in term infants with NEC (67). In a review of term NEC cases at Intermountain Health, all cases of term NEC occurred in infants with gavage feeding, overfeeding, and/or feeding with formula (83). Moreover, overfeeding has been shown to be sufficient to elicit NEC injury in a mouse model (84). Thus, a possible unifying hypothesis regarding the pathogenesis of term NEC is

the combination of underlying conditions that impair mesenteric blood flow with feeding.

Acquired intestinal injury phenotypes that mimic NEC

Spontaneous intestinal perforation (SIP)

While SIP also develops in extremely preterm infants it is a distinct entity from NEC. SIP tends to occur earlier, even before feeds have been initiated, and is associated with exposure to postnatal indomethacin and hydrocortisone (85, 86). While both can present with abdominal distention, SIP often presents with a bluish discoloration of the abdomen (87). Gross examination of the intestine in SIP reveals the perforation localized to the antimesenteric border of the small intestine with healthy tissue surrounding it. In NEC with perforation, the surrounding bowel is not healthy (88). The absence of bowel injury allows for SIP to have simpler surgical treatment with either peritoneal drainage, direct repair, or resection and primary anastomosis (87). In contrast, surgical NEC often requires resection of injured tissue with creation of stomas. Mortality from SIP is also lower compared to surgical NEC (89), but surprisingly morbidity and neurodevelopmental outcomes were not better (90, 91).

Cow milk protein allergy (CMPA)

CMPA, also known as Food Protein-Induced Enterocolitis or FPIES, can present in both term and preterm infants with bloody stools and is thus an important differential for NEC (92). CMPA tends to occur much later, after several weeks of established feeds with formula or breastmilk that contains cow's milk protein (8). Severe cases can present with *pneumatosis intestinalis*, but otherwise do not progress towards systemic and multi-organ dysfunction (93). It can be difficult to distinguish CMPA from NEC. Typically, CMPA is suspected when reintroduction of feeds that contain cow-milk protein leads to "reoccurrence" of NEC-like symptoms (94). The pathogenesis of CMPA is non-IgE mediated allergic reaction to cow milk protein resulting in infiltration of intestinal mucosa with eosinophils, lymphocytes, and mast cells (95). In contrast to NEC, CMPA is a benign condition with low morbidity and typically improves with elimination of cow's milk protein from the infant's or mothers diet.

Machine learning in NEC risk identification, diagnosis, and endotype classification

While clinicians have strived to define NEC more precisely and differentiate it from conditions that mimic NEC, these classifications still rely on prior conditioned learning (11). The potential for artificial intelligence (AI)-based approaches to classify in an unbiased fashion disease endotypes has resulted in several studies applying machine learning (ML) to classify NEC. AI is particularly useful in analyzing large datasets to detect intricate patterns not discoverable to human intelligence, and holds promise to improve diagnosis, classification, and management of acquired intestinal injury (96). When AI is utilized to analyze data within frameworks such as specific diagnosis/labels, known risk factors, or pre-determined outcomes it is commonly known as *supervised* ML. When AI is used to analyze data without labels or pre-determined framework/outcome, it is considered *unsupervised* analysis. In Table 2, a collection of ML models is depicted, along with a concise explanation and their contextual applications in NEC research.Through these models, patterns of disease in NEC that were not readily appreciated can be discovered (97).

Apart from prematurity, formula milk feeding, African American race (either as a social determinant of health or genetic risk), and potentially genetic factors, risk factors that are consistently associated with NEC remain unclear (1, 98, 99). Recently, Mueller et al. (100) used artificial neural networks to identify small for gestational age and use of artificial ventilation as additional risk factors for NEC. The utilization of continuous vital signs data has proven to be highly beneficial in diagnosing life-threatening diseases and improving outcomes for sepsis and

TABLE 2 Summary of different machine learning models used in NEC research.

ML model	Category	Contextual applications in NEC research	Description
Artificial Neural Network (ANN)	Supervised/Unsupervised	Used to predict NEC risk based on clinical features and patient data.	Comprises interconnected nodes that simulate neural processes.
Deep Learning (DL)	Supervised/Unsupervised	Used for examining imaging data related to NEC with pixel-level analysis.	An effective multi-layer variant of ANN designed for handling large datasets.
Logistic regression	Supervised	Used to classify the presence or absence of NEC through binary classification.	A probability-based statistical approach for binary outcomes.
Decision tree	Supervised	Used for risk stratification and outcome prediction in neonatal patients.	A flow-chart-like structure that facilitates decision-making processes.
Random forest	Supervised	Utilized for the identification of significant risk factors associated with NEC.	Using a combination of multiple decision trees to improve accuracy.
Naïve bayes	Supervised	Employed for the categorization of neonatal patient data according to predetermined characteristics.	A probabilistic model that relies on Bayes' theorem and assumes independence.
Support Vector Machine (SVM)	Supervised	Used to distinguish between neonates at risk of NEC and those who are not.	A classification method that identifies the optimal hyperplane in high-dimensional space.
Back-propagation neural network	Supervised	Utilized to train ANN models specifically for NEC outcomes.	An algorithm that updates neural network weights through error feedback.

other conditions in preterm infants (101). Vital signs data can also be leveraged using ML techniques to accurately predict NEC. Doheny et al. (102) analyzed the high frequency component of heart rate variability, an indicator of baseline vagal tone, in 70 preterm infants. The authors found that decreased vagal tone was a highly accurate predictor of NEC. ML can be used to identify white blood cell patterns to diagnose and prognosticate NEC. In a retrospective cohort of 246 infants, Pantalone et al. (103) reported that the onset of NEC in more mature infants (born after 33 weeks) was associated with lower neutrophil counts at diagnosis compared to controls. In less mature infants, a sharp decrease in monocytes and lymphocytes, as well as an elevation in bands at the time of diagnosis, predicted surgical intervention. The type of ML algorithm employed can also affect the findings as shown by Cho et al. (104) who compared the ability of several ML models to predict NEC. The study dataset consisted of over 10,000 very low birthweight infants and 74 variables, including environmental factors. Logistic regression and random forest (RF) exhibited superior performance achieving accuracy rates of 0.93, compared to artificial neural network, decision tree, naïve Bayes, and support vector machine methods. Birth weight, maternal age, gestational age, sepsis, male sex, and environmental factors such as ambient temperature were highlighted as key predictors, among others.

ML models have been used to predict intestinal perforations in NEC patients (NEC-IP). Using a Back-propagation neural network model, Irles et al. (105) identified that platelet counts, neutrophil counts, intubation, birth weight and arterial blood gas parameters can accurately predict NEC-IP. Recent ML studies have also demonstrated its utility to differentiate SIP from NEC-IP. Models such as random forest, ridge logistic regression model (106), and artificial neural network (107) have shown accuracy rates higher than 90% in differentiating these two conditions even before surgery, which can help guide optimal management strategies. Recent studies have also used ML models to predict need for surgical intervention in NEC (108, 109).

Researchers have also examined stool microbiome and metabolomic data using unsupervised ML algorithms to predict NEC (97). Notably, Lin et al. (110) used a multiple instance learning (MIL) architecture for predicting NEC based on stool microbiota data. Through incorporating past data with analysis of crucial bacterial taxa, this approach achieved timely and precise prediction of NEC risk, with an average lead time of 8.3 days. Their RF model emphasized the importance of Firmicutes, Proteobacteria and Enterobacteriaceae in NEC prediction with high level of sensitivity and specificity, thus emphasizing its potential in enabling personalized risk assessment and disease prevention (110). Other studies examined stool metabolomic (111) and urine peptides data (112) to find specific patterns to predict NEC. Recent endeavors have undertaken an unbiased assessment of distinct patterns of acquired intestinal injuries in preterm infants. By utilizing an unsupervised hierarchical clustering algorithm, Gipson et al. (113) successfully identified five distinct clusters of acquired neonatal intestinal injuries from a sample of 183 infants who experienced 210 episodes of such injuries. These clusters were classified as (1) low mortality, (2) immature with high mortality, (3) mature with inflammation, (4) late injury at full feeds, and (5) late injury with intestinal necrosis. These studies provide encouraging data for improving the prediction, accurate diagnosis and prognosis of NEC and other intestinal phenotypes that mimic NEC. One limitation of current AI studies includes limited data from single center design, smaller cohorts, and non-uniformity of variables used for analysis. As the accuracy and reliability of AI models rely solely on the quality of the input provided, reliability and generalizability of these models can be enhanced by using standardized datasets across multiple centers. Another important limitation is the complex and multi-factorial nature of NEC pathogenesis, which makes capturing all relevant variables and their interactions in an AI model challenging. AI models would also need to be continuously updated to incorporate new insights and research findings as our understanding of NEC evolves.

Conclusion

While our understanding of NEC has evolved over time from a clinical/pathological description to a better understanding of pathophysiology and NEC endotypes, only limited progress has been made in in differentiating classical NEC from endotypes that mimic it but have different etiologies and prognosis. We speculate that characterizing endotypes of NEC based on pathophysiology, clinical variables and radiological/biochemical tests using traditional clustering methods augmented by machine learning (ML) is important for precision approaches directed at disease prevention and management of NEC and acquired intestinal injury phenotypes in neonates.

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AC: Investigation, Writing – original draft, Writing – review & editing. NK: Investigation, Writing – original draft, Writing – review & editing. VS: Investigation, Supervision, Visualization, Writing – original draft, 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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EDITED BY
Minesh Khashu,
University Hospitals Dorset NHS Foundation Trust, United Kingdom

REVIEWED BY
Tuuli Metsvaht,
University of Tartu, Estonia
Yao Mun Choo,
University of Malaya, Malaysia

*CORRESPONDENCE
Pradeep Suryawanshi
✉ drpradeepsuryawanshi@gmail.com

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A pilot randomized controlled trial comparing noradrenaline and adrenaline as a first-line vasopressor for fluid-refractory septic shock in neonates

Reema Garegrat[1], Suprabha Patnaik[1], Sonali Suryawanshi[2], Chinmay Chetan[3], Nishant Banait[4], Pari Singh[1], Aditya Kallimath[1], Naharmal B. Soni[5], Yogen Singh[6] and Pradeep Suryawanshi[1]*

[1]Department of Neonatology, Bharati Vidyapeeth Hospital and Research Institute, Pune, India, [2]Department of Pharmacology, Bharati Vidyapeeth Hospital and Research Institute, Pune, India, [3]Department of Neonatology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, India, [4]Department of Neonatology, AIIMS, Nagpur, India, [5]Department of Neonatology, Sidra Medicine, Doha, Qatar, [6]Department of Pediatrics, Division of Neonatology, University of California Davis Children's Hospital, Sacramento, CA, United States

Background and study design: Limited data exists on noradrenaline therapy in neonatal septic shock. We compared the efficacy of noradrenaline with adrenaline in neonatal septic shock. This single center, open label, pilot randomized controlled trial included neonates with clinical evidence of sepsis and shock.
Study outcomes: Primary outcomes were: 1) resolution of shock one hour after treatment, and 2) mortality during hospital stay. Secondary outcomes included: need for additional vasopressors; hemodynamic stability without further administration of vasopressors for ≥2 h; changes in blood pressure and heart rate after 1 h of vasopressor treatment; and morbidities during the hospital stay.
Results: Of 65 eligible neonates, 42 were randomized (21 each in adrenaline and noradrenaline treatment arms) between August 2020 and January 2022, at level III neonatal intensive care unit (NICU) of Bharati Vidyapeeth Deemed University Medical College and Hospital (BVDUMCH). The mean (SD) gestational age and mean (SD) birth weight were 36.1(4.2) weeks and 1.8 (0.2) kilograms birth weight for noradrenaline and 36.9 (4.1) weeks and 1.7 (0.7) kilograms for adrenaline. Shock resolved within 1 h of vasopressor therapy in 76.2% neonates in the noradrenaline arm and 61.9% in adrenaline arm (p value-0.53). Mortality during hospital stay was 28.6% (6/21) in noradrenaline group and 33.3% (7/21) in adrenaline group (p value- 0.58). Additional vasopressors were required in 23.8% neonates of the noradrenaline group compared to 38.1% neonates in adrenaline arm (p value-0.53). Median (SD) duration of intensive care stay was 6 (SD) days in the noradrenaline group and 10 (SD) days in the adrenaline group (p value-0.045).
Conclusion: Among neonates with septic shock, the efficacy of noradrenaline was comparable to adrenaline in resolving septic shock after one hour of infusion and on the mortality during hospital stay.

Clinical Trial Registration: https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=NDI2NTc=&Enc=&userName=noradrenaline, Clinical Trials Registry – India with identifier CTRI/2020/08/027185 (17/08/2020).

KEYWORDS

adrenaline, neonate, noradrenaline, sepsis, septic shock

Introduction

Sepsis remains a leading cause of neonatal morbidity and mortality (1). Fluid-refractory septic shock, an important consequence of sepsis, is managed according to guidelines developed for intensivists and pediatricians. The surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children of the society of critical care medicine does not recommend any specific drug as the first-line vasopressor agent and instead suggests either adrenaline or noradrenaline can be used and guided by "clinician preference, individual patient physiology, and local system factors" (2). The American College of Critical Care Medicine/Pediatric Advanced Life Support Clinical Guidelines for hemodynamic support of neonates and children with septic shock recommends adrenaline as the first-line agent to begin with but shifting to noradrenaline in case of vasodilatory shock (3). Neonatal sepsis studies have shown mild cardiac dysfunction in infants with neonatal septic shock and some developing pulmonary hypertension (4, 5). The newborns present with a haemodynamic pattern similar to children and adults with warm shock or cold shock, depending upon the compensatory mechanisms. In such a clinical scenario, choice of cardiovascular medication is not clearly defined. In neonatal septic shock, although adrenaline is commonly used but noradrenaline can give additional benefit of pulmonary pressure reduction, decrease in peripheral vasodilatation and thus increasing blood pressure. However, noradrenaline is often not used as first line therapy based on the assumption that use of noradrenaline may further compromise left ventricular function in infants with moderate to severe cardiac dysfunction. There are no guidelines as of now for the usage of the drugs interchangeably. Considering this, the current study was designed to compare noradrenaline and adrenaline as the first-line vasoactive medication in neonatal septic shock to objectively see the effectiveness and the hemodynamic impact from use of either of these drugs.

Material and methods

Study ethics and registration

The study was approved by the institutional review board of Bharati Vidyapeeth Deemed University Medical College and Hospital (BVDUMCH), Pune, India, and registered in Clinical Trials Registry – India with identifier CTRI/2020/08/027185 dated 17/08/2020. Informed consent was obtained from parents of the neonates for their enrolment in the study.

Study design

The open label, parallel arms, randomized study was conducted in the level III neonatal intensive care unit (NICU) of BVDUMCH between August 2020 and January 2022.

Sample size calculation

Successful resolution of shock within one hour of adrenaline occurred in around 25% of the neonates (6). To detect an increase in resolution from 25% in the adrenaline group to 60% in the noradrenaline group, at 80% power and 0.05 significance, 30 neonates per arm (60 total) were to be recruited. However, the trial was discontinued after recruitment of 42 neonates due to the COVID pandemic.

Study population

Neonates admitted in the NICU with fluid-refractory septic shock were eligible for enrollment. Septic shock was defined as systemic hypotension with decreased perfusion: mean blood pressure < 10th percentile of the normal for birth weight (BW) and postnatal age for Indian children (7) with at least three of these five criteria satisfied: resting heart rate > 20 above normal, feeble or non-palpable peripheral pulses, pale or bluish discoloration of palmar/plantar surfaces, palmar/plantar capillary refill time > 3 s, and urine output < 1 ml/kg/h. Neonates with congenital malformations, hypovolemic shock, cardiogenic shock, clinically suspected or echocardiographically proven congenital heart disease including hemodynamically significant patent ductus arteriosus (hsPDA), moderate to severe hypoxic ischemic encephalopathy with blood pH < 7 at birth or APGAR score < 5 at 5 min, or those already on inotropic or vasopressor drugs were excluded. HsPDA was defined as duct diameter >1.6 mm with retrograde descending aorta flow with Qp/Qs > 1.5.

Over the study period of 22 months, 42 of the 65 neonates considered eligible for the study were enrolled after parental

Abbreviations

BVDUMCH, Bharati Vidyapeeth Deemed University Medical College and Hospital; NICU, Neonatal intensive care unit; BW, Birth weight; hsPDA, Hemodynamically significant patent ductus arteriosus; AKI, Acute kidney injury; IVH, Intraventricular hemorrhage; Periventricular leukomalacia (PVL); NEC, Necrotizing enterocolitis.

consent. Twenty neonates receiving other inotropes and three with congenital anomalies were excluded from the study.

Intervention and clinical care

At baseline, demographic and clinical data, including hemodynamic status (extremity perfusion, mental status, heart rates, and BP) was recorded in a pre-designed form. The first dose of broad-spectrum antibiotics was administered within 1 h of sepsis recognition, and samples were collected for relevant cultures, blood gas analyses, and lactate measurements.

Forty two enrolled neonates were randomized using computer generated random numbers (Random Allocation Software) (8) to receive either adrenaline or noradrenaline (21 in each group). The neonates first received a fluid bolus of 10 ml/kg of crystalloids, after which functional echocardiography was performed. Continuous infusion of adrenaline or noradrenaline was then started at 0.1 or 0.2 µg/kg/min, respectively, via peripheral venous access. If there was no hemodynamic response to the initial dose, vasopressor dose was incremented to 0.3 or 0.5 µg/kg/min, respectively by increasing the fluid flow rate up to two times during 20 min. Reduction of adrenaline/noradrenaline in steps of 0.1 µg/kg/min was initiated as per the treating neonatologist after resolution of shock. In the case of no response to the highest possible study drug dose, the selection of another vasopressor was left to the physician's discretion. Functional echocardiography and arterial lactate assay were performed at baseline and at 1 h after start of treatment with the study drugs. Urine output was measured hourly till the withdrawal of vasoactive drugs. Data on fluid balance, blood and body fluid cultures, serologic assays, respiratory support, and antibiotic therapy were recorded.

Serious adverse events of tachycardia, hypertension, arrhythmia, renal ischemia, pulmonary oedema, hyperglycaemia, and hypokalaemia during infusion of the study drugs were recorded. Blood pressure was monitored by a non-invasive oscillometric method (Nihon Kohden VISMO multipara monitor). Echocardiography was performed by a single investigator using Phillips 50G with 12-4 MHz high-frequency phased array transducer probe using published methods at the beginning after fluid bolus and again 60 min later. Functional parameters were measured twice in the echocardiography procedures.

