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CLINICAL RESEARCH ARTICLE

Outcome prediction for late-onset sepsis after premature birth

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BACKGROUND: Our aim was to develop a quantitative model for immediately estimating the risk of death and/or brain injury in late-onset sepsis (LOS) in preterm infants, based on objective and measurable data available at the time sepsis is first suspected (i.e., time of blood culture collection).
METHODS: Retrospective study on neonates ≤36 weeks' gestation with a positive blood and/or cerebrospinal fluid culture after 72 hours from birth.
RESULTS: Among 3217 preterm live births, 94 cases were included (median gestational age 26.5 weeks' IQR 25.0;28.0), of whom 26 (27.7%) had poor outcomes (17 death; 9 brain injuries). Infants with poor outcomes showed lower postnatal age (11.5 vs 12.5 days, $p < 0.001$), lower mean blood pressure (30.5 vs 43 mmHg, $p < 0.001$) and higher lactate levels (4.4 vs 1.5 mmol/l, $p < 0.001$). Our multivariable model showed good discrimination and calibration (c statistic=0.8618, Hosmer-Lemeshow $p = 0.8532$), stratifying the population into 3 groups: low-risk (sensitivity 97%, specificity 52%), middle-risk, and high-risk (sensitivity 77%, specificity 80%).
CONCLUSION: This predictive model performs well as a practical and easy-to-use tool to help clinicians early identify the sickest neonates who may benefit from timely and aggressive support (e.g., central line, haemodynamic assessment) and close monitoring (e.g., 1:1 nursing assignment, frequent reassessments).

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IMPACT:

- We lack data to early identify the severity of neonatal late-onset sepsis in preterm infants.
- Delay in treatment contributes to poor prognosis.
- We developed a model for early prediction of poor outcomes (mortality and brain injuries).
- The model utilizes immediately available and measurable data at the time sepsis is first suspected.
- This can help clinicians in tailoring management based on individual risks.

INTRODUCTION

Improved survival, along with prolonged hospitalisation, exposes preterm infants to high risk of late-onset sepsis (LOS, occurring > 72 hours of life).[1] The incidence of LOS in preterm infants is approximately 13-fold higher compared to full-term infants, with mortality rates being almost 60 times higher.[1] Although initial symptoms may be vague and nonspecific, the clinical course can be tumultuous.[2,3] We lack data to timely identify the severity of a LOS episode in its early stages, making it difficult to predict the risk of death and severe complications. This results in treatment delay, contributing to the poor prognosis of LOS.[4]

The updated guidelines for the management of septic shock in children and term newborns[5,6] provide algorithms and recommendations for the timing of various treatments, including the administration of the first fluid bolus within 5 minutes and initiation of vasopressors within 15 minutes. However, no consensus definition of neonatal septic shock has been established, preventing the early identification of infants who require immediate haemodynamic evaluation, aggressive treatments (such as central venous line placement, fluid boluses, and inotropes) and close monitoring. Furthermore, current guidelines do not offer specific recommendations for the management of septic shock in preterm infants. Due to their less mature immune responses, it may be inappropriate to directly apply practices used for older children to the care of preterm infants.

The availability of highly predictive information regarding the risk of death or poor outcomes at the initial suspicion of sepsis would enable the prompt initiation of targeted and effective supportive therapies.[7] Our aim was to investigate whether measurable and objective data, immediately available when sepsis is first suspected, may accurately predict the risk of poor outcomes (mortality or brain injury) in preterm infants with LOS.

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METHODS

Study design

This retrospective cohort study was conducted at the Neonatal Intensive Care Unit (NICU) of Polyclinic University Hospital of Modena. The study was approved by the Institution's Ethical Committee (prot. 978/2019). Given the impossibility of retrospectively retrieving consent for all the infants included in the study, the research ethics committee waived the need for the consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patient selection

