Research Article

Procalcitonin and nSOFA at Sepsis Evaluation: Diagnostic Accuracy for Late-Onset Sepsis and 7-Day Mortality in Preterm Neonates: A Cross-Sectional Analytic Study

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Abstract

Background: Late-onset sepsis (LOS) in preterm neonates is difficult to confirm at clinical deterioration, yet early risk stratification is crucial. This study evaluated the diagnostic accuracy of procalcitonin (PCT) and neonatal Sequential Organ Failure Assessment (nSOFA) score for culture-confirmed LOS and 7-day mortality.
Methods: This cross-sectional analytic study included 200 preterm neonates (<34 weeks' gestation, >72 hours of age) evaluated for suspected LOS in the NICUs of Cairo University Children's Hospital. Clinical and laboratory assessment included gestational age (GA), anthropometry, complete blood count, CRP, PCT, blood culture, and nSOFA score. Culture-confirmed LOS was defined by positive blood culture.
Results: Mean GA was 30.77±2.15 weeks, mean PCT 6.25±9.93 ng/mL, and mean nSOFA 5.5±3.27. Neonates who died had lower GA (29.14 vs 31.15 weeks, P<0.001), higher PCT (12.83 vs 4.71, P<0.001), and higher nSOFA (8.47 vs 4.80, P<0.001). Neonates with sepsis had lower GA (30.26 vs 31.14 weeks, P=0.003), higher PCT (8.26 vs 4.79, P<0.001), and higher nSOFA (6.43 vs 4.82, P=0.001). For sepsis prediction, PCT had the highest AUC (0.69), followed by nSOFA (0.64) and CRP (0.57). For mortality, nSOFA showed the highest AUC (0.82), followed by GA (0.78) and PCT (0.77). lnPCT independently predicted sepsis (OR 1.56, P=0.003), while lower GA, higher nSOFA, and higher lnPCT independently predicted mortality.
Conclusions: At sepsis evaluation in preterm neonates, PCT was the strongest individual predictor of culture-confirmed LOS, whereas nSOFA was the best predictor of 7-day mortality. Combined assessment of inflammatory response and organ dysfunction may improve early bedside stratification in suspected LOS.
Keywords: Procalcitonin, Late-Onset Sepsis, Preterm Neonates, Neonatal Sequential Organ Failure Assessment, Mortality.

Introduction

Late-onset sepsis (LOS) remains a major cause of morbidity and mortality in preterm neonates admitted to neonatal intensive care units (NICUs) [1]. The difficulty is rarely the decision to suspect infection, but rather how to judge its likelihood and severity at the time of clinical deterioration. In very preterm infants, the early manifestations of sepsis are often subtle and nonspecific, and this uncertainty contributes to frequent empirical antibiotic exposure. While early treatment is essential, broad antibiotic use in this population is increasingly recognized as a consequence of diagnostic imprecision and is itself associated with important adverse effects [2].

Blood culture remains the reference standard for confirming LOS and is central to both diagnosis and antimicrobial stewardship in neonatal care [3]. However, culture results are not immediately available, and the clinical picture at the time of evaluation often requires urgent decisions before microbiological confirmation. For this reason, circulating biomarkers have been studied as adjuncts to early diagnosis. Among these, procalcitonin (PCT) has attracted particular attention because it may rise in bacterial infection earlier than many conventional inflammatory markers and has shown value in neonatal sepsis assessment [4]. Even so, the diagnostic performance of PCT has not been uniform across studies, partly because of differences in case definitions, timing of sampling, patient characteristics, and applied cutoff values, which limits its standalone use in routine practice [3].

An additional limitation of biomarker-based assessment is that it does not directly capture the degree of organ dysfunction at the time sepsis is suspected. This is especially relevant in preterm neonates, in whom prognosis is shaped not only by the presence of infection but also by the extent of physiologic compromise. The neonatal Sequential Organ Failure Assessment (nSOFA) score was developed to quantify organ dysfunction in this setting and has shown strong associations with mortality in preterm infants with LOS, including when measured at the time of sepsis evaluation [5, 6]. More recent work has supported its prognostic relevance in infants with suspected LOS and suggests that nSOFA may help standardize bedside severity assessment during the initial evaluation period [7].

Therefore, evaluating both inflammatory response and early organ dysfunction during suspected LOS may provide useful information for diagnosis and short-term risk stratification in preterm infants. Hence, this study assessed the diagnostic accuracy of PCT and nSOFA for culture-confirmed LOS and examined their ability to predict 7-day mortality in preterm neonates born before 34 weeks' gestation who were evaluated for suspected LOS.