Outcome measures

Primary outcomes were: (1) resolution of shock one hour after treatment, and (2) mortality during hospitilisation. Secondary outcomes included: need of additional vasopressors; hemodynamic stability without further administration of vasopressors for ≥2 h; changes in blood pressure and heart rate after 1 h of vasopressor treatment; and morbidities during the hospital stay in terms of duration of ventilation support and incidence of acute kidney injury (AKI), cerebellar or intraventricular hemorrhage (IVH), nosocomial infection, periventricular leukomalacia (PVL), and stage II/III necrotizing enterocolitis (NEC).

Statistical analysis

Data was analysed using SPSS software (version 21). Standard t test was used for two-group comparisons of continuous variables. Chi square test was used for categorical variables, unless observed frequency in at least one cell was <5, in which case Fisher's exact test was used.

Results

A total of 2,035 neonates were admitted in the NICU during the study period (August 2020 to January 2022). Of these, 197 neonates (9.7%) had sepsis and 65 (33.0%) of them developed septic shock. There were 4 culture positive neonates in the noradrenaline arm and 8 culture positive cases in the adrenaline arm. 4 organisms in the noradrenaline group were in the blood, namely klebsiella pneumoniae, pseudomonas aueruginosa, eneterobacter cloacae and acinetobacter baumanni. The 8 organisms in the adrenaline group were in the blood, namely 2 klebsiella pneumoniae, 1 escherichia Coli, 1 acineobacter baumanii, 2 strenotropomonas maltophilia, 1 enterobacter cloacae and 1 serratia marcescens.

Forty-two of the 65 neonates eligible were infants with signs and symptoms suggestive of septic shock that got enrolled in the study and were randomized into two groups: 21 cases in each group receiving either adrenaline or noradrenaline as the first-line vasopressor treatment (Figure 1). The two groups were similar at baseline in terms of important maternal and neonatal characteristics (Table 1), clinical features (Table 1), and echocardiographic findings of ventricular function (Table 2A).

Resolution of shock without a second vasopressor or inotrope was achieved in 76.2% of cases in the noradrenaline group and 61.9% in the adrenaline group (p-value = 0.53). Dose increment was needed in 42.9% of cases receiving noradrenaline and 28.6% for adrenaline (p-value = 0.33). Mortality during hospitalisation was similar in two groups, 28.6% and 33.3% for noradrenaline and adrenaline, respectively (p-value = 1.00). Changes in ventricular function, vital signs, and blood acid-base parameters after one hour of starting the study drug infusion were also similar for the two groups (Table 2B). Mean requirement of fluid boluses was not significantly different for the two groups (1.67 vs. 1.48; p-value = 0.46).

The administration of noradrenaline via peripheral venous access was found to be safe with no adverse effects. Tachycardia occurred in 19.0% cases managed by noradrenaline and 28.6% cases managed by adrenaline (p-value = 0.77). Incidence of AKI, nosocomial infection, brain hemorrhage, and NEC were similar between the two groups (Table 3). Mechanical ventilation was required in 71.4% and 81.0% of cases in the noradrenaline and adrenaline groups, respectively (p-value = 0.34). Duration of

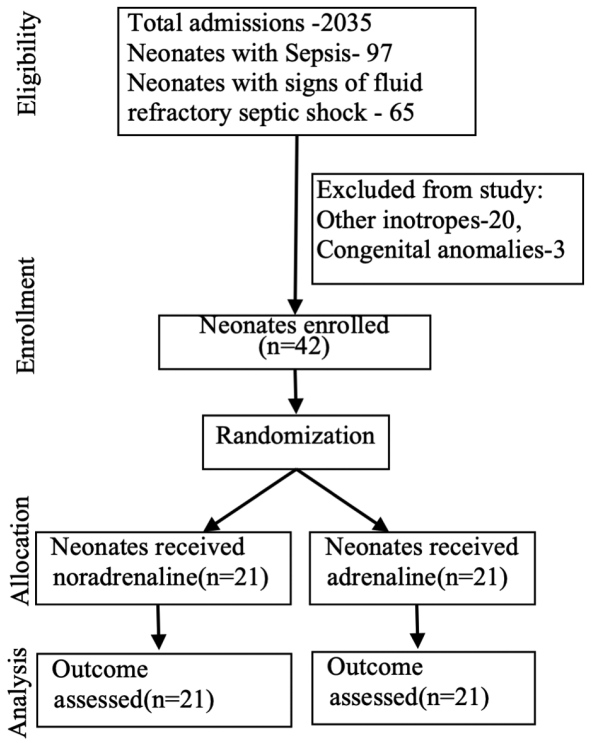

FIGURE 1
Study flowchart.

hospital stay was similar for the two groups (12 and 15 days, respectively; p-value = 0.43).

Discussion

Our study showed no difference in resolution of fluid-refractory septic shock within an hour in 76% of neonates treated with noradrenaline as compared to 62% cases treated with adrenaline (p-value = 0.53) with no difference in mortality during hospitalisation. Baske et al. reported reversal of such shock in 25% of 20 neonates in the adrenaline group (0.2 to 0.3 to 0.4 µg/kg/min) in their study (6), which is comparable to our study's finding. Similarly, Ramaswamy et al. reported that shock resolved in 48% of 29 children of age 3 months to 12 years with use of adrenaline (0.1 to 0.2 to 0.3 µg/kg/min) (9). In their trial of noradrenaline (0.1–0.3 µg/kg/min) in pediatric septic shock, Tourneux et al. found that hypoperfusion was reversed in 81% of cases within 6 h after starting treatment (10). In a 10-year review study on the use of noradrenaline in pediatric septic shock, Lampin et al. concluded that greater noradrenaline doses than those suggested in the literature may be required to correct hypotension and hypoperfusion (11). Kallimath et al. has described the noradrenaline cohort of this study in detail (12).

The groups in our study were comparable with respect to baseline parameters (Tables 1, 2). Males accounted for 71.4% of our study population of 42 neonates with septic shock. This male predominance, suggesting role of some sex-related element in vulnerability to neonatal sepsis, has been observed by multiple groups (13–15). The mean gestational age and birth weight of our cases were 36.8 weeks and 1.9 kg, with 69% and 80.1% of the neonates being pre-term and small for gestational age, respectively. Prevalence of pre-term birth among indian neonates with sepsis has been reported at 55%–73% (16–18), and neonatal septicemia has been associated with low birth weight (16–21). Seizures (19%), lethargy (17%), feed refusal (14%), and fever were the most common symptoms in our study population, more than half of which were observed to have hypotension (98%), cold peripheries (86%), icterus (81%), pallor (74%), weak pulse (60%), low oxygen saturation (55%), edema (52%), and tachypnea (52%). Seizures (39%), lethargy (27%), reluctance to

TABLE 1 Characteristics of the study groups.

	Adrenaline (n = 21)	Noradrenaline (n = 21)	p-value[a]
Maternal characteristics			
Primigravida, n (%)	10 (47.6%)	12 (57.1%)	0.64
Anemia, n (%)	3 (14.3%)	3 (14.3%)	1.00
Pregnancy-induced hypertension, n (%)	2 (9.5%)	2 (9.5%)	1.00
Cesarian delivery, n (%)	17 (81.0%)	13 (61.9%)	0.31
Antenatal steroids, n (%)	16 (76.2%)	15 (71.4%)	1.00
Neonatal characteristics			
Male sex, n (%)	13 (61.9%)	17 (81.0%)	0.31
Gestational age (w), mean (SD)	36.9 (4.1)	36.1 (4.2)	0.21
Birth weight (kg), mean (SD)	1.9 (0.7)	1.8 (0.2)	0.64
APGAR at 5 min, mean (SD)	7.8 (1.8)	7.3 (1.8)	0.49
Clinical features			
Hypotension, n (%)	21 (100%)	20 (95.2%)	1.00
Cold extremities, n (%)	19 (90.5%)	17 (81.0%)	0.66
Icterus, n (%)	17 (81.0%)	17 (81.0%)	1.00
Pallor, n (%)	18 (85.7%)	13 (61.9%)	0.08
Weak or non-palpable pulse, n (%)	12 (57.1%)	13 (61.9%)	0.76
Low blood O_2 saturation, n (%)	13 (61.9%)	10 (47.6%)	0.53
Edema, n (%)	13 (61.9%)	9 (42.9%)	0.22
Tachypnea, n (%)	10 (47.6%)	11 (52.4%)	0.76
Seizures, n (%)	5 (23.8%)	3 (14.3%)	1.00
Lethargy, n (%)	4 (19.0%)	3 (14.3%)	1.00
Bradypnea, n (%)	4 (19.0%)	3 (14.3%)	1.00
Refusal to feed, n (%)	3 (14.3%)	3 (14.3%)	1.00
Moderate hypothermia, n (%)	4 (19.0%)	1 (4.8%)	0.34
Fever, n (%)	0 (0%)	1 (4.8%)	1.00
Resuscitation required, n (%)	5 (23.8%)	10 (47.6%)	0.22
Duration of shock in hours, median (IQR)	6 (2–8)	4 (2–8)	0.47

[a]for continuous variables, standard t test, and for categorical variables, chi square test or Fisher's exact test in case of any observed frequency ≤ 5.

TABLE 2A Echocardiographic findings of the study groups at baseline.

	Adrenaline (n = 21)	Noradrenaline (n = 21)	p-value
Left ventricle – mean (SD)			
Heart rate (per min)	153.3 (16.8)	148.6 (16.6)	0.41
Velocity time integral (m)	9.8 (3.9)	9.4 (2.6)	0.74
Aortic Outflow Cross Sectional area (AoCSA) (cm^2)	6.1 (1.3)	6.0 (1.2)	0.81
Output (ml/kg/min)	212.9 (96.8)	208.8 (83.5)	0.89
Fractional shortening (%)	34.1 (19)	29.0 (13.5)	0.46
Right ventricle – mean (SD)			
Heart rate (per min)	154.0 (17.0)	147.2 (16.5)	0.24
Velocity time integral (m)	10.6 (4.3)	9.9 (3.0)	0.60
Pulmonary Outflow Cross Sectional area (PoCSA) (cm^2)	6.5 (1.2)	6.3 (1.2)	0.63
Output (ml/kg/min)	268.3 (154.0)	237.0 (134.1)	0.52
Tricuspid annular plane systolic excursion (TAPSE) (mm)	7.5 (3.2)	9.0 (2.6)	0.18

TABLE 2B Echocardiographic findings of the study groups after 1 h.

	Adrenaline (n = 21)	Noradrenaline (n = 21)	p-value
Left ventricle – mean (SD)			
Heart rate (per min)	153.9 (13.3)	152.6 (22.3)	0.83
Velocity time integral (m)	10.0 (0.4)	10.0 (3.2)	0.98
Aortic Outflow Cross Sectional area (AoCSA) (cm^2)	5.9 (1.2)	6.3 (1.4)	0.44
Output (ml/kg/min)	246.0 (109.2)	292.2 (163.9)	0.33
Fractional shortening (%)	41.8 (21.6)	45.1 (21.1)	0.69
Right ventricle – mean (SD)			
Heart rate (per min)	154.0 (13.3)	154.1 (21.9)	0.99
Velocity time integral (m)	10.9 (2.8)	11.3 (3.5)	0.78
Pulmonary Outflow Cross Sectional area (PoCSA) (cm^2)	6.2 (1.2)	6.4 (1.4)	0.73
Output (ml/kg/min)	322.6 (158.0)	329.5 (145.3)	0.89
Tricuspid Annular Plane Systolic Excursion (TAPSE) (mm)	8.8 (3.2)	9.8 (2.5)	0.36

TABLE 3 Associations of study drugs with outcomes.

	Adrenaline (n = 21)	Noradrenaline (n = 21)	Odds Ratio (95% Confidence interval)	p-value[a]
Primary outcomes				
Resolution of shock within 1 h, n (%)	13 (61.9%)	16 (76.2%)	0.71 (0.14–3.64)	0.32
Death, n (%)	7 (33.3%)	6 (28.6%)	1.45 (0.39–5.50)	0.74
Secondary outcomes				
Other vasopressor required, n (%)	8 (38.1%)	5 (23.8%)	0.62 (0.17–2.25)	0.53
Dose escalation within 2 h required, n (%)	6 (28.6%)	9 (42.9%)	0.61 (0.17–2.25)	0.33
Intraventricular hemorrhage, n (%)	9 (42.9%)	7 (33.3%)	1.5 (0.43–5.25)	0.75
Nosocomial infection, n (%)	8 (38.1%)	4 (19.0%)	2.65 (0.64–10.61)	0.31
Tachycardia, n (%)	6 (28.6%)	4 (19.0%)		0.77
Acute kidney injury, n (%)	2 (9.5%)	3 (14.3%)	0.63 (0.09–4.23)	1.00
Necrotizing enterocolitis (stage II/III), n (%)	2 (9.5%)	1 (4.8%)	2.10 (0.17–25.17)	1.00
Cerebellar hemorrhage, n (%)	1 (4.8%)	1 (4.8%)	1.00 (0.06–17.12)	1.00
Periventricular leukomalacia, n	0	0		1.00
Hospital stay (days), median (IQR)	15 (6–33)	12 (5–19)		0.44
NICU stay (days), median (IQR)	10 (5–30)	6 (3–10)		0.04
Mechanical ventilation (days), mean (SD)	1.24 (0.54)	1.29 (0.46)		0.76

[a]For continuous variables, standard t test, and for categorical variables, chi square test or Fisher's exact test in case of any observed frequency ≤ 5.

feed (19%), and fever (6%) were the most common presenting symptoms of neonatal sepsis in one study from India (16). In our study, all cases with septic shock had hypotension and around three quarters of them had cold extremities and a weak pulse.

Tachycardia was the only adverse event observed, occurring in 19% and 29% of cases of the noradrenaline and adrenaline groups, respectively. In neonates with fluid-refractory septic shock treated with adrenaline, Ramaswamy et al. noted a 14% frequency of adverse events, with tachycardia and arterial gangrene occurring in 3% and 10% of cases, respectively (9). We did not observe arrhythmia or hypertension with noradrenaline unlike previous study (11), which were dose related. Although very large doses of noradrenaline were found safe while allowing for a 33% survival rate in adults (22), there is a need for further studies of dose optimization in neonates.

The noradrenaline and adrenaline groups had similar mortality rates (28.6% vs. 33.6%, p-value = 0.77) statistically. In the study cohort, the baseline characteristics, clinical and hemodynamic parameters were similar in neonates who survived and those who succumbed. As in previous studies from our unit, we have found pulmonary hypertension in cases of septic shock, we hypothesised that noradrenaline might be beneficial from that perspective where we had cases of late onset sepsis with pulmonary hypertension and high cardiac output (4). Hence, we wanted to study noradrenaline with effects of an vasopressor and a pulmonary vasodilator.

The mortality rates in sepsis in infancy have varied from 18% (10), 27% (16), 37% (23), 45% (11) to 58% (9), depending on the treatment drugs and the age group. These high mortality rates reinforce the need for early sepsis recognition with appropriate management and further research to identify the first line medication and optimal doses.

The study had few limitations. The study sample size could not be reached and it was a underpowered study. Also usage of non-invasive blood pressure recordings with reliability on reduction of blood pressure to less than 10th centile for definition of shock was used. The bolus fluid therapy at 10 ml/kg might be inadequate for defining fluid refractory septic shock.

Conclusion

In this single centre open labelled study in neonates with fluid-refractory septic shock, noradrenaline was comparable to adrenaline in resolution of shock at one hour of infusion and mortality during hospitalisation. Also, it had similar hemodynamic and adverse reaction profile. The study being underpowered, could not conclude non-inferiority of noradrenaline to adrenaline. Further studies with larger sample sizes to evaluate the efficacy and safety of these two drugs as a first-line agent in neonatal septic shock are required.

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 Bharati Vidyapeeth Medical College Institutional Ethics 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

RG: Data curation, Formal Analysis, Investigation, Project administration, Validation, Visualization, Writing – original draft. SP: Formal Analysis, Project administration, Validation, Visualization, Conceptualization, Methodology, Resources, Software, Supervision, Writing – review & editing. SS: Supervision, Validation, Visualization, Writing – review & editing. CC: Project administration, Writing – review & editing, Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Validation. NB: Writing – review & editing, Conceptualization, Funding acquisition, Resources, Supervision, Visualization. PS: Writing – review & editing, Data curation, Project administration. AK: Writing – review & editing, Project administration. NS: Conceptualization, Supervision, Validation, Writing – review & editing, Visualization. YS: Conceptualization, Supervision, Visualization, Writing – review & editing. PS: Conceptualization, Supervision, Writing – review & editing, Funding acquisition, Methodology, Resources.

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EDITED BY
Minesh Khashu,
University Hospitals Dorset NHS Foundation Trust, United Kingdom

REVIEWED BY
Daniel Vijlbrief,
University Medical Center Utrecht, Netherlands
Zoheir Sabeur,
Bournemouth University, United Kingdom

*CORRESPONDENCE
Brooke A. Krbec
✉ brooke.krbec@tuftsmedicine.org

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Emerging innovations in neonatal monitoring: a comprehensive review of progress and potential for non-contact technologies

Brooke A. Krbec[1]*, Xiang Zhang[2], Inbar Chityat[2], Alexandria Brady-Mine[2], Evan Linton[2], Daniel Copeland[2], Brian W. Anthony[2], Elazer R. Edelman[2] and Jonathan M. Davis[1,3]

[1]Division of Newborn Medicine, Tufts Medical Center, Boston, MA, United States, [2]Institute for Medical Engineering and Science, Department of Mechanical Engineering, Center for Clinical and Translational Research, Massachusetts Institute of Technology, Cambridge, MA, United States, [3]Tufts Clinical and Translational Science Institute, Tufts University School of Medicine, Boston, MA, United States

Continuous monitoring of high-risk neonates is essential for the timely management of medical conditions. However, the current reliance on wearable or contact sensor technologies for vital sign monitoring often leads to complications including discomfort, skin damage, and infections which can impede medical management, nursing care, and parental bonding. Moreover, the dependence on multiple devices is problematic since they are not interconnected or time-synchronized, use a variety of different wires and probes/sensors, and are designed based on adult specifications. Therefore, there is an urgent unmet need to enable development of wireless, non- or minimal-contact, and non-adhesive technologies capable of integrating multiple signals into a single platform, specifically designed for neonates. This paper summarizes the limitations of existing wearable devices for neonates, discusses advancements in non-contact sensor technologies, and proposes directions for future research and development.