The base population consisted of all neonates admitted at ≤36 weeks' gestation at the study site from 1 January 2010 to 31 December 2022. Subjects were included who had a positive blood and/or cerebrospinal fluid culture for a bacterial pathogen after age 72 hours. Cultures that grew coagulase-negative staphylococci (CoNS) or other potential contaminants (e.g. Micrococci, Corynebacteria) were excluded, according to previous research,[8–12] due to the challenges related to distinguishing true infections from contamination. Additionally, infants with chromosomal abnormalities or major congenital anomalies, as defined by the Vermont-Oxford Network, were excluded because their potential intrinsic vulnerability to infections could compromise the model's predictability. Infants with a positive culture in the context of necrotizing enterocolitis (NEC) stage ≥2a (according to Bell's criteria[13]) were also excluded in line with previous literature, as its mortality rate and associated illness markers may be unique.[8–10] For infants who had two or more episodes of LOS during their hospital stay, only the first one was included for analysis, to avoid the issue of interdependency.

Data collection

Cases to be included in the study were identified by searching the microbiology laboratories' database. Additionally, the Vermont Oxford Network database at the study site was utilized to cross-check and minimize the likelihood of missing any cases. At our centre, we utilize a computerized electronic medical record system (Metavision Electronic Medical Record, iMDsoft, Tel Aviv, Israel). The medical chart contains sections filled in separately by nurses and physicians, facilitating accurate data collection. To ensure maximum reliability, data extraction was performed from September 2022 to February 2023 by two clinicians who consulted the nursing diary as needed. To ensure objective data, the first suspicion of LOS was defined as the time when the blood culture was collected. Data were defined as the first values obtained after the blood collection for culture (i.e., the values closest to the blood collection for culture, within a timeframe of 2 hours). Measurements of blood pressure (BP) were obtained non-invasively, using the oscillometric standard technique (DINAMBP Pro; GE Healthcare, Tampa FL). In keeping with previous literature, non-invasive BP measurement was considered for the analysis, because invasive BP monitoring is typically initiated in high acuity cases, introducing a selection bias.[9] The use of non-invasive BP measurement ensured the inclusion of all eligible patients and higher generalizability of study findings. Lactate and base deficit levels were obtained via blood gas analysis from any sample (capillary, venous, or arterial) drawn at the time of blood culture collection.

We defined poor outcomes of LOS as follows:

- Sepsis-related death: death occurring within 7 days from the blood culture collection, or clearly related to complications arising from LOS.[14]
- Brain injury: any new brain lesion first detected at neuroimaging (ultrasound and/or magnetic resonance imaging) after the onset of LOS, including intraventricular haemorrhage (IVH grade ≥2, according to the Papile classification scheme),[15] white matter injury, or other relevant brain injuries among survivors. At our centre, premature infants routinely undergo serial cerebral ultrasounds, beginning within the first 48 hours of life. Considering the timing of brain injury appearance in preterm infants (ranging from a few hours to several days after the insult),[16,17] when an episode of LOS occurs, a brain ultrasound is typically performed 3 to 7 days after its onset, and follow-up is continued until discharge to detect any associated lesions. In preterm infants < 32 weeks' gestation and/or when brain injuries are suspected, the ultrasound follow-up continues after discharge and is completed with a brain MRI at the corrected term age.[18] To maximize accuracy, two authors (A.B. and E.D.) individually reviewed neuroimaging data to include cases that developed clear brain lesions after the LOS. We included the development of brain injuries among the poor outcomes because, although patients survive, these lesions still indicate a more severe illness with organ damage, deserving maximal treatment. In case of multiple adverse outcomes, the worst outcome was considered for the analysis.

Statistical analyses

We performed all analyses by using R (4.2.2). For bivariate comparisons, we used Pearson's χ^2 or Fisher's exact tests for categorical variables, and *t* test or Wilcoxon-Mann-Whitney test for continuous variables. We selected variables on the basis of previously published findings[8–10,12,19–21] and ease of extraction from an electronic medical chart. We examined the bivariate associations of specific variables to identify the 3 predictors to be included in the multivariable model. Results from the logistic regression models were reported as odds ratios (OR), relative 95% confidence intervals (95%CI) and *p* values. We made an a priori decision to consider the final model successfully validated if it had an area under the receiver operator characteristic (*c* statistics) ≥0.75. Calibration was assessed with the Hosmer-Lemeshow *p* value. Model performance was also assessed by visual examination of observed and expected poor outcome rates by risk deciles. We estimated the relative contribution of individual predictors to the overall predictive value by using the differences between the log likelihood of the full model and the log likelihood of a model without each predictor. Relative contribution was defined as the ratio of the predictor's log-likelihood difference to the sum of the model's 3 log-likelihood differences, multiplied by 100. Three risk groups of poor outcomes were defined on the basis of the poor event's probabilities estimated by the multivariable model. The probability cutoffs were obtained by binary recursive partitioning, exploiting a decision tree.