Patients and methods

Study design and setting

This cross-sectional analytic study was carried out on 200 preterm neonates who were admitted to the neonatal intensive care units (NICUs) of Cairo University Children's Hospital and underwent evaluation for suspected LOS after the first 72 hours of life. The study was approved by the Research Ethics Committee of Cairo University Faculty of Medicine (REC code: MD-357-2023). Written informed consent was obtained from the guardians of all enrolled neonates before inclusion in the study.

Definition of suspected and culture-confirmed late-onset sepsis

Clinical suspicion of LOS was defined according to the International Consensus Conference on Pediatric Sepsis (ICCPS) criteria [8, 9], with adaptations appropriate for preterm neonates [5]. In this study, the clinical criteria for suspected sepsis required systemic inflammatory response findings compatible with neonatal sepsis assessment, taking into account the specific physiologic characteristics of premature infants. Temperature abnormality was defined as a core temperature greater than 38°C or less than 36°C. Leukocyte abnormality was defined as a leukocyte count increased or decreased for age, the presence of 20% immature neutrophils, or a CRP level greater than 10 mg/dL. Heart rate criteria were interpreted cautiously, as infrequent self-resolving bradycardic episodes may occur in premature neonates in the absence of sepsis. Culture-confirmed LOS was defined as a positive blood culture obtained during the sepsis evaluation.

Eligibility criteria

Preterm neonates with a gestational age of less than 34 completed weeks, older than 72 hours after birth, and evaluated for suspected LOS were eligible for inclusion. Clinical suspicion of sepsis was harmonized with the ICCPS framework [8, 9], requiring at least two of the four systemic inflammatory criteria, with at least one criterion being an abnormal temperature or leukocyte count, while taking into account the physiologic characteristics of preterm neonates. Neonates were excluded if they had hydrops fetalis, congenital malformations, perinatal asphyxia, congenital heart disease, inborn errors of metabolism, or congenital immunodeficiency syndromes.

Sample size and sampling process

Sample size planning was based on estimation for a cross-sectional study using sepsis prevalence, with a 95% confidence level, a margin of error of 5%, and an additional allowance of 5% to 10% for missing or incomplete data. The final study sample included 200 preterm neonates assessed at the time of sepsis evaluation.

Study procedures and data collection

At the time of clinical sepsis evaluation, each enrolled neonate underwent assessment of baseline demographic and anthropometric data, including gestational age, body weight, length, and head circumference. Laboratory evaluation included total leukocyte count, platelet count, hemoglobin level, CRP, and PCT. A blood culture was obtained during sepsis evaluation for microbiological confirmation. A positive blood culture was considered evidence of culture-confirmed sepsis. In parallel with laboratory sampling, the nSOFA score was calculated at the time of assessment to quantify the degree of organ dysfunction present at sepsis evaluation.

Outcomes

The principal diagnostic outcome of the study was culture-confirmed LOS, defined by a positive blood culture collected during the sepsis workup. The primary prognostic outcome was 7-day mortality following sepsis evaluation. The study was therefore designed to assess the relation of early PCT and nSOFA measurements to both microbiologically confirmed sepsis and short-term mortality risk in this high-risk preterm population. In addition, CRP was evaluated as an inflammatory marker alongside PCT, and gestational age was considered among the clinical variables examined in the prognostic analysis.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 26, together with Microsoft Excel 2019. Numerical variables were summarized as mean and standard deviation when normally distributed, or as median with range or interquartile range when non-normally distributed. Categorical variables were presented as frequencies and percentages. Normality of numerical data was assessed using the Kolmogorov–Smirnov test. For comparisons between two groups, Student's t-test was used for parametric data and the Mann–Whitney U test for non-parametric data. Categorical variables were compared using the chi-square test or exact tests when expected cell counts were less than 5. Correlation analysis was performed using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation coefficient otherwise. ROC curve analysis was performed to determine the diagnostic and prognostic performance of PCT, CRP, and nSOFA for sepsis, as well as gestational age, PCT, and nSOFA for mortality, and the AUC was reported. All statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

Results

Baseline demographic, anthropometric, laboratory, and nSOFA characteristics of the studied preterm neonates at sepsis evaluation are shown in **Table 1**.

Table 1: Baseline demographic, anthropometric, laboratory, and nSOFA characteristics of the studied

	Mean ±SD	Median (range)
GA (weeks)	30.77 ±2.15	31 (25.1 - 34.0)
Weight (g)	1552.79 ±380.26	1579 (730.0 - 2760.0)
Length (cm)	38.3 ±3.8	38.2 (29.4 - 50.0)
Head circumference (cm)	28.15 ±2.68	28 (20.6 - 39.0)
Total leukocyte count (×10³/µL)	8.61 ±4.05	7.8 (2.3 - 21.3)
Platelet count (×10³/µL)	232.28 ±112.77	221.5 (12.7 - 551.0)
Hemoglobin (g/dL)	15.96 ±26.84	14.4 (7.2 - 387.0)
C-reactive protein (mg/L)	5.56 ±3.25	4.6 (1.0 - 18.2)
Procalcitonin (ng/mL)	6.25 ±9.93	2.91 (0.09 - 90.77)
nSOFA score	5.5 ±3.27	5 (0.0 - 15.0)

GA: Gestational age, SD: Standard deviation, nSOFA: Neonatal Sequential Organ Failure Assessment.