KEYWORDS

neonatal monitoring, vital signs, non-contact technologies, sensors, innovation, artificial intelligence, radar, camera

Introduction

Historically, pediatric medical devices have been modified or directly adapted from adult versions, with a mere 10% of FDA approvals from 2008 to 2018 awarded for patients <18 years of age (1). This approach is especially problematic for neonatal patients, as prototypes designed for adults are ill-suited for neonates who are smaller, more fragile, and have vastly different physiologic parameters than adults. Unlike the stable and predictable physiology of adults, neonatal physiology represents the dynamic transition from intrauterine to extrauterine life, presenting a unique opportunity for the development of specialized monitoring devices. Current technologies have limitations, including risks of iatrogenic injury and barriers to effective care. Therefore, advancements in multi-modal, non-adhesive, and wireless sensors for neonates are urgently needed to improve patient care.

Current wearable technologies

Wearable sensor technologies play a crucial role in modern neonatal care, providing continuous monitoring of heart rate (HR), respiratory rate (RR), and oxygen saturation (SpO_2), along with the potential to measure additional physiological signals. Significant advancements have been made in wearable and wireless sensors for neonates and infants, offering a comprehensive range of monitoring capabilities. However, these devices still have significant limitations that can adversely affect neonatal outcomes. Typically designed for adults and then adapted for neonates, these sensors often result in poor fit, discomfort, and increased risk of injury. For example, the strong adhesive used on electrocardiogram (ECG) electrodes can damage the very thin epidermis of a preterm neonate upon removal causing significant injury, pain, and the potential for infection (2). Approximately 4% of neonates leave the NICU with cosmetically or functionally significant scars (3). Exposure to pain in the most immature neonates has been associated with suboptimal brain growth and poorer long-term neurodevelopmental outcome (4). The rigidity and bulkiness of these devices can also hinder nursing care and restrict parental interactions. Issues such as sensor displacement or calibration problems can also lead to delayed diagnoses (5).

Wire- tethered wearable devices can impede essential neonatal care and prevent parental contact and bonding (6). The physical barriers created by wired sensors complicate routine care such as feeding, diaper changes, and skin-to-skin contact (e.g., kangaroo care), a practice shown to improve neurodevelopment, weight gain, and parental confidence (7). Furthermore, the reliability of wearable sensors is often compromised by issues such as sensor displacement and calibration shifts, particularly in an active neonatal environment where the constant movement and handling of tiny patients can easily disrupt sensor placement and accuracy. Minor changes in sensor signals, typically dismissed as artifacts in adults, may be significant in neonates. Sensor displacement can lead to inaccurate monitoring, false alarms, and increased stress and costs for healthcare providers. Calibration drifts can cause erroneous readings and alarms, undermining the reliability of these devices for precise monitoring (5). A key example is the use of contact-based ECG, which serves as a fundamental diagnostic and measurement tool in the cardiovascular field (8). HR measurements developed in the 1960s remains the staple sensor technology used to this day. The ability to detect the heart's electric field is influenced by many factors including the skin, electrolytic paste, electrodes, and their mechanical contact (8). Additionally, capacitive sensing is highly susceptible to body motion, as poor sensor coupling can negatively affect ECG recordings (5).

ECG and SpO_2 correlate 94% of the time, but less so as HR increases (5, 9). Accurate recording of the electrical potential generated by the heart also requires proper electrode placement (operator dependent), which may interfere with the neonate's movements and interaction with parents and/or caretakers (10). Detaching the adhesive electrode not only carries the risk of iatrogenic skin injury, but also requires opening the isolette more frequently to adjust the sensors, thereby increasing the neonate's risk of heat loss and infection (11, 12). This has resulted in attempts to increase the distance between the ECG electrodes and the patient by using non-adhesive ECG electrodes placed a few millimeters from the infant, usually embedded in a mattress, fabric, or clothing (5). However, integration of such approaches into standard NICU clinical practice remains limited, necessitating further refinement to ensure compliance, accuracy, and reliability (13).

Additionally, while RR can be continuously assessed through technologies such as respiratory inductive plethysmography or nasal airflow, these methods are not generally tolerated by neonates. Alternative methods like piezoelectric sensors and electrical impedance pneumography (EIP) have been explored, but they are significantly affected by noise and motion artifacts (14). Currently, RR is monitored through chest impedance, which cannot detect obstructive apnea and often confuses cardiac signals with breathing during apneic episodes (15, 16). Moreover, while temperature is typically monitored using wired thermistors attached to the skin, these sensors often dislodge which can cause errors in temperature regulation (17). Finally, techniques for measuring SpO_2 such as doppler ultrasound and photoplethysmography (PPG) pose challenges such as motion artifacts, delayed HR display times, and the potential risk of burns specifically associated with PPG (18, 19).

Frequent issues with adhesive sensors often necessitate their removal and replacement multiple times during a patient's hospital stay (20). In low-resource hospitals, the lack of access to quality electrodes and the need to dispose of inaccurate ones further increases costs (10, 21). To address these challenges in monitoring vital signs in neonates, current research is focusing on non-contact approaches (22).

Remote sensing technologies

Non-contact devices offer the potential for continuous monitoring without the adverse effects associated with direct skin contact. The developmental processes for these technologies are complex, involving extensive research and testing to ensure accuracy, reliability, and safety. Over the last 15 years, developments in camera technology have coincided with improved availability and affordability, leading to increased interest in their use in healthcare settings (23). Remote sensing technologies that apply machine vision (visible/infrared), audio recording, and motion tracking (radar/accelerometer) for health monitoring have mainly focused on adults, while related studies in neonates have been constrained by the size of the population, safety, and the need for large equipment at the bedside. Sensors with potential applications for neonatal monitoring are classified into image-based visible, image-based infrared, and radar-based sensors (Table 1).

Investigations have focused on optical and camera-based systems using inexpensive webcams and smartphone/tablet cameras in the visible and near-infrared spectrum (400–1,000 nm) to detect HR, RR, and SpO_2 from subtle changes in skin color or volume, with

TABLE 1 Description of Non-contact technologies.

Technology	Vital signs	Description	Scenarios	Pros	Cons
Image-based Visible light	HR, HRV, RR, SpO2	Uses visible light to detect subtle changes in skin color or motion	Pilot studies included all patient positions in isolettes and open cribs, most have infants in supine position ± wrap/clothes, stable patients, very few with resp support, most have ROIs manually selected	High spatial resolution	Affected by ambient light, limited performance in low light
Image-based infrared	RR, Temperature, SpO2	Detects infrared emission/ absorption of the body to monitor blood flow, temperature, and RR	Supine and prone in isolettes and open cribs ± wrap/clothes, ROI selected	Works in low light, measures temperature distribution	Lower spatial resolution compared to visible light, prone to drift
Radar-based	HR, HRV, RR	Uses radar waves to detect minute movements caused by cardiac and respiratory activities	Supine, prone, and side-lying, some co-bedded with twin, isolettes and open cribs ± wrap/ clothing, acute patients, respiratory support	Not affected by lighting conditions, can work through clothing	Requires precise calibration and more complex algorithms

HR, heart rate; HRV, heart rate variability; RR, respiratory rate; ROI, region of interest.

the first report of camera-based non-contact technology for monitoring HR reported by Villarroel et al. in 2014 (14, 23). Technological advancements now incorporate advanced algorithms capable of filtering out noise from movement and ambient light, thereby improving accuracy, reliability, and the capacity to measure expansive fields of view. Video-based sensing is inexpensive and safe, yet certain modalities are susceptible to ambient light variations that influence signal quality and have difficulties identifying suitable periods and regions for analysis (14, 24). These regions of interest (ROI) are rectangular areas on the patient's skin such as the face, head, or neck which are used to estimate alterations in color and volume with each heartbeat by reflectance (14). Most studies have focused on information generated from the skin, with many monitoring periods lasting under 5 min (23). Thermal imaging utilizes infrared cameras to measure temperature variations around the nose and mouth, which correlates with RR (23). This method is particularly advantageous as it is less affected by the visual obstructions that can compromise other camera-based systems.

Radar technologies employ radio frequency signals to detect movements related to HR and RR (11, 25). Radar offers a promising non-contact method for continuous monitoring of neonates, capable of operating under various conditions without requiring direct line-of-sight or contact with the skin. Other advantages include the ability to penetrate various materials and minimal responses to changes in lighting or variations in skin complexion; such issues have affected RGB cameras and pulse oximeters (11). Radar can be packaged compactly, has low power consumption and high spatial resolution, and is affordable, easy to use, and resilient against multipath interference (26). Three main types of radar systems have been proposed for the recording of vital signs in neonates: continuous wave (CW), frequency modulated continuous wave (FMCW), and ultra-wideband (UWB) (22). CW radar is effective for tracking steady or slow-moving objects, making it suitable for monitoring stable vital signs. FMCW radar is excellent for precise measurements of chest displacement during breathing cycles, providing detailed data on RR and patterns of respiration (27). UWB radar provides high-resolution detection of finer movements due to its high spatial resolution, which is critical for monitoring the subtle physiological changes in neonates. UWB technology is accurate and can differentiate between voluntary movements and those attributed to breathing or cardiac activity (28).

Radar systems are highly sensitive to micro-movements, enabling the detection of minute motions of a neonate's chest or abdomen to provide reliable vital sign monitoring. Studies from Japan have demonstrated that radar can be used to measure RR, HR, inspiratory to expiratory ratio, and heart rate variability (HRV) with unique advanced signal processing methods (24). Radar technologies can also penetrate non-metallic materials such as clothing and blankets, allowing monitoring to occur without disturbances. Despite its appeal, radar is limited by motion and noise interference, commonly seen in neonates. Most of the reported research in clinical settings places the radar devices only a few cm from the infant's chest, typically attached to a tripod at the bedside or on top of the isolette (5).

Remote sensing technologies offer the potential for simultaneous data collection from multiple regions to allow for estimation of more than one vital sign by a single monitor (23). Highly developed remote sensing techniques can provide very-high-resolution (VHR) in both spatial and spectral domains. However, the complexity requires novel algorithms to process these images and extract spatial/structural features. A preferred approach is to explore effective spatial features and integrate them with spectral information to improve performance of image interpretation (29). Research is ongoing to enhance signal processing algorithms by filtering out irrelevant movements and improving the accuracy of vital sign detection. Research in neonates has been limited to short-term studies with tightly controlled conditions and healthy subjects (14). For widespread adoption, these technologies must be robustly validated against clinical standards and seamlessly integrated into existing clinical workflows without disrupting care.

Artificial intelligence (AI)

The wealth of existing and capturable data in healthcare is well suited for implementation of AI methods to synthesize, analyze, and extract valuable underlying health metrics. Deep learning is

a form of AI that is based on artificial neural networks that consolidate prior data to quantify and predict new data. It has the capability of extracting features like subtle changes in movement or skin color that correlate with vital signs and various pathologies.

Convolutional Neural Networks (CNNs) are essential for advancing non-contact monitoring technologies focused on processing image data. CNNs leverage a hierarchical learning framework (or layers of processing units) to automatically learn, generalize, and extract high-level features from raw image data, making them adept at capturing robust spatial features crucial for precise monitoring (29). Traditional frameworks are often challenged to recognize important spatial patterns in images. CNNs overcome this by learning representations layer by layer, which allows for the extraction of deep features necessary for tasks like image classification, segmentation, and action recognition (29–31). CNNs can combine convolutional and fully connected layers in innovative ways, enabling large-scale image classification and higher levels of performance (31–33). In neonatal care, these networks are able to detect whether a patient is within the camera's field of view and undergoing a clinical intervention (31). Although CNNs appear to be able to adapt to the unique challenges posed in monitoring neonates, these systems face challenges performing in low light conditions and exhibit false readings due to abrupt changes in light or motion. Additionally, false negatives can be caused by the movement of individuals in the field of view that are not the subject (31).

Recent research has focused on the need for training these networks across different camera setups and positions, with ongoing attempts to address the unique challenges of neonatal whole-body proportions in human parsing (or body part segmentation) (34, 35). Neural networks can be trained to recognize patterns associated with physiological processes and detect anomalies, where early detection may lead to more timely interventions (36). Additionally, deep learning can help mitigate errors in sensor data by providing more accurate estimations of vital signs through sophisticated algorithms that learn over time (37).

Deep learning models do face their own challenges and limitations. Effective training of neural networks requires large datasets, which depend heavily on the diversity, inclusiveness, and representation of the population. Additionally, the need for manual annotations by clinicians and the "black box" nature of deep learning models pose significant challenges. In clinical settings, it is crucial for clinicians to understand the basis of the model's predictions (36). Assimilation into clinical workflow involves not only integrating the technology itself, but also ensuring its accessibility and usefulness for clinicians (36).

Heart rate (HR) and HR variability (HRV)

HR monitoring has evolved significantly with the advancement of imaging technologies and signal processing algorithms. The primary methodology involves PPG which analyzes subtle color and volume changes on the skin surface, detectable through multichannel cameras operating within the visible spectrum (23). These invisible skin color variations can be used to measure cardiac activity and determine HR by magnifying the hemoglobin absorption in illuminated tissue in systole vs. diastole (2). HR estimation in infant populations has been achieved by using this methodology to monitor skin color fluctuations synchronized with the cardiac cycle, utilizing the green channel of an RGB camera and then applying a Fast Fourier Transform (FFT) analysis (38). Furthermore, in 2014 Blanik et al. integrated passive infrared thermography imaging for surface temperature measurement with active optical measurement of skin perfusion for HR, highlighting potential synergies between different sensing modalities (31, 39) (Table 2A).

Another approach involves quantifying chest movements induced by heart muscle contractions, at amplitudes ranging from 0.2 to 0.5 mm, which is sufficient to extract HR measurements (2). Scalise et al. have utilized webcam-based tracking of skin surface movement to estimate HR by using a large light band source to illuminate the subject's skin surface uniformly while the camera was placed 20 cm from the infant's face (40). While successful in propagating a hemodynamic waveform, this method was impractical in hospital settings due to the constant need for illumination.

Radar technologies have also been refined to detect small chest wall movements in adults, but this is challenging in neonates due to their smaller heart size, faster HR, and lower cardiac output (26). Additional steps are required, including the use of band-pass filters to eliminate respiratory effort frequencies and the development or adaptation of data processing algorithms specifically tailored for neonates (26).

Different neonatal pathological states can be associated with changes in HRV and may represent a possible prognostic marker that can be extracted from various monitoring technologies (26). HRV describes the oscillation of the R-R interval between consecutive beat-to-beat, as well as the oscillations between consecutive instantaneous heart rates. For example, HRV has shown promise as a potential predictor of sepsis and its associated mortality (41).

Respiratory rate (RR)

Monitoring of RR in neonates has been approached through various non-contact techniques (Table 2A,B). RR can be measured by analyzing the movement of the torso due to inhalation and exhalation from a variety of cameras including near-infrared (NIR), mid-wave infrared (MWIR), long-wave infrared (LWIR), and visible light spectrum (23). Detecting subtle changes in diaphragm movement forms the foundation of motion-based sensing techniques (2, 16). However, breathing movements are complex, involving different patterns of motion in the chest wall surface, abdomen, shoulders, and back. This makes it difficult to identify time-domain models that fully characterize respiratory signals and separate them from movements unrelated to breathing (16, 42).

Another challenge of camera-based technologies is that neonatal movements can have low spatial amplitudes which are

TABLE 2 Description of studies.