RESULTS

During the study period, 3217 live births ≤36 weeks' gestation occurred at the study site. A total of 201 positive blood or cerebrospinal fluid cultures among preterm infants older than 72 hours of age were identified. Of those, 85 tested positive for a contaminant (42.3%), while 116 (57.7%) tested positive for a bacterial pathogen and were examined for potential eligibility. Of these 116 cases, 22 were excluded: the reason being chromosomal abnormalities and/or congenital malformations ($n = 7$), concomitant presence of NEC ($n = 6$), and previous episode of LOS in the same infant ($n = 9$). A final sample size of 94 cases was included and analysed (of whom 84 were Very Low Birth Weight). The infecting organism was Gram negative in 52.1% of cases ($n = 49$) and Gram positive in 41.5% ($n = 39$). Polymicrobial infections accounted for 6.4% of cases ($n = 6$). The most frequently identified infecting microorganisms were *Enterobacterales* ($n = 29$, 30.9%), followed by *Streptococci* (*Group B Streptococcus* $n = 15$, 16.0%; other, $n = 3$, 3.2%), *Staphylococcus aureus* ($n = 14$, 14.9%), *Escherichia coli* ($n = 10$, 10.6%), *Enterococci* ($n = 8$, 8.5%), *Pseudomonas* ($n = 5$, 5.3%) and fungi ($n = 2$, 2.1%); other microorganisms, $n = 3$, 3.2%; polymicrobial infections, $n = 5$, 5.3%. A total of 26 infants (27.7%) experienced poor outcomes, which consisted of 17 deaths and 9 survivors with brain injuries (multiple lesions in white matter, basal ganglia and thalami, $n = 4$; ventriculitis and ventricular enlargement, $n = 2$; grade 2 IVH, $n = 1$; grade 3 IVH, $n = 1$; cerebellar haemorrhage, n = 1). The remaining 68 infants (72.3%) had a favourable outcome (survivors with no brain injury).

Table 1 summarises the demographic and clinical characteristics observed at the time of blood culture, distinguishing between infants with favourable versus poor outcomes. No differences were observed in most demographic characteristics, except that infants with poor outcomes were younger. Infants with poor outcomes presented with lower BP including systolic, diastolic, and mean BP. Infants with poor outcomes more frequently exhibited altered consciousness, and higher lactate and base

Table 1. Comparison of baseline demographic and clinical characteristics immediately available at the first suspicion of late-onset sepsis (i.e. the time of blood culture), in the overall cohort, and between infants with favourable (survivors with no brain injury) versus poor outcomes (death or brain injury).