2A – Image-based technologies								
Study & year	Msmt parameter	Population [gestational age (weeks) & weight (gr)]	Study environment	Sample size and recording duration	Sensor type	Sensor placement	Major limitations	Results
(48), 2011	RR	29; NA	NICU; single center	$n = 7$; 2 min phases	IRT camera, manual ROI selection	IR camera 70–80 cm from patients in in isolette/radiant warmer, nostrils in direct optical contact and visible	Temp changes from interventions, IRTR higher in isolette, small Vt in neonates, no true comparison sensor	Clear changes in temp over the nasal region, IRTR msmt not correlated with a classical reference sensor but quality approaches ECG
(40), 2012	HR	33 + 2.5; 2,204 + 800	NICU; single center	$n = 7$; 4 min	Digital web camera, manually selected ROIs	Large band light source used to illuminate subject skin surface placed 1 m away	Environmental conditions always stable, light intensity always controlled	BA[a]: HR −0.90 ± −9.79 to 7.99 bpm; PC[b] 0.94 for HR
(38), 2023	HR	25–42; 470–3,810	NICU; muti-center	$n = 19$; 1–5 min	Digital camera aimed at uncovered body parts, manually selected ROIs, PPG	Camera on tripod 1 m distance from open/closed isolette	Infants never touched or repositioned during study, signals disrupted by motion/fluctuating light, KC, HFOV, dark skin, phototherapy	BA: HR 0.3 ± 1.96 bpm
(14), 2014	HR, RR, SpO2	28; 1,200	NICU; single center	$n = 2$; 4 days	Digital camera, PPG, ROI extraction	Camera over drilled 3 cm diameter hole in isolette mounted on an arm apparatus	No monitoring during active CC and KC, issues with major lighting changes, movement artifact, lack of visible skin area	HR within ±4 bpm, RR ± 10 rpm, SpO2 values within 81.2%
(39), 2014	Temp	NA	NICU; single center	$n = 7$; 10 min	Camera hybrid: simultaneous PPG and space-resolved IRTI	IRT outside of isolette window covered in polyethylene cling film (higher IR transparency)	Feasibility study, nasal region has to be visible for RR, hybrid camera needed for other VS	Temp changes (±0.3°C) during RR clearly visible in IRT recordings of nasal region; Skin temp of non-covered regions could be monitored
(49), 2014	Temp, motion tracking	NA	NICU; single center	$n = 10$; 20 min	IR camera with automatic non-uniformity calibration, ROI selection, VERSENS approach for movement tracking	Images taken with neonate on radiant warmer and while inside a convective isolette through IR transparent window	Lack of matching matrix for ROI resulted in failed tracking, only proof of concept	VERSENS scoring rate success 74–89.02%
(56), 2014	HR, RR	24–39; 1,670–3,000	NICU; single center	$n = 7$; NA	RGB and IR-thermal cameras, manual ROI selection	Cameras next to open crib on tripod with adjustable arm	Feasibility study, no correction algorithms applied, no real-time recordings/ retrospective analysis	Preliminary results: Good agreement for HR against ECG, RR had 20% difference
(44), 2016	RR	32–34 (33.3); 1,400–1,800	NICU; single center	$n = 3$; 30 s × 5	RGB-D sensor: IR and RGB cameras, microphones, Asus Xtion Pro live depth sensor to provide depth	Camera on an arm 70 cm over the open crib perpendicular to supine neonate, focus on thoraco-abdominal area	Proof of concept study, removed cardiac activity from analysis	PC: RR 0.95; heat map of movements successfully created

(*Continued*)

TABLE 2 Continued

2A – Image-based technologies								
Study & year	Msmt parameter	Population [gestational age (weeks) & weight (gr)]	Study environment	Sample size and recording duration	Sensor type	Sensor placement	Major limitations	Results
					map reconstruction			
(45), 2017	RR	<37;	NICU; single center	$n = 30$; 4 days	Digital camera avg of blue color channel, skin segmentation to select ROI	Camera over drilled 3 cm diameter hole in isolette mounted on an arm apparatus	False positives from artefacts in IPG signals, phototherapy saturated images in blue region of spectrum decreasing SNR	74% of false positive apneic events identified, 70% of true events identified, reduced false alarm rate by 77.3%
(50), 2017	RR	33 ± 0.5; NA	NICU; single center	$n = 4$; 1.5 min	Thermal sequences, manual ROI	Long wave IR camera placed on side with isolette door open, neonates in both supine and prone positions	Small dataset, no true comparison sensor, short monitoring period	Avg relative error of RR was 3.42%
(10), 2018	HR, RR	25–40; >500	NICU; muti-center	$n = 9$; several recordings (time not discussed), avg every sec into 6 s stacks	Digital camera, PPG, image separated into three RGB channels	Camera outside of isolette focused on abdominal area 50 cm away	Large movements affected accuracy, issues with poor lighting/darkness, structure/algorithm not tested in real time	BA: HR −1.5 ± −9.7 to 5.8 bpm, RR −0.6 ± −9.2 to 10.3 bpm; PC: HR 0.94, RR 0.86
(2), 2019	HR, RR	≤37; 800–3,020	NICU; single center	$n = 10$; at least 10 s, otherwise NA	Digital Camera, PPG, Motion Magnification, ROI selection	Camera & tripod 1–2 m away	Small dataset, limited acute patients, inaccuracies in the comparison device	REG: HR mean difference 4–5 bpm ($p <$ 0.005), RR 0.8 rpm ($p <$ 0.586); BA: HR −8.3 ± 17.4 bpm, RR −22± rpm
(5), 2019	HR, RR	28.7–32.7 (30.7); 830–1,746 (1,240)	NICU; single center	$n = 30$; 4 days	Video camera and AI, PPG resp signals, skin filters, CNN and ROI selection	Regular ambient light, daytime, camera over drilled hole in isolette	Mostly light-skinned infants, not evaluated in complete darkness, highest accuracy during stable/quiet periods, bystander interference	HR MAE 2.3 bpm for over 82% of time, RR MAE 3.5 rpm for over 82% of the time
(31), 2019	Patient & clinical intervention detection	28.9 ± 3.2; 1,172.2 ± 284.3	NICU; single center	$n = 15$; 4 days	Digital camera, charged-coupled device image sensors, two CNN models working in sequence	Camera on arm over the top of the isolette, perpendicular to patient in any position	Difficulty with low-light images, small skin regions not identified, false positives with movement interference, false negatives with outside intervention	Patient detection accuracy 98.8%; Mean IOU score skin segmentation 88.6%; Clinical intervention accuracy 94.5%
(46), 2019	RR	27.0–33.6; 755–2,410	NICU; single center	$n = 5$;	Fixed-position high-definition camera, optical and deep flow methods	Camera focused on infant's entire body, inside isolette at feet pointing to head	Automated processing underestimated RR, accuracy of resp signal affected by image resolution and sensor noise	BA: RR Optical flow −4.8 ± −13 to 3, Deep flow −2.7 ± −11 to 5.2; PC: RR Optical flow 0.64, Deep flow 0.63
(51), 2019	RR	27.3–40; 950–3,100	NICU; single center	$n = 8$; 5 min × 2	IRT camera, automatic ROI using "black-box"	Thermal camera mounted on tripod, recordings from each side of	Camera not able to record through plexiglass, movement	BA: RR 0.24 ± −8.1 to 8.6 rpm; Mean RMSE: RR 4.15 ± 1.44 rpm;

(*Continued*)

TABLE 2 Continued

2A – Image-based technologies								
Study & year	Msmt parameter	Population [gestational age (weeks) & weight (gr)]	Study environment	Sample size and recording duration	Sensor type	Sensor placement	Major limitations	Results
					or grid-based approach	open crib or through door of isolette, all sleeping positions	interference, delays in data stream led to high errors, IRT is expensive	MAE RR 3.36 ± 1.25 rpm; Mean CCC 0.79 ($P < 0.05$)
(15), 2021	RR	26.3–40.2; NA	Medium care unit; single center	$n = 17$; 43 h	RGB video, thermal	Thermal on 15 infants, RGB on 2 infants; some videos collected from the side and others from top	Segments containing events/interventions were excluded, difficultly separating movements from resp signals, reduced sensitivity of motion classification in validation set	BA: −0.42 training set and 0.18 rpm testing set; RR testing set MAE 3.31 rpm, validation set MAE 5.36 rpm
(47), 2021	Resp flow pixel, RR, apnea	26.3–40.1; NA	Medium care unit; single center	$n = 15$; 1.86–33.84 min	FLIR Lepton (LWIR) camera, automatic resp flow pixel detector	Three cameras around open crib, most in supine position	Absence of body motion, manual annotation of motion, removal of periodic breathing, subpar visibility	MAE: Correct pixel detection 84.28%; MAE: RR 2.20/1.85/2.11 rpm; accuracy of apnea detection 94.35%
(52), 2021	HR, RR	6 PT, 1 FT; NA	NICU; single center	$n = 7$; 10 min	DSLR camera, automatic ROI selection with CNN, signal decomposition for noise	Camera on tripod 1–2 m distance	Small dataset, unstable control data, preprocessing challenges	BA: HR 0.44 ± −3.9 to 4.8, RR 0.7 ± −4.5 to 5.9; PC: HR 0.9864, RR 0.9453
(57), 2022	Temp	29–40; 1,500–3,010	NICU; single center	$n = 19$; 10 min	IRT camera, RGB camera, monochrome camera with a green interference filter, deep learning, key point detector for ROIs	3 cameras in a triangular formation attached to a 3 mm thin aluminum base plate with 4 OLED panels for illumination on a stand	No ambient light, covered body parts may have caused negative values (unphysiological temp), non-central patient position caused distortion	BA: Temp −0.16 ± −1.49 to 1.16 (°C); MAE 0.55 ± 0.67 °C
(16), 2023	RR	NA	Newborn unit; single center	$n = 10$	Integrated visible and thermal images (RGB-T), automatic ROI selection, face detection	Cameras on tripod positioned parallel, 1 m from subjects	Cameras expensive, motion interference, HR and RR overlap, subpar visibility	BA: RR 0.51 ± −3.6 to 4.6 rpm; MAE: RR 1.5 rpm; CCC: RR 0.9244
(58), 2023	Face detection	≥34; 1,745–3,650	Dept of Pediatrics; single center	$n = 5$; >3,000 images for each subject	Fusion of thermal, RGB, and 3D ToF cameras, two CNNs for face detection	Thermal camera, RGB with fisheye lens, 3D ToF camera at a short distance from the subject	Small dataset, unable to accurately detect nose	AP: RetinaNet 0.9949, YOLOv3 0.9949
2B – Radar-based technologies								
Study & year	Msmt parameter	Population [gestational age (weeks) & weight (gr)]	Study environment	Sample size and recording duration	Sensor type	Sensor placement	Major limitations	Results
(25), 2019	RR	37.0–41.0 (38.0); 2,790–3,960 (3,100)	NICU; single center	$n = 42$; 5 100–160 min	7.29 GHz freq, 1.5 GHz bandwidth IR-UWB radar, movement characterization	Encased radar on a tripod placed 35 cm orthogonal to chest, open crib ± covering	No touching/repositioning during study, any movement interfered with	BA: RR 1.17 ± −10.4 to 12.7 rpm, $P <$ 0.001 in one sample t-test

(*Continued*)

TABLE 2 Continued

2B – Radar-based technologies								
Study & year	Msmt parameter	Population [gestational age (weeks) & weight (gr)]	Study environment	Sample size and recording duration	Sensor type	Sensor placement	Major limitations	Results
							signals, bulky equipment	
(26), 2020	HR, RR	32.4–39.4 (38.6); 1,690–3,370 (3,085)	NICU; single center	$n = 34$; 20.3 min avg ± 44 min	IR-UWB radar, movement characterization	Encased radar on a tripod placed 35 cm orthogonal to chest, open crib with blanket cover	Supine position, fixed angle, device far from chest, difficult to differentiate HR vs. RR when overlapping, motion interference	BA:RR vs. IPG 0.17 ± −7.0 to 7.3 rpm ($p < 0.001$), HR vs. ECG −0.23 ± −5.3 to 4.8 bpm; CCC: RR vs. IPG 0.95, HR vs. ECG 0.97
(53), 2021	Sleep/wake states using RR	31.2–40.6; 2,130–3,200	NICU; single center	$n = 4$; 13.0 (7.0–20.5) h	8.748 GHz Freq, -10dB bandwidth 1.5 GHz IR-UWB radar, video camera, actigraphy, 2-channel EEG (aEEG), manual behavioral data characterization	Encased radar on arm 40 cm perpendicular angle, camcorder on arm attached to open crib, actigraphy sensor on R ankle, aEEG on scalp, neonate clothed	Minimal light/noise needed, motion interference, difficulty with differentiating certain states (i.e. quiet awake, REM)	Wake state agreement 0.81, sleep state agreement 0.72; mean Cohen's kappa 0.49 (0.41–0.59, overall accuracy 0.75 (0.70–0.81)
(24), 2022	RR, HRV (IBI)	NA (6 days–3 mo); 2,735–5,730	NICU; single center	$n = 3$; 140–300 s	24 GHz radar, LoPASS filter to separate HR and RR, template matching, adaptive peak detection algorithm	Radar installed in mattress of open crib, 5 cm below subject	Motion interference, HR and RR overlap,	BA: RR Conv −13 ms ± 91 ms, RR Prop 0 ± 21 ms; CCC: RR Conv 0.31 ms, RR Prop 0.93, IBI Conv 0.31 ± 91 ms, IBI Prop 0.93 ± 21
(42), 2022	RR	26–36; 850–2430	NICU; single center	$n = 12$; 25 min × 3 days	24 GHz ISM band CW radar, random body movement mitigation	Radar outside of neonatal cot with plastic cover on a low-vibration tripod, 45–50 cm away	External interference, poor raw data quality, high ADC saturation, device recording issues, inaccuracies with reference device	BA: RR 0.262 ± −11.48 to 12.01 rpm, RR in prone position −0.296 ± -8.24 to 7.64 rpm; Avg RMSE RR 4.3 rpm, prone RR 4 rpm
(54), 2023	Sleep stage classification using RR	25.1–31.2 (29.6); 1253 ± 386	NICU; single center	$n = 10$; 1 min for each sleep stage (total for all subjects 123 ± 39 min)	6.0–8.5 and 7.25–10.2 GHz UWB radar, machine learning classifiers (SVM, KNN, AdaBoost, NB, Dtree, LDA)	Camera and UWB radar attached to isolette canopy	Movement interference, algorithm only usable in specific GA range, small chest wall movement difficult to measure	Moderate-to-high accuracy, AS and QS detected with a Cohen's kappa of 0.54 and balanced accuracy of 81% with AdaBoost

NA, not available; IRT, Infrared Thermography; ROI, Region Of Interest; RGB, Red-Green-Blue; IRTR, Infrared Thermal Respiration; LWIR, Long-Wave Infrared; DSLR, Digital Single-Lens Reflex. ToF, Time of Flight; ISM, Industrial Scientific Medical; IR-UWB, Impulse-Radio Ultra-Wideband; CW, Continuous Wave; Vt, Tidal Volume; BA, Bland-Altman; PC, Pearson's Coefficient; CCC, Concordance; REG, Regression; MAE, Mean Absolute Error; IOU, Intersection Over Union; RMSE, Root Mean Square Error; AP, Average Precision; IBI, Inter-Beat Interval; PPG, Photoplethysmography; IPG, Impedance Pneumography; SNR, Signal to Noise Ratio; CC, Clinical Care; KC, Kangaroo Care; HFOV, High Frequency Oscillatory Ventilation; VERSENS, Virtual InfraRed SENsor; AI, Artificial Intelligence; CNN, Convolutional Neural Network; Conv, Conventional; Prop, Proposed; SVM, Support Vector Machine; KNN, K Nearest Neighboring; AdaBoost, Adaptive Boosting; NB, Naïve Bayes; Dtree, Decision Tree; LDA, Linear Discriminant Analysis; AS, Active Sleep; QS, Quiet Sleep.

[a]BA = bias ± limits of agreement (LOA).

[b]PC = r^2.

difficult to recognize. Thus, magnification and modification of data processing algorithms are necessary for small chest sizes and rapid, variable RRs (2, 43). Several studies have demonstrated the utility of RGB cameras to track chest wall movement with 81.2% accuracy (14, 44, 45) (Table 2A). However, limitations include potential interference from fluctuations in artificial lighting, motion artifacts caused by activity, alterations in results due to covering or swaddling, and the considerable size and bulkiness of the devices which can occupy significant space.

Radar can also detect small periodic displacements of the chest wall in the respiratory cycle with promising results (42). CW radar leverages the doppler effect to detect changes in frequency caused by rhythmic chest movements during breathing. Beyond estimating RR, it may also provide insights into respiratory irregularities such as dyspnea, apnea, neonatal seizures, and sleep-wake cycles due to its sensitivity to minute movements. Recent work has demonstrated that UWB radar offers high-resolution detection capable of identifying breathing patterns in both supine and prone positions as well as through clothing, using certain mitigation techniques (5, 25, 42) (Table 2B). This is particularly advantageous in the NICU, where neonates often require monitoring under less-than-ideal conditions. The implementation of impulse-radio ultra-wideband (IR-UWB) radar systems has demonstrated the ability to continuously track RRs with minimal error, even amidst frequent clinical interventions and the neonate's natural movements (43). While the system was accurate, the prototype was cumbersome and 36% of data were excluded due to artifacts from clinical care interventions (42, 43). The effectiveness of a simpler, 24 GHz CW radar system was reported by Beltrao et al. in 2022. The device was positioned outside the isolette and was able to effectively penetrate the plastic cover. Detection of breathing patterns was possible when prone and side-lying with displacement as low as 0.5 mm. The overall error magnitude between radar and reference measurements was consistently below 5–7 bpm (42).

The fusion of deep learning and thermal imaging techniques could revolutionize non-contact respiratory monitoring in neonates, offering robust alternatives to traditional methods. Deep learning frameworks have been adeptly applied to analyze skin area properties such as center of mass, area, and perimeter, effectively deriving respiratory signals from these parameters (31). A breathing-induced motion matrix was developed by filming the neonate's entire body with a high-definition camera positioned at the foot of the bed (46). These deep learning flow methods can reduce errors significantly when compared to optical flow methods, especially when breathing rates are less than 50 bpm (46). Moreover, thermal imaging techniques leverage the small temperature variations around the nose during the inspiratory and expiratory phases to estimate respiratory flow and motion (5). This method detects convective heat transfer changes at the infra-nasal region and allows the differentiation between different types of apnea and monitoring under various clinical conditions (47). In 2011 Abbas et al. conducted a study in preterm neonates, with one receiving continuous positive airway pressure (CPAP), and estimated RR using temperature difference with clear changes visible in inspiration and expiration (48). This methodology has been expanded to track several geometric regions of interest, aiding in calibration against motion (49). Furthermore, the utilization of high-definition infrared cameras and partial-filter based tracking enables the isolation of respiratory movements without requiring direct nostril detection (50, 51). Other investigators have further explored the capabilities of long-wave infrared cameras to detect respiratory flow and motion, capturing extensive data over 42 h from 15 neonates (47). They used a combination of thermal and non-thermal camera solutions and/or facial/body/landmark detection. Despite their potential, these techniques face several challenges such as requiring careful calibration against temperature-controlled reference sources or industrial black body systems to ensure accuracy (5). Additionally, temperature readings are easily influenced by the opening of isolette doors or changes in ambient conditions. If the infant is in a suboptimal position the only source of respiratory flow may be the detection of thermal variations on the bedding (47) (Table 2A).

Combined HR and RR

With more technological advancements, the simultaneous monitoring of multiple vital signs has become possible using non-contact methods (Table 2A,B). One such approach utilizes the Laser Doppler Vibrometer (LDV) which measures vibrations caused by chest wall movements related to the cardiac cycle and lung inflation. This technique uses a laser beam that is directed onto a surface area of interest, measuring the vibration's amplitude and frequency due to surface motion. The approach has shown promise in extracting RR from abdominal movements. Another innovative method involves dual-camera systems that measure HR and RR by focusing on the abdominal area, capturing diaphragm and thoracic movements which are unique in neonates compared to adults (10). Significant strides have also been made using video cameras combined with CNNs (Table 2A). In a pivotal study conducted by Villarroel et al., 90 video sessions were recorded in a clinical setting featuring 30 preterm neonates (5). CNNs successfully identified suitable intervals for vital sign estimation while discarding irrelevant data from other individuals. Numerous limitations were observed including: (1) a significant amount of excluded data (loss of focus), (2) phototherapy and/or clinical interventions interfering with measurements, and (3) a bias towards individuals with lighter skin tones (Table 2A). It was noted that CNNs could be expanded and integrated into the hospital system to recognize multiple individuals and support the simultaneous estimation of vital signs from multiple patients.

Non-contact computer vision systems have integrated PPG and motion magnification to enhance the detection of HR and RR, showing that while movements can introduce noise, video magnification can help improve accuracy. However, one study found that magnification created more noise and data analyzed with and without magnification was still inaccurate (2). Yet with new ROI selection methods, accuracy can be significantly improved (52). Similarly, IR-UWB has been investigated for its feasibility to measure both HR and RR simultaneously in neonates (Table 2B). Lee et al. (26) used this technology to conduct 51 measurements in 34

neonates, demonstrating excellent concordance for both HR and RR despite large discrepancies between the ground-truth devices with some exaggerated movements of the subject. This study was the first to evaluate radar in ventilated neonates and it had extremely narrow mean bias and limits of agreement, indicating superb accuracy. However, this study continued to have limitations of a large, cumbersome device and exclusion of critically ill neonates including those with congenital anomalies significant respiratory disease (26).

SpO_2 monitoring

Peripheral arterial oxygen saturation (SpO_2) monitoring in neonates has also seen innovative approaches using non-contact methods (Table 2A). Studies have predominantly used a combination of visible and NIR spectrum measurements through video cameras to derive SpO_2 values, providing a non-invasive alternative to traditional sensors (23). Only a few studies have been conducted in the neonatal population where optical methods based on dynamic light scattering, video, or PPG are being attempted without direct skin contact (14, 42). One study demonstrated that video-derived SpO_2 signals, obtained by estimating outputs of red and blue video channels, could track decreases in saturation during apneic episodes over an extended period of time (14).

Temperature measurement

Temperature monitoring through non-contact methods has primarily involved thermal imaging cameras that measure the long-infrared radiation emitted by the body (14). This technique allows for the estimation of temperature distribution across the neonate's body, with studies employing passive infrared thermography to monitor temperature changes within the isolette (39) (Table 2A). The setup often requires calibration to adjust for environmental factors such as humidity and radiant heat highlighting the complexity of accurately capturing temperature variations in a controlled clinical setting (39).

Miscellaneous studies

Other studies have explored radar capabilities for assessing various physiological parameters and conditions (Table 2B). Lee et al. integrated movements and breathing signals with a sleep/wake decision algorithm, successfully distinguishing sleep/wake states but not sleep stages (53). Arasteh et al. identified movement as key for sleep stage classification using UWB radar (54). Na et al. demonstrated IR-UWB radar's potential in early screening for developmental delays, detecting movement asymmetries indicative of conditions like cerebral palsy (55). Understanding neonatal sleep-wake cycles and movement patterns could be used to time care, mitigate disruptions, and identify unique biomarkers for disease states.

Sensor fusion

Several combination techniques have been employed to enable simultaneous vital sign monitoring (Table 2A,B). In a proof-of-concept study, Klaessens et al. mounted an RGB camera with an infrared thermal camera over an open isolette to monitor neonates (56). An open-source code was utilized to amplify color variation and visualize the pulse. RR was estimated using software that tracks temperature changes around the nostrils. Despite limitations related to the need for open incubators or specialized IR transmitting windows, the agreement was good when compared to the ECG (56).

Other studies have performed sensor fusion of visible and thermal cameras with deep learning algorithms to perform automatic extraction of local surface temperatures or automated ROI selection (Table 2A). Lyra et al. used image restriction and thermographic recordings to extract body surface temperature in various regions to determine central-peripheral temperature differences (57). Mauyra et al. combined visible images to find facial landmarks with thermal images to extract respiratory signals (16). This integration of image sequences outperformed other state-of-the-art methods. In other studies combining time-of-flight (TOF) cameras and radar demonstrated accurate RR measurements, but had sensitivity to noise and was prone to overestimating low RRs (22). In 2023, the same author proposed an innovative technique fusing thermal, RGB, and 3D TOF cameras for enhanced neonatal facial detection and reliable HR, RR, and body temperature measurements using dual neural networks (58).

These multifaceted approaches demonstrate that combining different modalities can minimize any individual weakness and enhance non-contact monitoring. However, challenges such as motion artifacts, subject positioning, and calibration requirements has limited the widespread adoption of these approaches. Ongoing research shows promise in addressing these challenges. A recent review by Zhou et al. outlines many approaches to using radar and camera data fusion ranging from traditional to deep learning algorithms (59). Similarly, a recent review of human monitoring systems emphasizes the ability of data fusion to improve machine learning models (60). There are a wide range of unique approaches to data fusion. Advancements in the field continue to unlock new opportunities for increased data fidelity and accuracy in data collection and monitoring. Through the integration of multiple data streams, we believe that data integration is a viable approach to the improvement of neonatal care.

Lack of integration into clinical medicine

Despite significant interest and general success of many of these studies, non-contact technologies have yet to be adopted into clinical practice. The reasons behind this are complex, with necessary validation processes unable to overcome multiple barriers. The core issue is that wired technologies are dominant in medicine and represent the standard of care. Healthcare systems are driven to sustain inexpensive and readily available equipment. While wired technologies are perceived as cost-effective, they

can lead to substantial expenses and risks, especially in low-resource settings where equipment is frequently reused. This practice increases the risk of infection and breakdown of adhesive interfaces, which results in inaccurate monitoring (2). Consequently, there is a push to achieve results with inexpensive, lower performance cameras (23). Although it is improbable that novel technologies will ever cost less than current wired ones, cost mitigation will be evident through enhanced accuracy and precision in monitoring, reduced adverse effects from adhesives, and less disruptions in care stemming from false alarms or the need for manual adjustments.

Since many weaknesses have been found with each of these novel approaches, there is insufficient evidence that these technologies can or should replace existing standards of care. Many studies have never made it past the proof-of concept stage and even adult studies have used small, heterogeneous sample sizes (23). Most studies in neonates have primarily involved small numbers of participants and excluded critically ill neonates, attempting to capture "normal" neonatal vital sign profiles. In the studies that did include these populations, modifications to the isolette environment were often made such as cutting holes or removing doors. Although these studies tested the internal environment to demonstrate there was no change in temperature or humidity, it is likely that this caused disruptions, considering neonates are very susceptible to even small alterations in the environment and are extremely sensitive to heat loss (61). Furthermore, some studies omitted the use of a clinically validated reference device, limiting the clinical applicability and performance of image-based methods which often yielded inferior results in actual clinical populations (23).

Compared to adults, there are technical challenges when monitoring neonates due to their naturally higher signal frequency for both HR and RR and lower amplitude in signals of interest (14, 48). The signal is frequently lost and some technologies rely on controlled lighting with minimal noise and movements (23). High melanin concentrations absorbs more energy, with less energy reflected from the skin surface leading to low signal-to-noise ratio for optical based technologies (5). This is not an issue unique to neonatal populations, as it has been experienced by other devices such as wired pulse oximeters. Neonates with HR in lower ranges (bradycardia) may have signals that overlap with the respiratory cycle further limiting accuracy.

In all studies, the major barrier to accuracy, precision, and success of non-invasive devices is motion artifact and body position. Motion artifact will never be completely eliminated in non-invasive devices, even though current gold standard monitoring modalities are affected by it. Many studies have restricted neonates to the supine position, excluding care times, interventions, and parent bonding from the analysis. This approach poses challenges in establishing real-world device success, considering most infants in the NICU are prone-positioned and frequently engage in skin-to-skin care (62, 63).

Overall, neonates are a challenging population to study, and their outcomes are difficult to measure. The need for informed consent can create an additional barrier for devices that have never been used in hospital settings. Neonatal research requires competent staff and miniaturized equipment, both of which come with high costs. Moreover, the NICU environment is often not conducive to bulky prototypes and limitations in space at the bedside is a serious obstacle (2). Device research is inherently a high risk, high reward endeavor, characterized by numerous barriers. To advance clinical care while ensuring equitable care, it is imperative that these barriers be addressed.

Future innovation

As neonatal care continues to evolve, the focus on non-contact technologies will likely intensify due to their potential to revolutionize monitoring practices for both inpatient and outpatient settings. These technologies have strengths and limitations that have hindered their translation to real-world clinical care. The next essential steps must involve sensor fusion, as the integration of signals from various novel sensors is anticipated to enhance the accuracy and efficiency of monitoring. Centralized integration of data from each source is crucial to seamlessly incorporate new sensor hardware and software additions. By integrating multiple data streams, there is potential for improvement in existing non-contact sensing methods through sensor fusion, AI, and sophisticated algorithms. A collaborative development of cutting-edge systems will require involvement of many key stakeholders including innovators, scientists, physicians, clinical staff, nurses, and families. This is necessary to ensure adaptability to the unique needs of neonatal care. Moreover, refining technology to address the specific challenges of neonatal physiology can translate to benefits across the lifespan.

Technologies need to be miniaturized and able to overcome motion artifacts. Integrating movement detection with vital sign monitoring can reduce false alarms and prevent invalid measurements by automating the cancellation of motion-contaminated data (26). Furthermore, innovators should focus on designing technologies that can minimize the impact of factors such as skin color, phototherapy, and ambient lighting conditions. These technologies should be capable of penetrating clothing or blankets while still capturing high-resolution signals (25, 26). Device placement must also be flexible, accommodating a range of distances from the subject to ensure that the care of the patient is uninterrupted (25). The position of the subject should not be restricted, as prone positioning has shown better results for defined respiratory motion (42).

Another promising area is the management of apnea, with some studies suggesting that this condition can be effectively predicted, monitored, and classified with non-contact technologies (47). Monitoring neonates with congenital heart disease and early signs of heart failure is also an area of interest. Remote sensing technologies have the potential to track physical activity, detect distress, identify adverse clinical events, or develop predictive models for various outcomes of interest which should drive innovators to further explore these technologies.

The fusion of non-contact and wearable sensors into multi-modal platforms can enhance reliability and provide a more comprehensive set of physiological data (64). This innovative trajectory will enhance the effectiveness of neonatal care and

transform the broader pediatric care landscape by integrating advanced, efficient, and patient-centered technologies.

Author contributions

BK: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Methodology, Resources, Supervision. XZ: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. IC: Writing – review & editing. AB: Writing – review & editing. EL: Writing – review & editing. DC: Writing – review & editing. BA: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. EE: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. JD: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, 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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EDITED BY
Karel Allegaert,
KU Leuven, Belgium

REVIEWED BY
Folashade Omokhodion,
University of Ibadan, Nigeria
Barbara Królak-Olejnik,
Wroclaw Medical University, Poland
Nora Saraco,
Garrahan Hospital, Argentina
Melinda Matyas,
University of Medicine and Pharmacy Iuliu Hatieganu, Romania

*CORRESPONDENCE
Aneta Soltirovska-Šalamon
✉ aneta.soltirovska@kclj.si

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Postnatal levels of glycated albumin and glycated hemoglobin A1c in mothers of large-for-gestational-age newborns

Mojca Železnik[1], Alenka Trampuš Bakija[2], Darja Paro-Panjan[1,3] and Aneta Soltirovska-Šalamon[1,3]*

[1]Department of Neonatology, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Clinical Institute of Special Laboratory Diagnostics, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]Department of Pediatrics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Background: Gestational diabetes mellitus (GDM) is an important cause of macrosomia. The value of glycated albumin (GlyA) has been demonstrated to be a useful marker of glycemic control in pregnancy and a predictor of adverse perinatal outcomes. The aim of this study was to investigate the relationship between the postnatal levels of GlyA and glycated hemoglobin A1c (HbA1c) regarding the prenatal diagnosis of GDM in mothers of large-for-gestational-age (LGA) newborns.
Methods: The study included mothers and their LGA newborns born between July 2017 and September 2019. The mothers were grouped according to the prenatal diagnosis of GDM, and measurements of GlyA and HbA1c levels in their serum were performed on the first day after delivery of a LGA newborn.
Results: A total of 61 LGA newborns and their mothers were enrolled in the study. The median GlyA level was higher, at 16.4% (81.0 μmol/L), whereas the HbA1c level was lower in the group without a prenatal diagnosis of GDM; the differences between groups regarding the GlyA and HbA1c levels were not significant ($p > 0.05$). The postnatal level of maternal GlyA was positively correlated with birth weight ($\beta = 0.022$, $p = 0.007$), but no correlation with the presence of other adverse perinatal outcomes was found.
Conclusion: Mothers of LGA newborns who were not diagnosed with GDM during pregnancy had higher median levels of GlyA and lower HbA1c levels than mothers with prenatal diagnosis of GDM. Values of GlyA in mothers were positively correlated with the birth weight of their newborns but no correlation with other adverse perinatal outcomes was found. Our results indicate the potential value of GlyA for screening of GDM in the last trimester of pregnancy.

KEYWORDS

gestational diabetes mellitus, glycated albumin, glycated hemoglobin, large for gestational age, newborn

Abbreviations
LGA, large-for-gestational-age; GlyA, glycated albumin; HbA1c, glycated hemoglobin; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

1 Introduction

Anthropometric measurements at birth are an important parameter for predicting the health status of newborns, and are closely related to postnatal morbidity and complications during childbirth, as well as to long-term consequences (1–3). Large-for-gestational-age (LGA) newborns are defined as having birth weight and/or birth length above the 90th percentile for gestational age and sex (4). They are at increased risk for adverse perinatal outcomes, including hypoglycemia, polycythemia, hyperbilirubinemia, respiratory distress and the need for mechanical ventilation, traumatic delivery, congenital malformations, and neonatal mortality (5, 6). In addition, studies have shown that being born LGA is associated with an increased risk of morbidity later in life, which underscores the significance of anthropometric measures as alternative clinical parameters for *in utero* programming (7–10). Etiologically, apart from maternal obesity, gestational diabetes mellitus (GDM) is the most important cause of macrosomia (11). It is defined as impaired glucose tolerance of variable degrees, with onset or being first recognized during pregnancy (12). In developing countries, the prevalence of GDM has increased significantly in recent years and is expected to increase further in the future (12, 13). Studies have shown that 15%–45% of newborns born to mothers with GDM can be macrosomic, a rate that is three times higher compared to those born to normoglycemic mothers (14). According to the World Health Organization and International Association of Diabetes and Pregnancy Study Groups, GDM should be diagnosed when the fasting plasma glucose level is ≥5.1 mmol/L in the first trimester of pregnancy, or when it is diagnosed between the 24th and 28th week of pregnancy following a 75-g oral glucose load if the 1-h plasma glucose level is ≥10.0 mmol/L or the 2-h plasma glucose level is ≥8.5 mmol/L (15, 16).

Glycated hemoglobin A1c (HbA1c) is one of the most commonly used biomarkers for evaluating long-term glycemic control, and reflects changes in plasma glucose values over the preceding 2–3 months (13, 17, 18). One of its limitations is the influence of external factors such as erythrocyte lifespan and other factors known to affect red blood cell survival, such as hyperglycemia (19, 20). Indices revealed that HbA1c levels are insufficient for monitoring glycemic control in pregnancy, and it has been reported that glycated albumin (GlyA) is a useful marker of glycemic control (21–23). Its value as an alternative glycemic marker during pregnancy has been examined in several studies (6, 18, 24–26). GlyA is not affected by hemoglobin metabolism or iron-deficiency anemia, and it reflects the status of blood glucose more rapidly than HbA1c; this makes it more sensitive indicator of intermediate-term glycemia, capturing fluctuations in blood glucose over the past 2–3 weeks (17, 20, 24, 27).

Hiramatsu et al. defined the reference intervals of GlyA in healthy pregnant Japanese women for each trimester (18). Furthermore, the cut-off values of GlyA levels in women with GDM for predicting adverse perinatal outcomes in their newborns were reported to be 13.6%–14.7% (28). Japanese authors also found a positive correlation between GlyA levels in diabetic mothers and the number of adverse perinatal outcomes in their newborns (28). Conversely, Dong et al. found a decreasing trend of GlyA levels throughout the pregnancy, and concluded that the GlyA level has limited importance for the diagnosis of GDM in the late second trimester and in predicting birth outcomes (29).

To further elucidate the relationship between GlyA levels, prenatal diagnosis of GDM, and the most common complication of GDM (delivery of an LGA newborn), we aimed to explore postnatal values of GlyA in the serum of mothers who delivered LGA newborns. Assuming that the level of GlyA reflects intermediate-term glycemia in pregnancy, we hypothesized that (i) mothers of LGA newborns who were not diagnosed with GDM during pregnancy using standard procedures had higher values of GlyA and (ii) the value of maternal GlyA after delivery is positively correlated with birth weight and other adverse perinatal outcomes.

2 Materials and methods

2.1 Study population

A cross-sectional study was conducted at the Department of Neonatology, University Children's Hospital, University Medical Centre Ljubljana (approximately 500 referrals per year). The study included mothers and their newborns born between July 2017 and September 2019. Newborns born at ≥36 weeks of gestation as LGA [birth weight, length, or head circumference above the 90th percentile for gestational age and sex according to the growth curve for Slovenian singletons in 2000 (30)] and their mothers were studied. Birth weight was recorded to the nearest 10 g. Exclusion criteria were: gestational age <36 weeks, perinatal hypoxia (Apgar score <5 at 10 min), the need for mechanical ventilation, sepsis (clinical characteristics and positive blood culture) and thyroid dysfunction. Prenatal, perinatal and postnatal clinical and laboratory data were collected.

Adverse perinatal outcomes in newborns were defined as follows: Hypoglycemia was defined as a blood glucose threshold of <2.61 mmol/L (47 mg/dl) (31). A venous hematocrit level >65% or a hemoglobin concentration >220 g/L (≥22 g/dl) was defined as polycythemia (32). Structural or functional heart abnormalities were defined when detected by electrocardiogram or echocardiogram due to clinical suspicion (33). Hyperbilirubinemia was defined if the newborn was clinically jaundiced and required phototherapy (34). Newborns showing one or more clinical signs of respiratory distress for >2 h and requiring oxygen support were considered to have respiratory distress. Neurological examination was performed and graded using the Amiel–Tison Neurologic Evaluation; mildly abnormal neurological signs were defined as abnormalities in muscle tone and excitability (35). Birth trauma was defined as skin damage, extracranial injury of the head, facial or brachial nerve palsy, a fractured bone, or adrenal hemorrhage. The structural abnormality of a single organ, with the exception of heart abnormalities, was defined as anomalies. The number of adverse

perinatal outcomes was defined as the sum of all previously mentioned categories.