	Overall cohort ($n = 94$)	Favourable outcome ($n = 68$)	md	Poor outcome ($n = 26$)	md	p
Female sex, No. (%)	49 (52)	39 (57)	0	10 (38)	0	0.16
Gestational Age, median (IQR), weeks	26.5 (25.0;28.0)	27.0 (25.0;28.3)	0	26.0 (24.3;28.0)	0	0.71
Postnatal days, median (IQR)	17.5 (10.0;30.8)	22.5 (12.8;34.0)	0	11.5 (8.0;17.8)	0	<0.001
Birth weight, median (IQR), g	834.0 (667.0;1221.5)	824.0 (692.8;1247.0)	0	861.5 (654.0;1171.8)	0	0.80
Body weight, median (IQR), g	1085.0 (742.0;1459.5)	1140.0 (827.0;1598.8)	0	915.5 (619.8;1222.5)	0	0.12
SBP, median (IQR), mmHg	60.0 (50.0;69.0)	63.0 (54.0;70.0)	11	46.0 (38.3;60.0)	0	<0.001
MBP, median (IQR), mmHg	40.0 (31.0;51.0)	43.0 (35.0;53.0)	11	30.5 (26.0;39.5)	0	<0.001
DBP, median (IQR), mmHg	32.0 (23.0;42.0)	34.0 (26.0;45.0)	11	22.0 (19.3;34.0)	0	<0.001
HR, median (IQR), bpm	170.0 (157.3;186.8)	169.5 (156.8;185.3)	0	180 (163.0;187.8)	0	0.32
RR, median (IQR), bpm	45.5 (37.3;57.0)	45.0 (35.0;57.5)	1	47.0 (40.0;55.0)	3	0.92
Fever >38°C, No. (%)	16 (18)	12 (19)	4	4 (16)	1	>0.99
Progressive apnoeas, No. (%)	51 (55)	38 (57)	1	13 (50)	0	0.72
Consciousness, No. (%)			3		1	0.02
Normal	24 (27)	22 (34)		2 (8)		
Drowsiness/ Irritability	65 (72)	42 (65)		23 (92)		
Lethargy	1 (1)	1 (2)		0 (0)		
Lactate, median (IQR), mmol/l	1.7 (1.0;3.7)	1.5 (0.9;2.0)	4	4.4 (2.3;6.0)	0	<0.001
Base Deficit, median (IQR), mmol/l	−2.9 (−6.0;−0.9)	−1.2 (−3.9;2.3)	4	−6.2 (−13.1;−3.7)	0	<0.001
Already on antibiotics, No. (%)	8 (9)	6 (9)	0	2 (8)	0	>0.99
CVC already in place, No. (%)	61 (66)	42 (63)	1	19 (73)	0	0.48

Percentages are calculated by excluding data that were unavailable (missing data, md).
BE Base Excess, *CVC* Central Venous Catheter, *DBP* Diastolic Blood Pressure, *HR* Heart Rate, *MBP* Mean Blood Pressure, *md* missing data, *SBP* Systolic Blood Pressure, *RR* Respiratory Rate.

deficit levels. Additional characteristics were similar between the two groups. Supplemental Table 1 presents clinical and microbiologic information that was not immediately available at the time of blood culture collection, comparing infants with favourable vs poor outcomes. Infants with poor outcomes were more likely to have persistent low mean BP (<30 mmHg) and high lactate levels (>2 mmol/l) 24 hours after blood culture collection; they were more likely to complicate with meningitis, and to be infected by Gram negative pathogens or pathogens resistant to empirical antimicrobials.

Bivariate analyses

At the time of blood culture collection, low postnatal age, low BP (systolic, mean and diastolic), altered consciousness, high blood lactate level and high base deficit emerged as strong individual predictors of poor outcomes (Table 2). Twenty-four hours after blood culture collection, persistent low BP and high lactate levels emerged also as strong predictors of poor outcomes. Cases complicated with meningitis exhibited a nearly 8-fold increase in the risk of poor outcomes. The bivariate relationships between the risk of poor outcomes and postnatal days, mean BP and lactate are shown graphically in Fig. 1.

Risk of poor outcomes decreased monotonically with increasing number of postnatal days (Fig. 1a). Risk of poor outcomes increased slowly with decreasing mean BP from 50 mmHg to 30 mmHg, but rapidly raised under that level (Fig. 1b). Similarly, we observed a nearly linear increase in risk of poor outcomes between 0 and 6 mmol/l in lactate levels, with a more rapid increase in risk above that level (Fig. 1c).

Multivariable analyses

Table 2 lists the components and performance of our final multivariable model. We included in multivariable analysis objective and measurable data that would be immediately available at the time of blood culture collection. The score was defined using a combination of three variables based on the logistic regression model for poor outcomes:

$$Prob(Adverse\ outcome|D,L,P) = \frac{1}{1+e^{-(1.14-0.08*D+0.40*L-0.04*P)}}$$

Where D is postnatal days [days];
L is lactate [mmol/l];
P is mean BP [mmHg].

The model had good discrimination (c statistic = 0.8618) and calibration (Hosmer-Lemeshow p value = 0.8532; model error rate = 0.1875). In the multivariable model, the most important predictor was blood lactate level (which accounted for more than half of the model's predictive ability), followed by postnatal days (which accounted for approximately one-third, Table 3).