Mothers of LGA newborns were grouped according to the diagnosis of GDM during pregnancy. The diagnosis followed the Slovenian national guidelines: fasting plasma glucose level ≥5.1 mmol/L in the first trimester of pregnancy, or 1-h plasma glucose level ≥10.0 mmol/L, or the 2-h plasma glucose ≥8.5 mmol/L after a 75-g oral glucose tolerance test (OGTT) performed between the 24th and 28th week of pregnancy (36). Mothers diagnosed with GDM self-monitored their blood glucose levels, preprandial and postprandial, to achieve target fasting blood glucose levels between 3.5 and 5.3 mmol/L and 90 min after meals ≤6.6 mmol/L. HbA1c values were monitored every 4–8 weeks. Mothers with prepartum body mass index >25 kg/m^2, multiple pregnancies, conception after infertility treatment, serum albumin below 25 g/L, abnormal renal function, dyslipidemia, hyperthyroidism, liver cirrhosis, and hematological disorders were excluded from the study. The following data were collected: maternal age, type of diabetes and treatment during pregnancy, blood pressure during pregnancy, and smoking status.

Measurement of GlyA and HbA1c levels in the mother's serum was performed within the first day after delivery of the LGA newborn.

2.2 Laboratory methods

The GlyA measurements were performed at the Clinical Institute of Special Laboratory Diagnostics, University Children's Hospital, University Medical Centre Ljubljana. GlyA results were calculated as the ratio of GlyA to albumin. Albumin was assayed on an automated biochemical analyzer (Olympus AU400; Beckman Coulter, CA, USA) using the bromocresol green method (albumin cat. no. OSR 6102, Beckman Coulter). GlyA was measured using a manual competitive inhibition enzyme-linked immunosorbent assay (Human GlyA ELISA kit; cat. no. EKC33864, Biomatik, Canada). Briefly, samples/standards and horseradish peroxidase conjugated antibodies specific for GlyA were added to the microtiter plate wells. After the incubation, wells were washed and tetramethylbenzidine substrate solution was added. The color development is stopped and the intensity of color is measured at 450 nm using microplate reader.

2.3 Statistical analysis

The sample size was calculated to have sufficient statistical power to detect the diagnostic effect of GlyA determination in mothers who delivered LGA newborns. Data analyses were performed using IBM SPSS Statistics (version 22; IBM Corp., Armonk, NY, USA). Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) were calculated as appropriate. For normally distributed variables, the independent samples *t*-test was used to compare means. A nonparametric Wilcoxon signed-rank test was used to test the difference in the mean rank between the two groups. For the correlation between two nominal variables, the Pearson chi-square test was used, corrected for a 2 × 2 table. Multiple linear regression analysis was used to examine the relationship between GlyA levels and explanatory variables. Statistical significance was set at $p < 0.05$.

2.4 Statement of ethics

Research complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Declaration of Helsinki and has been approved by the National Medical Ethics Committee (approval no. 0120-582/2017/5). Written informed consent was obtained from all the individuals included in this study.

3 Results

3.1 Clinical characteristics of LGA newborns

Our study population consisted of 61 LGA newborns, with 38 (62%) boys. Their gestational age was 39 ± 1 weeks, and the mean birth weight was 4,268 ± 347.1 g (range 3,650–5,420 g). Adverse perinatal outcomes were found in 31 (51%) newborns. Twelve (20%) had abnormal neurological signs (three presenting abnormalities in muscle tone and others increased excitability), and 12 (20%) structural or functional heart abnormalities: seven (58%) ventricular hypertrophy and others structural or functional heart abnormalities—patent foramen ovale, pulmonary artery stenosis, atrioventricular block and atrial, perimembranous ventricular, and muscular ventricular septal defects. Five newborns had anomalies: two cleft palate or lip, one anomalies of the ears, and two hydronephrosis. In four newborns respiratory distress was present, the etiology being transient tachypnea of the newborn in three cases, and meconium aspiration syndrome in one. The demographic and clinical characteristic of the group are presented in Table 1.

Twenty-four LGA newborns were born to mothers diagnosed with GDM. They more frequently had abnormal heart ultrasound findings, mostly ventricular hypertrophy; otherwise, they did not differ from the group of newborns born to mothers without GDM (Table 1).

3.2 Clinical characteristics of mothers of LGA newborns

GDM was diagnosed prenatally in 24 of 61 mothers. All the women included took the recommended medication during pregnancy, for example, folic acid, iron, or vitamins; and some used progesterone in early pregnancy, none of the participants used drugs or alcohol, except for one woman who smoked during pregnancy. The median HbA1c level was lower in women without GDM (Table 2). The majority (20; 83%) of women with GDM followed a diet to regulate glucose levels, and the remaining four received insulin therapy. In two pregnancies with diagnosis of GDM, antenatal polyhydramnios were observed; one of them was treated with insulin.

TABLE 1 Demographic and clinical characteristics of newborns in correlation with maternal diagnosis of gestational diabetes mellitus.

Characteristics of newborns	Mothers with GDM (n = 24)	Mothers without GDM (n = 37)	Total (n = 61)	p-value
Sex, male, n (%)	12 (50)	26 (70)	38 (62)	0.185
Birth weight (grams), mean (SD)	4,275 (455)	4,220 (261)	4,268 (347)	0.907
Birth length (centimeters), mean (SD)	54.5 (1.9)	54.3 (2.0)	54.4 (1.9)	0.635
Head circumference (centimeters), median (SD)	36 (1.1)	36 (1.1)	36 (1.1)	0.856
Gestational age (week), median (SD)	40 (1.4)	40 (1.3)	40 (1.4)	0.866
Mother's age (year), mean (SD)	31.9 (5.0)	32.2 (5.5)	32.0 (5.3)	0.821
Adverse perinatal outcome, n (%)	13 (54)	18 (49)	31 (51)	0.874
Hypoglycemia, n (%)	3 (12.5)	2 (5.4)	5 (8.2)	0.331
Polycythemia, n (%)	3 (12.5)	1 (2.7)	4 (6.6)	0.134
Hyperbilirubinemia, n (%)	4 (16.7)	7 (18.9)	11 (18.0)	0.822
Respiratory distress, n (%)	1 (4.2)	3 (8.1)	4 (6.6)	0.532
Structural or functional heart abnormality, n (%)	8 (33.3)	4 (10.8)	12 (19.7)	0.031*
Mildly abnormal neurological signs, n (%)	6 (25.0)	6 (16.2)	12 (19.7)	0.403
Birth trauma, n (%)	3 (12.5)	3 (8.3)	6 (10.0)	0.601
Anomalies, n (%)	3 (12.5)	2 (5.4)	5 (8.2)	0.331

GDM, gestational diabetes mellitus; SD, standard deviation.
*$p < 0.05$.

TABLE 2 Glycated hemoglobin A1c and glycated albumin levels in mothers of large-for-gestational-age newborns in correlation with gestational diabetes mellitus.

	Mothers with GDM (n = 24)	Mothers without GDM (n = 37)	Total (n = 61)	p-value
HbA1c (%), median (SD)	5.45 (0.51)	5.15 (0.48)	5.20 (0.50)	0.102
GlyA (%), median (SD)	16.1 (4.68)	16.9 (4.65)	16.4 (4.6)	0.516
Minimum–maximum	9.7–25.8	10.7–32.2		
GlyA (µmol/L), median (SD)	79.5 (22.8)	82.0 (22.1)	81.0 (22.2)	0.842
Minimum–maximum	55.0–130.0	54.0–150.0		

GDM, gestational diabetes mellitus; GlyA, glycated albumin; HbA1c, glycated hemoglobin A1c; SD, standard deviation.

3.3 GlyA in mothers of LGA newborns regarding the presence of GDM

The median value of GlyA was 16.4% (range 9.7%–32.2%) or 81.0 µmol/L (range 54.0–150 µmol/L). Although the median value of GlyA was higher in the group without a history of GDM, no significant difference between the groups was detected ($p > 0.05$) (Figure 1 and Table 2).

3.4 Maternal glycated albumin in predicting birth weight and other adverse perinatal outcomes

A multiple linear regression model was applied to determine the correlation between maternal GlyA levels, birth weight, and the number of adverse perinatal outcomes. We found that maternal GlyA levels were positively correlated with birth weight ($\beta = 0.023$, $p = 0.007$). If the number of adverse perinatal outcomes is constant, an increase in birth weight by an average of 1 g indicated an increase in the GlyA level at 0.023 µmol/L (Figure 2A). No correlations between the GlyA level and the number of adverse perinatal outcomes ($\beta = 0.392$, $p = 0.855$) were found (Figure 2B).

4 Discussion

To the best of our knowledge, this study is the first to determine postnatal GlyA levels in mothers after delivery of LGA newborns. We found that mothers of LGA newborns who were not diagnosed with GDM during pregnancy had higher median levels of GlyA and lower HbA1c levels than mothers with prenatal diagnosis of GDM, but these differences were not statistically significant. Values of GlyA in mothers were positively correlated with the birth weight of their newborns but no correlation with other adverse perinatal outcomes was found.

GlyA could potentially provide insight into glycemic control in the last trimester of pregnancy and thus influence the management of pregnant women. Several studies have shown that both HbA1c and GlyA can be used for screening GDM, including a recent meta-analysis revealing a significant correlation between elevated levels of GlyA and HbA1c and an increased risk of GDM (37). HbA1c levels are affected by iron deficiency anemia, whereas GlyA levels are not affected by erythrocyte survival, and may reflect blood glucose levels in past 2–3 weeks. GlyA correlates more strongly with fasting and postprandial blood glucose levels and glucose fluctuations and may be a more sensitive indicator of GDM (13, 19, 27, 38). Many authors show that episodic hyperglycemia, which is not reflected in HbA1c, is more likely to

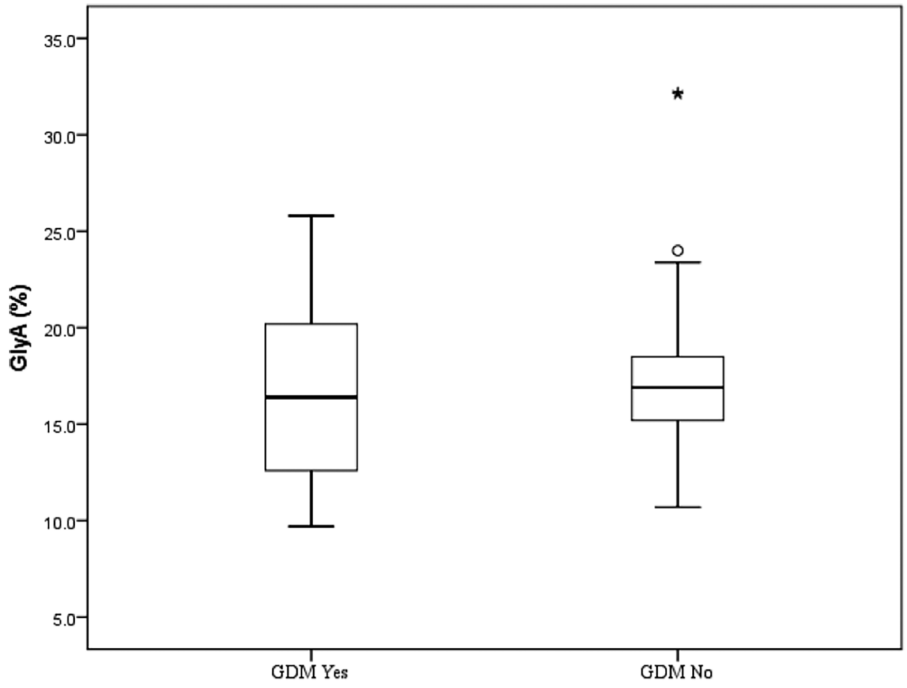

FIGURE 1
Glycated albumin (%) in mothers of large-for-gestational-age newborn in correlation with gestational diabetes mellitus. Each box represents the 25th to 75th percentiles. Lines inside the boxes ° represent the median. Lines outside the boxes represent the 10th and 90th percentiles. * Represents extreme value, represents potential outlier. GDM No, prenatal diagnosis of GDM not present; GDM Yes, prenatal diagnosis of GDM present; GlyA, glycated albumin.

contribute to fetal growth acceleration than basal levels of blood glucose (38–41). Furthermore, GlyA is relatively easy to measure and appears to be a useful indicator of GDM (18, 28). It reflects intermediate-term glycemia, and changes rapidly and markedly, which could more accurately reflect glycemic status (18, 25, 28). In contrast, a study in pregnant women with Type 1 diabetes showed that HbA1c has better predictive power for obstetric and neonatal outcomes than alternative laboratory markers, including GlyA (42).

The reference interval of GlyA in non-pregnant Americans was reported to be 11.9%–15.8% (43), which is comparable to that in the Chinese population (27). Studies demonstrated that the level

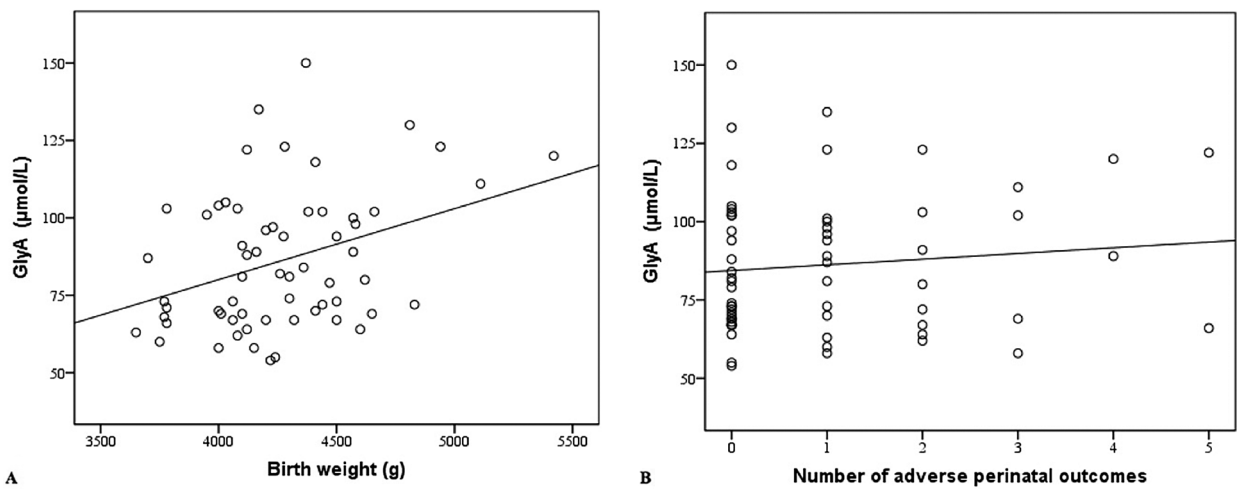

FIGURE 2
(A) Maternal glycated albumin in correlation with birth weight. (B) Maternal glycated albumin in correlation with number of adverse perinatal outcomes. GlyA, glycated albumin.

of GlyA decreased as pregnancy progressed (18, 44). A Japanese study showed that the reference range of GlyA in healthy Japanese pregnant women was between 11.5% and 15.7% (18). The value of GlyA in detecting adverse perinatal outcomes has also been investigated in several studies. Li et al. performed a study in Chinese women with GDM, and suggested that the risk of macrosomia increased significantly when the GlyA level was ≥13.0% and ≥12.0% at 24–28 and 26–38 weeks of gestation, respectively. They also found that the GlyA level decreased gradually in both normal and GDM pregnancies (25). In the study by Dong et al. the authors found no significant difference in GlyA levels between pregnant women with and without GDM, as well as the limited significance of GlyA in predicting LGA and other adverse perinatal outcomes (29). Similarly, Chinese authors found no significant difference in GlyA values between pregnant women with and without GDM, but they demonstrated that the frequency of LGA and caesarean section deliveries was significantly higher when GlyA levels exceeded 15.69% in the third trimester of pregnancy (26). Sugawara et al. reported that maternal GlyA levels were significantly higher in a group of LGA newborns, and considered that the cut-off values for GlyA during late pregnancy to predict complications ranged from 13.6% to 14.7% (28). Although we studied the levels of GlyA after delivery, our results could be compared with the results of the study in Portuguese pregnant women with GDM, in which the researchers showed that GlyA levels measured within 4 weeks before delivery was better in predicting adverse perinatal outcomes, particularly birth weight and LGA newborns, than HbA1c (45). Recently, Omokhodion and coauthors reported a good correlation between postnatal GlyA values in obese women and their newborns (46).

In our study, the median GlyA value in mothers of both groups of LGA newborns was higher than that in previously published studies of pregnant women with or without GDM (18, 25, 26, 45). We believe that this could be because we exclusively studied LGA newborns, and hypothesize that their accelerated growth could be caused by hyperglycemia during pregnancy. Although we did not find a significant difference in the level of GlyA between the two groups, the median value of GlyA was higher in the group without GDM. Considering this, and the fact that the HbA1c levels—as a blood glucose marker for the previous 2–3 months—were lower in women without prenatal diagnosis of GDM than in women with GDM, we may further hypothesize that the etiology of accelerated growth in our study was unrecognized and untreated GDM that developed after previous screening, in the third trimester of pregnancy. Moreover, our results show that the GlyA level is positively correlated with birth weight, indicating the importance of GlyA in predicting birth weight and adverse perinatal outcomes. Our hypothesis is also supported by the results of the study by Huidobro et al. in which the authors demonstrated that 35% of women with GDM developed GDM in the third trimester of pregnancy (47), as well as another prospective study in which the authors showed that out of 334 pregnant women, 13.5% had abnormal OGTT results in the third trimester after a negative test for GDM in the first and second trimesters (48). Recently, Guleroglu and coauthors demonstrated that GlyA or fetal pancreas size could be used for the early prediction of GDM (49). Additionally, some studies also suggest that women with a negative OGTT result in the second trimester may have glucose intolerance due to weight gain in late pregnancy (50). Several studies have also shown that the excessive fetal growth of LGA newborns begins in the second half of pregnancy and continues as pregnancy progresses (39, 40, 51), and that interventions initiated in the third trimester may reduce fetal growth (52).