Given the strong association between base deficit and poor outcomes, we created a model that incorporates base deficit in place of lactate, but the discrimination and calibration of this model were found to be lower (c statistic = 0.8262, Hosmer-Lemeshow p value = 0.558, Supplemental Table 2).

Risk stratification

Our model of risk stratification relying on objective data available at the time of blood culture collection is shown in Fig. 2.

Table 2. Bi- and multivariable analysis of risk factors associated with poor outcomes (death or brain injury) in preterm infants with late-onset sepsis.

	Bivariable Analysis OR (95% CI)	*p*	Multivariable Analysis OR (95% CI)	*p*
Female sex	0.46 (0.18–1.17)	0.10		
Gestational age	0.97 (0.84–1.12)	0.69		
Postnatal days	0.94 (0.89–0.98)	0.006	0.93 (0.86–0.98)	0.03
Birth weight	1.00 (0.99–1.00)	0.76		
Body weight	1.00 (1.00–1.00)	0.11		
SBP	0.92 (0.88–0.96)	<0.001		
MBP	0.92 (0.88–0.97)	<0.001	0.96 (0.90–1.01)	0.12
DBP	0.93 (0.88–0.97)	0.001		
HR	1.01 (0.99–1.04)	0.30		
RR	1.00 (0.97–1.03)	0.93		
Fever >38 °C at onset	0.83 (0.24–2.85)	0.76		
Progressive apnoeas	0.76 (0.31–1.89)	0.56		
Consciousness				
Normal	Reference			
Drowsiness/Irritability	2.04 (1.30–27.94)	0.02		
Lethargy	0.0000019 (/)	0.99		
Lactate level	1.60 (1.24–2.05)	<0.001	1.49 (1.18–2.02)	0.004
Base Deficit level	0.81 (0.72–0.89)	0.89		
Already on antimicrobials	0.86 (0.16–4.57)	0.86		
CVC in place	1.62 (0.60–4.38)	0.35		
Pathogen				
Gram +	Reference			
Gram −	2.92 (1.02–8.35)	0.05		
Polymicrobial	5.50 (0.89–34.00)	0.07		
MBP<30 mmHg 24 hours after blood culture collection	8.72 (2.51–30.31)	<0.001		
Lactate >2 mmol/l 24 hours after blood culture collection	6.16 (2.13–17.82)	<0.001		
Meningitis	7.80 (1.66–36.76)	0.009		
Pathogen resistant to empirical antimicrobials	4.36 (1.60–11.93)	0.01		

BE Base Excess, *CVC* Central Venous Catheter, *DBP* Diastolic Blood Pressure, *HR* Heart Rate, *MBP* Mean Blood Pressure, *RR* Respiratory Rate, *SBP* Systolic Blood Pressure.

The figure demonstrates that 2 cutoffs obtained from recursive partitioning categorize infants into 3 risk poor-outcomes groups.

1. The high-risk group (estimated probability from the model >0.25) consists of infants with a risk of poor outcomes of 59.0% (95%CI 42.2–74.0%). It seems reasonable that infants in this group (which represent 48.8% of preterm infants with LOS and account for 88.5% of all sepsis death/cerebral injury) should enter a clinical pathway with immediate aggressive treatment and closer monitoring. The Number Needed to Treat (NNT), that is the number of infants one would treat with maximal interventions per infant with poor outcome, is 1.7 (95%CI 1.35–2.38).
2. The middle-risk group consists of infants with estimated probability from the model 0.15–0.25 (15.0% of the cohort). This group has 16.7% incidence rate of poor outcomes (95% CI 2.9–49.1%). In this group, the NNT is 6.0 (95% CI 2.0–33.3).
3. The low-risk group consists of infants with estimated probability from the model < 0.15: it comprises 36.3% of all preterm infants with LOS, with a 3.5% incidence rate of poor outcomes (95% CI 0.2–19.6%). The NNT for this group is 29 (95% CI 5.1–555.6).

Mortality

The same model based on lactate, mean BP, and postnatal days performed even better when predicting the outcome of death alone (*c* statistic = 0.9248; Hosmer-Lemeshow *p* value: 0.222; model error rate: 0.1375). All observed deaths fell within the high-risk class (sensitivity 100%, specificity 64%; Supplemental Fig. 1).