A key strength of our study lies in examining GlyA levels in mothers of LGA newborns, thereby demonstrating valuable insight into GlyA as a potential biomarker for glycemic control in GDM. Despite this strength, our study has several limitations. First, GlyA levels were determined only once after delivery. We know from previous studies that GlyA levels decrease as pregnancy progresses, so we can assume that levels were higher during pregnancy. Second, we studied levels of GlyA and HbA1c only in a group of LGA newborns and did not compare them with values in the control group of appropriate for gestational age newborns according to the diagnosis of GDM in their mothers. Additionally, metabolic factors, such as weight gain, dietary patterns and maternal blood sugar values during pregnancy were not available for analysis. And, most importantly, the study was conducted at a single center and the sample was too small to detect significant differences between groups and to generalize our findings. We believe that our results should be validated in a large multicenter study to substantiate the present observations and to determine the utility and validity of GlyA as an alternative indicator of glycemic control in GDM and its diagnostic significance in predicting LGA newborns and their adverse perinatal outcomes. Finally, the reference intervals of GlyA at different gestational ages, in different ethnic communities and assay types, as well as cut-off values of GlyA, need further investigation.

In conclusion, we demonstrated that mothers of LGA newborns who were not diagnosed with GDM during pregnancy had higher median levels of GlyA and lower HbA1c levels than mothers with prenatal diagnosis of GDM, but these differences were not statistically significant. Values of GlyA in mothers were positively correlated with the birth weight of their newborns but no correlation with other adverse perinatal outcomes was found. Although additional larger studies are needed, our results indicate the potential value of GlyA for screening of GDM in the last trimester of pregnancy, especially as a biomarker associated with LGA newborns.

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 National Medical Ethics Committee Slovenia. 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

MŽ: Writing – original draft, Writing – review & editing, Conceptualization, Investigation, Methodology, Visualization. AT: Investigation, Methodology, Writing – original draft, Writing – review & editing. DP-P: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. AS-Š: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – original draft, 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

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Haramaya University, in collaboration with reviewer TA

*CORRESPONDENCE
Fentahun Meseret
✉ mesie1055@gmail.com

†PRESENT ADDRESS
Assefa Desalew,
Department of Obstetrics and Gynecology, Leiden University Medical Center, Leiden University, Leiden, Netherlands

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Treatment outcomes and its associated factors among neonates admitted with sepsis in Hiwot Fana Comprehensive Specialized University Hospital, Harar, Ethiopia

Betelhem Gezahegn[1], Ahmed Abdella[2], Fentahun Meseret[3]*, Ahmed Mohammed[2], Mulualem Keneni[3], Tesfaye Asfaw[3], Diribsa Tizazu[3] and Assefa Desalew[3†]

[1]Department of Pediatrics and Child Health, Sabian General Hospital, Dire Dawa, Ethiopia, [2]Department of Pediatrics and Child Health, School of Medicine, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia, [3]Department of Pediatrics and Child Health Nursing, School of Nursing, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

Background: Sepsis in the neonatal period is a major health challenge in neonatal medicine because of its potential for rapid progression to multi-organ dysfunction, leading to higher morbidity and mortality. Although efforts have been made to advance the outcomes of neonates admitted to hospitals, there is a paucity of data regarding neonatal sepsis treatment outcomes in the study setting. Hence, the study aimed to assess outcomes and prognostic factors of sepsis among neonatal patients admitted to the neonatal intensive care unit in Hiwot Fana Comprehensive Specialized University Hospital in Ethiopia.

Methods: A facility-based cross-sectional study was conducted among 311 neonates with sepsis admitted from 1 January 2021 to 30 December 2023. Neonates were selected using systematic random sampling. Relevant data were extracted from medical records using a checklist. The data were entered into EpiData version 4.6 and analyzed using STATA version 17. Bivariable and multivariable logistic regression analyses were performed to identify factors associated with the outcome variable.

Results: Eighty-four of 311 patients (27.8%) (95% CI: 22.7%–32.9%) died, while 218 (72.2%) were discharged after improvement. In the multivariable logistic regression analysis, low white blood cell (WBC) count [adjusted odds ratio (AOR) = 4.24, 95% CI: 1.5–12.5], desaturation (aOR = 3.00, 95% CI: 1.6–5.5), pre-term birth (aOR = 2.14, 95% CI: 1.1–4.0), lack of maternal antenatal care (ANC) follow-up (aOR = 2.4, 95% CI: 1.2–4.7), and chorioamnionitis (aOR = 2.8, 95% CI: 1.2–6.5) were significantly associated with neonatal sepsis mortality.

Conclusion: Approximately one-quarter of patients with neonatal sepsis died. The significant prognostic factors for sepsis were found to be low WBC count, desaturation, lack of ANC visits, and chorioamnionitis. Implementing targeted therapeutic interventions and addressing these prognostic factors could improve treatment outcomes.

KEYWORDS

neonatal sepsis, treatment outcomes, Hiwot Fana Comprehensive Specialized University Hospital, Harar, Ethiopia

Background

Neonatal sepsis is a serious infection in newborns within their first month of life, which can cause their bodies to become inflamed and weaken multiple organs (1). This can lead to septic shock, which can be life-threatening (2). Due to their immature immune systems, newborns are susceptible to infections due to exposure to bacteria during childbirth and early life (1). Neonatal sepsis is a serious condition in neonatal medicine that needs to be treated promptly (1, 2).

Neonatal sepsis is a major contributor to the global burden of neonatal mortality, with the WHO estimating that it causes about one-quarter of all neonatal deaths worldwide. Each year, it is responsible for 2.4 million newborn deaths (3, 4). The incidence of neonatal sepsis is increasing by 12.79% per year making it the third leading cause of neonatal deaths (4–6).

A systematic review conducted in 14 middle-income countries found that the incidence of neonatal sepsis was 2, 824 cases per 100,000 live births, with 17.6% of these cases resulting in death (7). Additionally, in middle- and low-income countries, neonatal mortality due to sepsis was 0.83 deaths per 1,000 live births, with the highest rates observed in South Asia and sub-Saharan African countries (8, 9). In SSA, severe forms of bacterial infections remain a leading cause of more than 1 million and 250,000 neonatal morbidity and mortality annually, respectively (10). Of these, sepsis accounts for 6.8% of neonatal deaths (11). The estimated economic burden due to these problems ranges from $10 to $469 billion (12). Neonatal mortality makes for approximately 40% of under-five deaths in Ethiopia; of these, neonatal sepsis accounts for approximately 30%–35% of neonatal deaths (13, 14).

The clinical features of neonatal sepsis can be vague and difficult to detect, making early diagnosis difficult (15). However, common signs and symptoms include drowsiness, poor feeding, temperature instability, respiratory distress, systemic inflammation, and increased heart and breathing rates (16).

The diagnosis of neonatal sepsis requires the use of comprehensive diagnostic tools, including clinical presentation, culture, complete blood cell count, and other predisposing factors (17). Other procedures such as molecular approaches, spectrometry, biomarker studies, and hematological analysis can also be used for diagnosis (16, 18). Blood cultures are considered the gold standard for diagnosis, with several adjunct tests used for clinical support (14).

The management of neonatal sepsis requires careful adherence to the latest neonatal intensive care unit (NICU) guidelines and a multidisciplinary approach (19, 20). Antimicrobial therapy targeting common pathogens associated with early- and late-onset sepsis (LOS) is typically recommended, with drug selection and duration based on culture results, clinical status, and response to treatment. For early-onset sepsis (EOS), ampicillin and gentamycin are generally administered for 7 days, while for LOSLOS, ampicillin and gentamycin are still recommended with triple antibiotics used in certain cases where the patient is critically ill (19–23).

Although the abovementioned guidelines provide a framework for management, various factors such as maternal demographics, socioeconomic issues, newborn-associated conditions, healthcare system, and institutional and professional-related factors can significantly influence the treatment outcome of neonatal sepsis (6). Antimicrobial resistance is another factor that can affect the prognosis, highlighting the importance of considering factors such as antepartum cephalosporin use and prolonged use of parenteral nutrition when selecting antibiotics (24).

Despite advancements in healthcare, neonatal sepsis remains the leading cause of morbidity and mortality among newborns worldwide, particularly in resource-limited settings. The successful management of neonatal sepsis depends on timely recognition, appropriate antimicrobial therapy, and supportive care (25). However, even with prompt intervention, the outcomes of neonatal sepsis treatment can vary widely, ranging from complete recovery to severe complications and death (26). This study focused on neonatal sepsis, as it is the most commonly identified and preventable cause of neonatal deaths in low- and middle-income countries (LMICs), contributing significantly to neonatal mortality rates (8–14). This study was intended to evaluate the progress made in accordance with the latest NICU guidelines, to support the achievement of sustainable development goals (19). So far many efforts have been made to enhance the positive outcomes of neonates admitted to hospitals in the country; however, they do not show satisfactory progress with a paucity of data specific to neonatal sepsis treatment outcomes in the study setting. Hence, this study aimed to assess the outcomes and prognostic factors of neonatal sepsis in patients admitted to the neonatal intensive care unit of Hiwot Fana Comprehensive Specialized University Hospital (HFCSUH) in Ethiopia.

Methods and materials

Study setting and period

The study was conducted in Harar City, located 526 km from Addis Ababa, the capital of Ethiopia. The Harari regional state has a total of seven hospitals, eight health centers, twenty-nine private clinics, twenty-six health posts, and one regional laboratory, catering to the healthcare needs of the region. This study was conducted at Hiwot Fana Comprehensive Specialized University Hospital (HFCSUH), which provides healthcare services to a population of more than six million people in the catchment area. The Pediatric and Child Health Department is one of the major units of the hospital and has four main subunits, namely, the pediatric ward, neonatal intensive care unit (NICU), outpatient units, and follow-up clinics. NICU is one of the subunits of healthcare services for newborns, with sixteen trained nurses, four working residents, and two pediatricians, and data were extracted from patient medical records between 1 and 30 January 2024.

Study design

The study utilized an institution-based retrospective cross-sectional.

Source and study population

The source population consisted of all neonatal patients with sepsis who were admitted to Hiwot Fana Comprehensive Specialized University Hospital, whereas the study population included all neonatal patients who were admitted with sepsis during the study period.

Inclusion and exclusion criteria

Those neonates admitted with a confirmed diagnosis of sepsis at the NICU of HFCUSH from 1 January 2021 to 30 December 2023 were included. However, medical records missing relevant data (laboratory, clinical, and discharge outcomes) during admission were excluded from this study.

Sample size determination and sampling procedure

A sample size of 311 neonates with sepsis was calculated using single population proportion formula $[n = (Z_{\alpha/2})^2 p(1-p)/d^2]$ where n is the minimum sample size required, p is the proportion of treatment outcome, $Z_{\alpha/2}$ is the value of the standard score at 95% confidence level, and d is the margin of error ($d = 0.05$); $p = 24.4\%$ (neonatal sepsis treatment outcome as a proportion) taken from a previous study conducted in Addis Ababa (27). Using the formula $n = (1.96)^2 \times 0.244 \times 0.756$ $(0.05)^2 = 283$ and by adding a 10% non-response rate, the final sample size was 311. The study subjects were identified using a systematic random sampling technique from the list of 1,310 neonates admitted to the NICU of the hospital from 1 January 2021 to 30 December 2023. The sampling interval (k) was determined by the study population (1,310 neonatal sepsis patients) divided by sample size ($1{,}310/311 = 4$). Data were collected for every four individuals followed by a simple random sampling technique in recruiting the first medical chart.

Data collection method

A structured data collection tool was developed after reviewing different literature and NICU guidelines. The data abstraction format was designed to collect relevant data focusing on sociodemographic, maternal, and neonatal factors including the outcomes.

Data were collected by two trained nurses and residents after training on the objective of the study, the tool, the data collection method, and the handling of the data. Strict supervision was undertaken daily during the data collection period by one supervisor and the investigators.

Data were collected by extraction from the patients' medical records into a structured checklist/questionnaire and checked manually for its completeness.

Operational definition

Neonatal sepsis: diagnosed based on laboratory screening, the neonatal sepsis risk calculator, and clinical observation (28).

Early-onset sepsis: occurring within 72 h–7 days of birth, whereas LOS occurs after this time period (14, 29).

Clinical diagnosis of sepsis: based on the presence of suspected infection and clinical or laboratory evidence of infection, as well as the presence of at least two of the four systemic inflammatory response criteria (SIRC), including derangement of one of the vital signs (body temperature, heart rate, respiratory rate), desaturations, and abnormal white blood cell (WBC) counts (neutrophilia above 12,000/mm^3 or neutropenia below 4,000/mm^3 with 10% or more of non-segmented peripheral blood neutrophils) (30).

Low white blood cell count: defined as a white blood cell count below 1,000 cells/ml (31).

Treatment outcome: the treatment outcome of neonates admitted with sepsis was determined at the time of discharge, with two categories of outcome: either improved or not improved.

Died: a patient's medical card with death summary and other significant indicators of death on the patient database in the hospital.

Improved: a patient who has been free from signs and symptoms of neonatal sepsis and has declared as having a stable vital sign and discharge summary with a remark of improvement.

Data quality control

Data collectors and supervisors were trained on the study objectives and data collection procedures by the principal investigator. A pretest was conducted on 5% of the sample size to ensure the validity of the data collection tool, which was then used to extract data from the patient medical charts by trained data collectors. Data quality was ensured through the use of a well-designed data abstraction tool and with continuous supervision. All collected data were checked for completeness and accuracy.

Data processing and analysis

The collected data were coded, entered, cleaned, and stored using EpiData version 4.6 and exported to STATA 17 statistical analysis. Descriptive statistics were reported as frequency, mean, and proportion. Bivariable analysis was performed to calculate crude odds ratio and candidate variables with a p-value of ≤ 0.25 were selected for multivariable analysis to minimize the rejection of potentially relevant variables and reduce confounding issues. The goodness of fit of the model was tested using the Hosmer–Lemeshow test (>0.05). A multicollinearity test was performed to determine the correlation between the independent variables using variance inflation factors (VIF <7). The adjusted odds ratio

(aOR) with 95% CI and a *p*-value of <0.05 were considered a statistically significant association.

Results

Admission characteristics of neonates

Among a total of 311 study participants, the analysis was performed on 302 of the 1,310 patients with a response rate of 97.1%. The mean (±SD) age of neonates was 4.77 (±5.2) days. Of the total, 245 (81.3%) were less than 1 week old at admission. Greater than half of neonates were male (58.6%) and had ≥2.5 kg (54.6%) (Table 1).

Laboratory and clinical characteristics

Half (47.0%) of neonatal sepsis patients had abnormal WBC counts (8.0% leukopenia and 39.07% leukocytosis). The majority (62.3%) of the participants had normal platelet count, and approximately 21.9% had a platelet count of $<150 \times 10^3$ cells/mm^3. Almost half (47.4%) of them had <90% SO_2. Regarding neonatal comorbidity, 54 (17.9%) of them had identified comorbidities (Table 2). As shown in Figure 1, jaundice was the predominant (15, 27.8%) comorbidity among neonatal sepsis patients, followed by perinatal asphyxia (PNA; 11, 20.4%), meconium aspiration syndrome (MAS; 9, 16.7%), and respiratory distress syndrome (RDS; 8, 14.8%).

Maternal-related characteristics

Almost a quarter (23.5% and 25.5%) of mothers had no antenatal care (ANC) follow-up and premature rupture of membrane (PROM), respectively, in their current pregnancy. In 36 (11.9%) mothers, chorioamnionitis was diagnosed, while 41 (13.6%) had rupture of membrane (ROM) ≥18 h duration (Table 3).

Medication-related characteristics

Among the study participants, 299 (99.0%) of neonatal sepsis patients were treated with dual antibiotic therapy, only 3 (1.0%) of them treated with triple antibiotics. Ampicillin and gentamicin were used to treat 243 (80.5%) patients, followed by ampicillin

TABLE 1 Admission characteristics of neonatal sepsis patients admitted to the neonatal intensive care unit in Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia, 2024.

Variables	Frequency	Percent (%)
Gestational week		
Pre-term	102	33.8
Term	191	63.3
Post-term	9	3.0
Age		
≤7 days	245	81.1
8–28 days	57	18.9
Sex		
Female	125	41.4
Male	177	58.6
Weight at birth		
<2.5 kg	137	45.4
≥2.5 kg	165	54.6
Resuscitated		
Yes	29	9.6
Surgery		
Yes	5	1.7
Temperature		
Normal	108	35.8
Hypo-/hyperthermic	194	64.2
RR >60 breaths/min		
Yes	187	61.9
IC or SC retraction		
Yes	98	32.5
Convulsion		
Yes	34	11.3
Fail to feed		
Yes	225	74.5

TABLE 2 Laboratory and clinical data of neonatal sepsis patients admitted to the neonatal intensive care unit in Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia, 2024.

Variables	Frequency	Percent (%)
WBC count (cell/mm^3)		
<5,000	24	8.0
5,000–21,000	160	53.0
>21,000	118	39.1
Platelet count (cell/mm^3)		
$<150 \times 10^3$	66	21.9
$150–450 \times 10^3$	188	62.3
$>450 \times 10^3$	48	15.9
Hemoglobin level		
Low	96	31.8
Normal	206	68.2
Oxygen saturation		
<90%	143	47.4
≥90%	159	52.7
Neonatal comorbidity		
Yes	51	16.9
Shock		
Yes	20	6.6
MODS		
Yes	19	6.3
DIC		
Yes	15	5.0
AKI		
Yes	26	8.6
Meningitis		
Yes	49	16.2

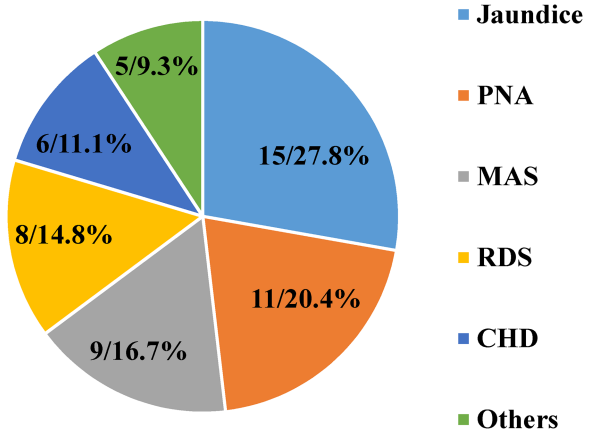

FIGURE 1
Comorbidities among neonatal sepsis patients admitted to the neonatal intensive care unit in Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia, 2024.

TABLE 3 Maternal characteristics of neonatal sepsis patients admitted to the neonatal intensive care unit in Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia, 2024.