DISCUSSION

We conducted a cohort study addressing early identification of preterm infants at risk of poor outcomes (death and/or brain injury) after LOS. Our aim was to establish a multivariable predictive model with two distinct characteristics: (1) being based on immediately available data at the time of the first suspicion of infection (2) relying solely on measurable and objective data. The purpose of our calculator is to determine the likelihood of poor outcomes at the precise moment it is applied, which corresponds to the exact time when LOS is first suspected, and management decisions are initiated. The aim is not to identify infants who should receive antibiotics, as all the infants included in the study have sepsis. Instead, the goal is to identify septic infants who are at higher risk of poor outcomes and may therefore benefit from

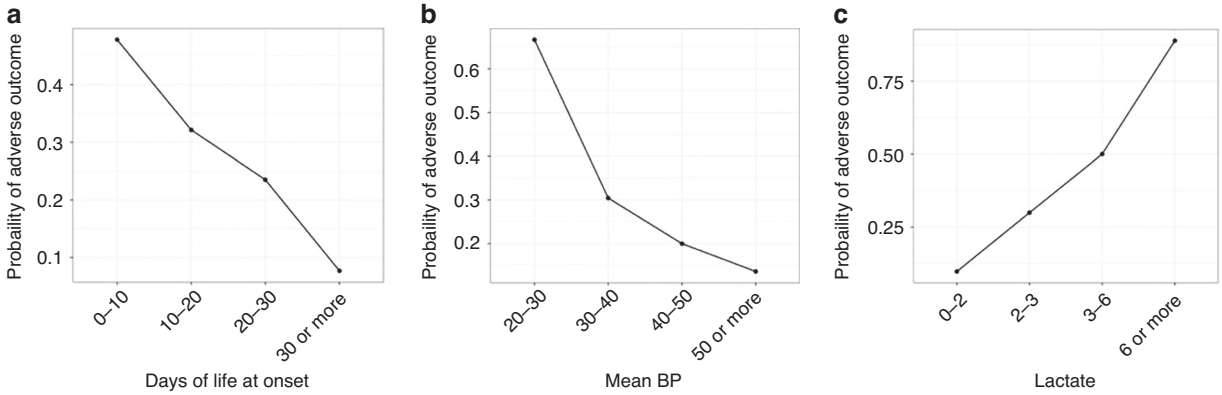

Fig. 1 Bivariate relationships between the risks of poor outcomes (death or brain injury) and predictive variables included in the model. Bivariate relationships between the risks of poor outcomes (death or brain injury) and postnatal days (**a**), mean blood pressure (mean BP, **b**), and lactate level (**c**) at the first suspicion of sepsis (i.e. the time of blood culture collection). The risk of poor outcomes decreased monotonically with increasing number of postnatal days (**a**). With regard to the mean BP, the risk of poor outcomes increased slowly with decreasing mean BP from 50 mmHg to 30 mmHg, but rapidly raised under that level (**b**). Similarly, we observed a slow, nearly linear increase in the risk of poor outcomes between 0 and 6 mmol/l in lactate levels, with a more rapid increase in risk above that level (**c**).

Table 3. Relative contribution of individual predictors of poor outcomes to the overall predictive value of the model.

Predictors	Difference in log-likelihood	Individual contribution (%)
Postnatal days	4.4	32.2
MBP	2.1	15.7
Lactate	7.0	52.1

Predictors are measured data at the first suspicion of late-onset sepsis (i.e. blood culture collection).
MBP Mean Blood Pressure.

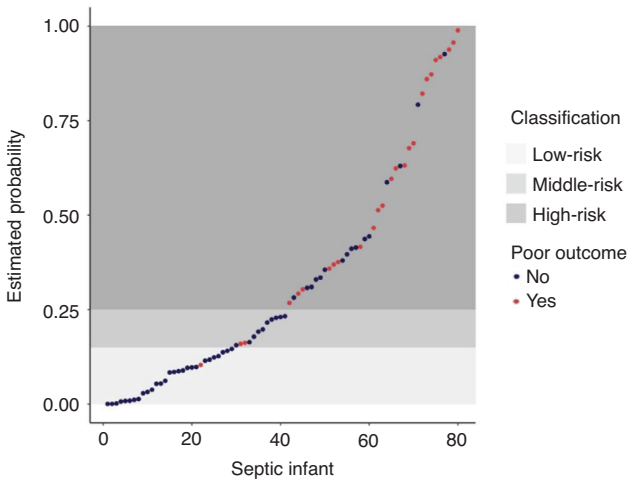

Fig. 2 Risk stratification model relying on objective and measurable data available at the first suspicion of late-onset sepsis, partitioning infants into 3 risk outcome groups (colour figure). Each septic infant is represented by a point. Neonates with poor outcomes are represented by a red point, while those with favourable outcomes are represented by a black point. The ordinate axis identifies the risk of poor outcomes provided by our predictive model. The figure demonstrates that two cutoffs obtained from recursive partitioning categorize infants into three increasing risk poor-outcomes groups.

more aggressive treatments (e.g., central line placement, early hemodynamic assessments including functional echocardiography, inotropes and/or fluids) and closer monitoring (i.e., 1:1 nursing assignment, frequent reassessments).

To ensure objectivity and comparability of the data, the time of the first suspicion of LOS was defined as the moment when the blood culture was collected, in keeping with previous studies.[8,22,23] Thus, these data are independent of subsequent management and treatments. Here we provide clinicians with a predictive tool that takes full advantage of available information when sepsis is first suspected (i.e., the time of blood culture) by 3 continuous variables: days of life, mean BP and lactate level. Indeed, the relationship between these variables and the risk of poor outcomes highlights the disadvantage of relying on cutoff values. While a lactate level ≥6 mmol/l identifies neonates at the highest risks, this approach overlooks that a lactate level between 3 and 6 mmol/l is associated with a risk of poor outcomes approximately 5 times higher than that of a value of 0–2 mmol/l (50% vs 9.8%). In keeping with previous paediatric research,[24–26] lactate level exhibits the strongest individual significance in predicting mortality. However, data from the neonatal literature are inconsistent: few studies demonstrate the relevance of lactate in neonatal sepsis. They include very small samples of infants,[19] early-onset sepsis,[12,20,27] full-term neonates,[20] culture-negative sepsis,[12] and CoNS bacteraemia.[19,20] Baczynski[10] created a highly predictive model with an excellent discrimination for sepsis–related mortality; this model was based on mean BP and base deficit at blood culture collection. However, base deficit is less specific than lactate levels in detecting haemodynamic compromise in premature infants who often have some degree of renal immaturity and metabolic acidosis due to bicarbonate loss. Consistently, according to our data, the predictive model where lactate level is replaced with base deficit has lower discrimination and calibration.

Other studies on LOS identified further indices predictive of poor outcomes, but most of these variables are not immediately available.[8,20,28–30] Similarly, an objective, automated, evidence-based organ dysfunction scoring system (nSOFA, based on respiratory, cardiovascular, and haematological parameters) was introduced to identify preterm patients at high risk of mortality among those with LOS.[22,23,31] However, the nSOFA score incorporates the use of amines or steroids as an indicator of cardiovascular dysfunction: these data are influenced by different treatment protocols and are somehow subjective, while BP (included in our predictive model) is an objective parameter. To ensure greater generalizability of results, we included the uncorrected BP in our model, in line with previous research.[10] In

fact, even though a recent systematic review has shown that BP increases with birth weight, gestational age, and postnatal age, these correlations are not linear, and there is high variability.[32]

Notably, in our cohort, the risk of poor outcomes increases much more rapidly when mean BP drops below 30 mmHg. However, even above this cutoff, infants with mean BP from 30 to 40 mmHg have a risk of poor outcomes more than twice that of those with a mean BP ≥ 50 mmHg. This finding is consistent with recent studies[9,12,19] showing that BP values still within the normal range, but significantly lower than baseline, may be a very early sign of incipient shock.[9,10,19] Notably, in line with our predictive model, a previous study on preterm infants ≤32 weeks' gestation showed that hypotension and raised lactate levels were the most prominent changes in the progression to septic shock.[19]

To our knowledge, this is the first study to incorporate postnatal age into a predictive model for poor outcomes in cases of LOS in preterm infants. Previous models have included gestational age among the predictors of poor prognosis.[30] However, in other studies, gestational age was not associated with mortality after adjusting for other variables.[10] Our data also do not show an association between gestational age and poor outcomes. In contrast, we found a significant correlation between days of life at blood culture and poor outcomes, which persists in the multivariate model. This finding is consistent with a previous report[33] suggesting that cases of fatal LOS become less frequent as the days of life increase.