Variables	Frequency	Percent (%)
ANC follow-up		
Yes	231	76.5
Chorioamnionitis		
Yes	36	11.9
Hypertensive disorder		
Yes	40	13.3
PROM		
Yes	77	25.5
ROM duration		
<18 h	261	86.4
≥18 h	41	13.6
Obstructed labor		
Yes	35	11.6
Labor duration		
< 6 h	104	34.4
6–12 h	154	51.0
13–24 h	36	11.9
>24 h	8	2.7
Multiple pregnancy		
Yes	19	6.3
Place of delivery		
Institution	293	97.0
Home	9	3.0
Mode of delivery		
CS	111	36.8
SVD	183	60.6
Instrumental	8	2.7

and third-generation cephalosporin (ceftriaxone or cefotaxime) in 36 (11.9%) patients and vancomycin with ceftazidime and cefepime in 15 (5.0%) patients (Figure 2).

Neonatal sepsis treatment outcome

Regarding the treatment outcome, 27.8% (95% CI: 22.7%–32.9%) of patients died, and the remaining 218 (72.2%) were discharged after improvement; three-fourths (75.8%) of neonates stayed for 7–14 days, and 59 (19.5%) of them stayed for more than fourteen days (Figure 3).

Associated factors with neonatal sepsis treatment outcome

In the bivariable logistic regression analysis, variables such as low birth weight, gestational age, abnormal body temperature, low WBC count, abnormal platelet value, oxygen saturation, lack of ANC follow-up, prolonged ROM, meningitis, shock, MODS, and chorioamnionitis were candidates for multivariable logistic analysis. However, low WBC count, SO_2 of <90%, no ANC visit, chorioamnionitis during pregnancy, and being pre-term neonates were statistically significant factors for neonatal sepsis mortality in multivariable analysis (Table 4).

Discussion

The primary aim of this study was to determine the treatment outcomes and associated factors among neonates admitted to the neonatal intensive care unit of Hiwot Fana Comprehensive Specialized University Hospital with the diagnosis of neonatal sepsis. According to this study, 27.8% (95% CI: 22.7%–32.9%) of neonatal sepsis patients died after treatment initiation. This result is analogous to studies conducted in Addis Ababa, Ethiopia, 24.4% (27); the Democratic Republic of the Congo, 21.1% (32); Nigeria, 31.8% (33); and Pakistan, 22% (34). However, the present finding accounts higher prevalence of mortality rate compared to studies conducted in the USA, 15.3% (35) and 3.3% (36); Saudi Arabia, 11.8% (37); and Switzerland, 11% (38). One potential reason for this difference could be the advanced healthcare infrastructure, availability of facilities, and high standards of care found in developed nations in comparison with the abovementioned low- and middle-income countries. Similarly in Brazil, 13% (39), lower mortality rates among neonatal sepsis patients were recorded. Another reason for the discrepancy between these findings could be associated with the fact that the study from Brazil was included only among LOSLOS neonatal patients.

On the other hand, the neonatal sepsis mortality rate in this study was lower compared to studies conducted in Tanzania, 37.1% (40); India, 44.4% (9); and Serbia, 37.5% (41). This disparity could be explained by a difference in the study population, data gathering methodology, and case classification. A study from Tanzania and India was conducted among neonates with culture-proven neonatal sepsis. In Serbia, only early-onset neonatal sepsis patients were recruited in the study, while in Tanzania, premature neonates were included. The

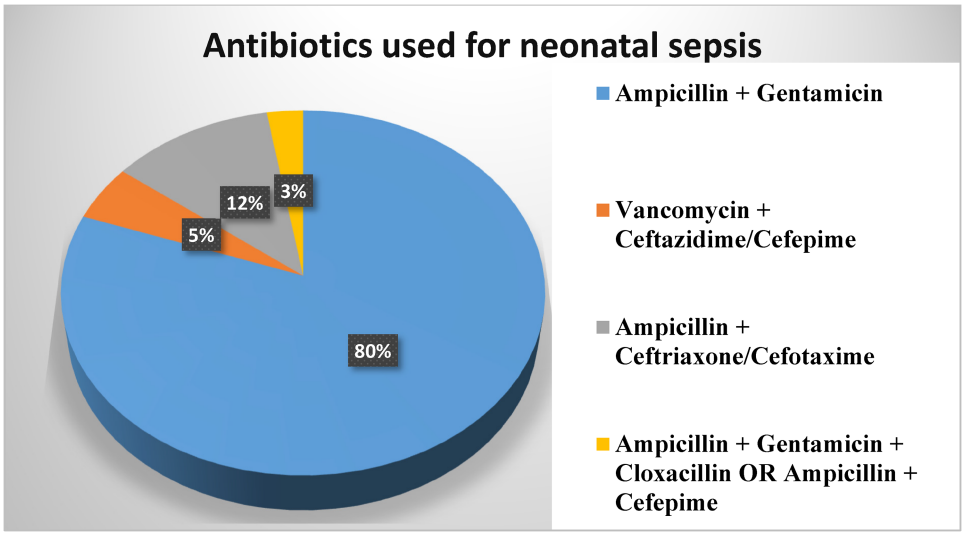

FIGURE 2
Antibiotics used in neonatal sepsis patients admitted to the neonatal intensive care unit in Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia, 2024.

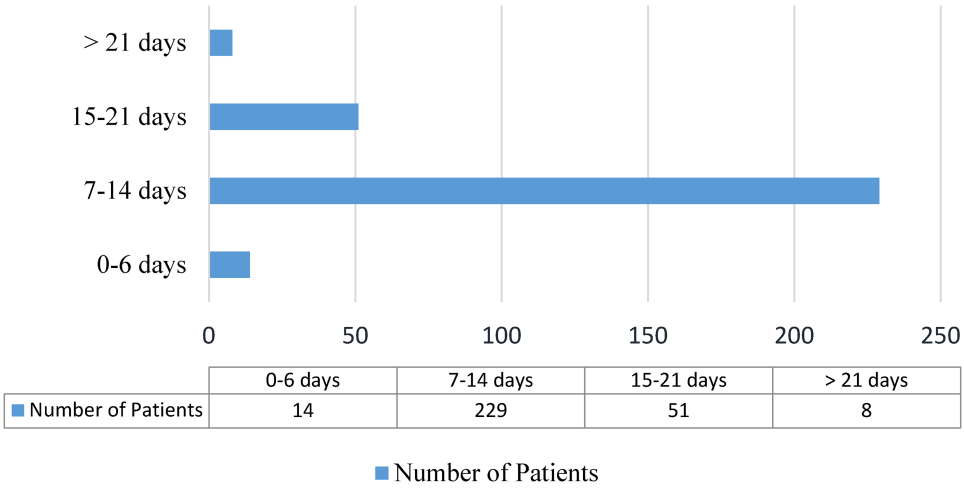

FIGURE 3
Length of hospital stay for neonatal sepsis patients admitted to the neonatal intensive care unit in Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia, 2024.

reason for this disparity may also be the current government's devotion to diminishing neonatal mortality through sustainable development goals intended to be implemented in the country (42).

Regarding determinant factors, WBC count, level of oxygen saturation, pre-term neonates, mothers with no ANC follow-up, and chorioamnionitis were significantly associated with neonatal sepsis-related mortality.

In this study, neonates with low WBC count were approximately four times more likely to experience death than neonates having normal values of WBC count. This discovery is supported by other studies carried out in Pakistan (43) and Japan (44). This could be because low WBC neutropenia persevering along with draining neutrophils stored in the bone marrow is associated with poor prognosis (45). Although neutrophils in adults have a variety of well-established functions, such as chemotaxis, phagocytosis, and degranulation, neonatal neutrophils have been found to have less deformation and mobility of their cell membrane, which can impair their ability to effectively perform these functions, potentially leading to decreased effectiveness in fighting infections (46). Neutropenia could happen because of the imbalance between production and destruction of neutrophils (47). On the other way round, an increased absolute neutrophil count has resulted in a decrease in mortality among neonates with evidence of sepsis (46, 47). Other

TABLE 4 Bivariate and multivariate logistic regression analysis of factors associated with treatment outcome of neonatal sepsis patients admitted to the neonatal intensive care unit in Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia, 2024.

Variables	Category	Treatment outcome		cOR (95% CI)	aOR (95% CI)
		Improved	Died		
Birth weight	<2.5 kg	92	45	1.6 (1.0, 2.6)	1.5 (0.8, 2.7)
	≥2.5 kg	126	39	1	1
Temperature	Normal	85	23	1	1
	Hypo-/hyperthermia	133	61	1.6 (0.9, 2.7)	1.8 (1.0, 3.5)
WBC	Low	13	11	2.9 (1.2, 7.1)	4.2 (1.5, 12.5)*
	Normal	124	36	1	1
	High	81	37	1.6 (0.9, 2.7)	1.7 (0.9, 3.3)
Platelet	Low	44	22	1.6 (0.9, 3.0)	1.5 (0.7, 3.1)
	Normal	144	44	1	1
	High	30	18	2.0 (1.0, 3.9)	1.5 (0.7, 3.4)
Oxygen saturation	<90%	85	58	3.5 (2.0, 6.0)	3.0 (1.6, 5.4)**
	≥90%	133	26	1	1
Shock	No	208	74	1	1
	Yes	10	10	2.8 (1.1, 7.0)	2.6 (0.9, 8.1)
Meningitis	No	187	66	1	1
	Yes	31	18	1.7 (0.9, 3.1)	1.3 (0.6, 2.8)
MODS	No	209	74	1	1
	Yes	9	10	3.1 (1.2, 8.0)	2.4 (0.7, 7.8)
ANC follow-up	No	40	31	2.6 (1.5, 4.6)	2.4 (1.2, 4.7)*
	Yes	178	53	1	1
Chorioamnionitis	No	203	63	1	1
	Yes	15	21	4.5 (2.2, 9.3)	2.8 (1.2, 6.5)*
ROM duration	<18 h	194	67	1	1
	≥18 h	24	17	2.1 (1.0, 4.1)	2.0 (0.9, 4.4)
Gestational week	Pre-term	64	38	2.0 (1.2, 3.4)	2.1 (1.2, 4.0)*
	Term	147	44	1	1
	Post-term	7	2	0.9 (0.2, 4.8)	0.9 (0.1,5.8)

*$P < 0.05$, whereas **$P < 0.001$; Hosmer–Lemeshow test = 0.62.

recent evidence also revealed that the levels of WBC on the day of sepsis onset are valuable indicators for predicting mortality in neonates with sepsis (48). However, no significant association was found between the neutrophil-to-lymphocyte ratio (NLR) and patient outcomes or length of stay (49).

Neonates who had low oxygen saturation/being desaturated had a higher chance of experiencing death than their counterparts with the odds of 3.0. The finding is analogous/aligns with the studies conducted in northwest Ethiopia (50), Tanzania (40), other low-income sub-Saharan African and South Asian countries (51), and the USA (52). The reason for this can be understood as the decrease in oxygen levels in the bloodstream impacting the oxygen supply to the body's tissues, such as organs and muscles, leading to cellular demise (53); organ dysfunction and death in neonatal sepsis are believed to be caused by bioenergetics failure due to inadequate oxygen supply to cells, indicating the importance of monitoring vital signs and clinical information to initiate timely treatment to prevent deaths and other complications in neonates (53). This highlights the need for the development of affordable and accessible tools for identifying oxygenation status in neonates, especially in limited resource settings where advanced monitoring technologies may not be readily available (40).

The study found that neonates born to mothers who did not receive antenatal care (ANC) during pregnancy were 2.4 times more likely to die from neonatal sepsis compared to neonates born to mothers who did receive ANC. This indicates that antenatal care is crucial in reducing the risk of neonatal sepsis and mortality. This is consistent with previous reports from Ethiopia (54). The failure to attend antenatal care appointments has an impact on neonatal mortality (55), possibly because it contributes to the neglect of other preventable factors during pregnancy (55). Programs that educate mothers on the importance of antenatal schedules and provide screening, monitoring, and treatment of maternal conditions during pregnancy could significantly reduce neonatal mortality rates due to neonatal sepsis. In fact, other evidence has shown that even one visit to a skilled provider during pregnancy can reduce the risk of neonatal mortality by 39% in sub-Saharan African countries (56). Hence, all pregnant women should receive ANC during pregnancy, which has important public health implications for neonatal mortality in the eastern region of Ethiopia.

Furthermore, neonates with sepsis who were delivered from mothers having a history of diagnosed chorioamnionitis had threefold odds of mortality rate as compared with those delivered from mothers with no history of chorioamnionitis. Similarly, an increased risk of neonatal sepsis mortality due to maternal chorioamnionitis has been reported in previous studies carried out in Tanzania (40) and Ethiopia (57). There is extensive evidence that histological and clinical chorioamnionitis is

associated with neonatal sepsis, which can progress to adverse outcomes including short and long-term morbidity including death (58); the colonization of disease-causing agents in the birth canal and the transmission of these microorganisms to the newborn during labor and delivery can lead to neonatal sepsis, which can have adverse clinical outcomes (58). This could be further explained by the fact that chorioamnionitis or inflammation of the placenta and amniotic can commonly lead to pre-term birth, which can have a devastating effect on the development of almost every organ in the fetus (59). This highlights the importance of monitoring and managing maternal conditions during pregnancy, as it can prevent premature births and reduce the risk of neonatal sepsis and mortality (58, 59). As a clinical implication, all infants born to mothers with chorioamnionitis should be therefore directly admitted to the neonatal intensive care unit (NICU) for evaluation and treatment of presumed sepsis for a minimum of 48 h, regardless of clinical appearance with the possible implementation of a risk-stratification system for high-risk infants based on the EOS calculator (60).

Finally, pre-term neonates with sepsis were found to be 2.14 more likely to die as compared to term neonates with sepsis. The finding is consistent with previous studies conducted in Ethiopia, Nigeria, and other low- and middle-income countries (51, 61–63). Neonatal sepsis remains a serious problem among infants born pre-term, particularly they were found to be at a higher risk for life-long morbidities and death (64). This might be explained by the fact that premature infants are at an increased risk of developing septicemia as a complication because of deficiencies in humoral and cellular immunity (65). It is also known that pre-term neonates face abundant physiological challenges as they adjust to extrauterine life, which in turn results in striving to respond to treatments (59). In countries with very high neonatal mortality, additional deaths occur due to infections such as sepsis (66). This implies that timely, efficient, and effective antimicrobial therapy and supportive care are principal components of neonatal sepsis therapy, and implementing basic neonatal care to prevent sepsis through continuous professional training/education and quality improvement initiatives remains so important.

Overall, this study provides useful insights for clinical care, healthcare management, and further research in the areas of neonatal sepsis management and neonatal care specialization. Clinically, healthcare workers can identify prognostic factors associated with mortality among neonates with sepsis and implement appropriate interventions. Healthcare managers can use this evidence to assess and improve the quality of care provided by clinicians. Researchers can be encouraged to conduct further advanced research on this critical issue to develop effective strategies to reduce neonatal mortality due to sepsis.

Limitation

Some limitations of this study include the inability to access detailed treatment protocol and laboratory results due to the reliance on medical records as well as the study being conducted in a single hospital, which may limit the generalizability of the findings to a wider population in the region or country.

Other potential limitations associated with the model we have used can also include sensitivity to outliers, linearity issues, and impact of irrelevant variables; however, to address these challenges, multicollinearity has been checked using VIF within consideration of removing highly correlated variables. We knob outliers through robust techniques with trough assumption analysis; we also conducted a thorough feature selection to include only relevant variables even from the very beginning/starting from tool preparation to have only relevant variables that can measure the intended outcome variable concisely.

Conclusion

More than a quarter of neonates admitted with sepsis have died. Low WBC count, desaturation, lack of ANC visits, chorioamnionitis during pregnancy, and pre-term birth were statistically significant factors for mortality. Implementing effective strategies using targeted therapeutic interventions to improve treatment outcomes by enhancing intensive care services in neonates with sepsis is vital. Moreover, attention should be given to neonates with low WBC count, desaturation, and pre-term birth, and ensuring maternal ANC and timely chorioamnionitis treatment is highly recommended to improve the treatment outcomes.

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 Haramaya University, College of Health and Medical Sciences Institution Health Research Ethical Review Committee (IHRERC) C/Ac/R/D/01/5525/24. 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

BG: Data curation, Formal Analysis, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Project administration, Supervision. AA: Formal Analysis, Methodology, Software, Supervision,

Validation, Visualization, Writing – review & editing. FM: Formal Analysis, Methodology, Software, Validation, Visualization, Writing – review & editing, Data curation, Resources, Writing – original draft. AM: Formal Analysis, Methodology, Resources, Validation, Visualization, Writing – review & editing. MK: Formal Analysis, Methodology, Validation, Visualization, Writing – review & editing. TA: Formal Analysis, Methodology, Validation, Visualization, Writing – review & editing. DT: Formal Analysis, Methodology, Validation, Visualization, Writing – review & editing. AD: Formal Analysis, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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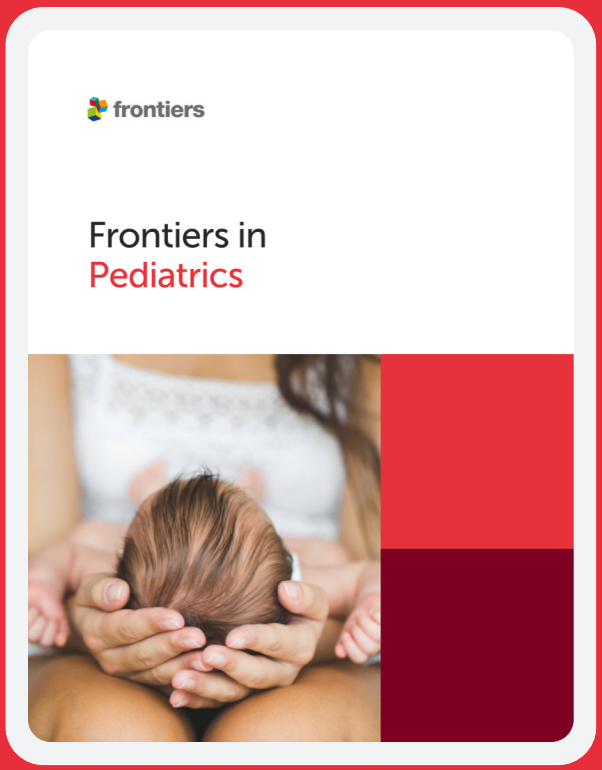

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