Our model can predict case fatalities with excellent accuracy (*c* statistic = 0.9248), as well as case fatalities and/or the development of brain injuries (*c* statistic = 0.8618). We use this model to categorize preterm infants with LOS into 3 groups having increasing risks of poor outcomes: low (<4%), middle (17%) and high (59%). Based on our model, risks of poor outcome would be calculated automatically through an app, or an online calculator (Supplemental Material 1, available at https://survivingneonatalsepsiscalculator.tiiny.site). Previous computer-based predictive models have been widely used to aid in decision making for early-onset[34] or LOS.[23]

Our data do not allow us to draw firm conclusions on which infants should undergo lumbar puncture at sepsis onset. However, in the absence of contraindications, it is reasonable to suggest performing a lumbar puncture in high- and middle-risk groups, given their risk of poor outcomes and the low NNT (1.7 and 6 for high- and middle-risk, respectively). For low-risk group, the decision could be made by the clinician on a case-by-case basis.

At this stage, the direct application of our model to neonatal clinical care is perhaps challenging to determine, but further research may clarify this. An objective calculator could provide significant support, particularly in low-resource settings.

This study has important limitations. First, the calculator is not intended to be a tool for early identification of preterm infants with LOS to guide the initiation of antibiotics. Instead, it is designed to assess the risk of poor outcomes in preterm infants with LOS at the precise moment when the attending clinician suspects sepsis and must decide on its management (e.g., central line placement, haemodynamic evaluations, patient-to-nurse ratio, frequency of re-assessments). Also, similarly to previous calculators, we have hypothesized a risk stratification scheme, but it is crucial to emphasize that the choice of treatment strategies is always based on a deemed acceptable level of risk. Second, we collected blood gas samples from all available sources, including arterial, capillary, and venous samples. This may overestimate the measured lactate levels. However, the variation between results taken from different compartments are within clinically acceptable limits.[35] This may also offer the advantage of greater generalizability of results, and has been used in previous research.[25] The study is also limited by a small sample size: the performance of the logistic model and score for sepsis outcome prediction will require independent validation using data from numerous settings with different bacterial ecology and treatment protocols. We are planning the application of our calculator in additional centres to obtain external validation of the results in different clinical settings. To make the information provided by the current tool more complete, we also began a prospective study that includes a control group of neonates showing clinical signs of sepsis but with negative cultures. The aim is to develop a multivariable model to distinguish neonatal sepsis from non-infectious conditions.

CONCLUSIONS

We have developed a surviving sepsis calculator, a multivariable model that provides predicted probability of death and/or brain injury in preterm infants with LOS based on user-provided, measurable, and objective data that are immediately available at the time of blood culture for suspect sepsis. We hypothesize that the implementation of our model can assist clinicians in customizing decision-making based on individual risks.

DATA AVAILABILITY

The dataset generated and analysed during the current study is freely available in the Mendeley Data repository to any researcher wishing to use them for non-commercial purposes, without breaching participant confidentiality. Miselli, Francesca (2024), "Septic shock mortality", Mendeley Data, V2, https://doi.org/10.17632/hwwdxx7ks6.2.

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AUTHOR CONTRIBUTIONS

Miselli, Berardi, Bedetti, Lugli, Rossi and Roversi contributed to study conception and design. Maugeri, Deonette and Mazzotti gave substantial contributions to acquisition of data. Cuoghi Costantini gave substantial contributions to analysis and interpretation of data. Miselli and Berardi drafted the article; Bedetti, Lugli, Rossi, Roversi, Maugeri, Deonette, Mazzotti and Cuoghi Costantini revised it critically for important intellectual content. All authors approved the final version to be published.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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