Compared with survivors, neonates who died had significantly lower gestational age (29.14 vs. 31.15 weeks, $P < 0.001$) and significantly higher PCT levels (12.83 vs. 4.71, $P < 0.001$) and n-SOFA 1 scores (8.47 vs. 4.8, $P < 0.001$). Likewise, compared with neonates without sepsis, those with sepsis had significantly lower gestational age (30.26 vs. 31.14 weeks, $P = 0.003$) and significantly higher PCT levels (8.26 vs. 4.79, $P < 0.001$) and n-SOFA 1 scores (6.43 vs. 4.82, $P = 0.001$). **Table 2, Figure 1 A-B**

Table 2: Gestational age, procalcitonin, and nSOFA score according to mortality and sepsis outcomes

	Survivors (mean)	Deaths (mean)	Test	P-value
GA (weeks)	31.15	29.14	Mann-Whitney	**<0.001***
PCT1	4.71	12.83	Mann-Whitney	**<0.001***
n-SOFA 1	4.8	8.47	Mann-Whitney	**<0.001***
	No Sepsis (mean)	**Sepsis (mean)**	**Test**	**P-value**
GA (weeks)	31.14	30.26	Mann-Whitney	**0.003***
PCT1	4.79	8.26	Mann-Whitney	**<0.001***
n-SOFA 1	4.82	6.43	Mann-Whitney	**0.001***

n: number, GA: Gestational age, PCT1: Procalcitonin, n-SOFA 1: Neonatal Sequential Organ Failure Assessment, *: Significant P-value.

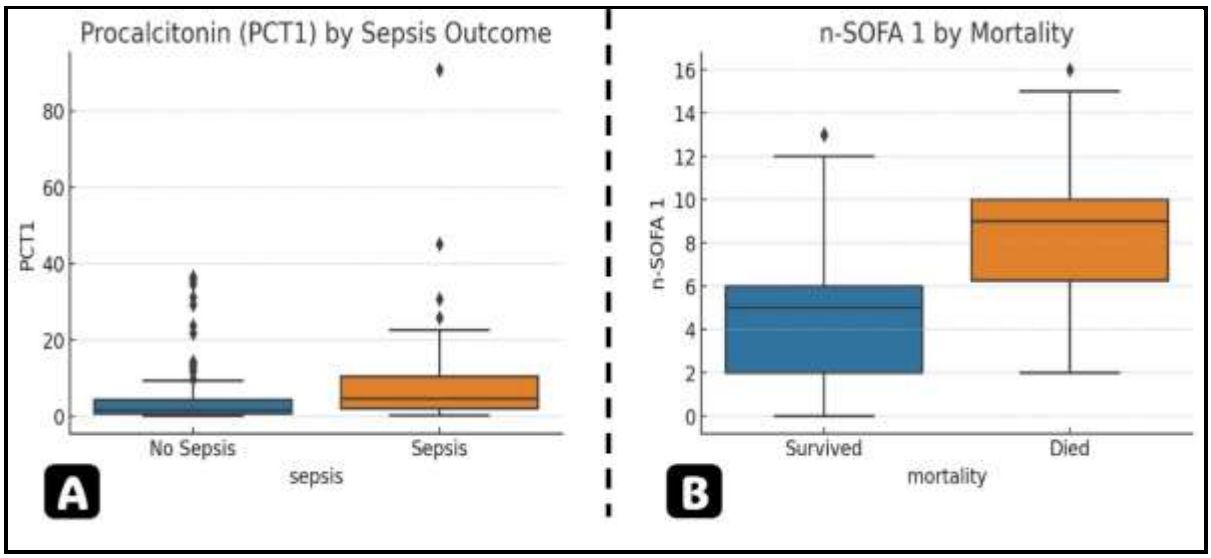

Figure 1: Procalcitonin and n-SOFA1 according to sepsis and mortality outcomes in preterm neonates: (A) PCT1 by sepsis outcome; (B) n-SOFA1 by mortality outcome

ROC curve analysis showed that PCT1 had the highest diagnostic performance for predicting culture-confirmed LOS (AUC = 0.69), followed by n-SOFA1 (AUC = 0.64) and CRP1 (AUC = 0.57). **Figure 2-A**

ROC curve analysis showed that n-SOFA1 had the highest prognostic performance for predicting 7-day mortality (AUC = 0.82), followed by gestational age (AUC = 0.78) and PCT1 (AUC = 0.77). **Figure 2-B**

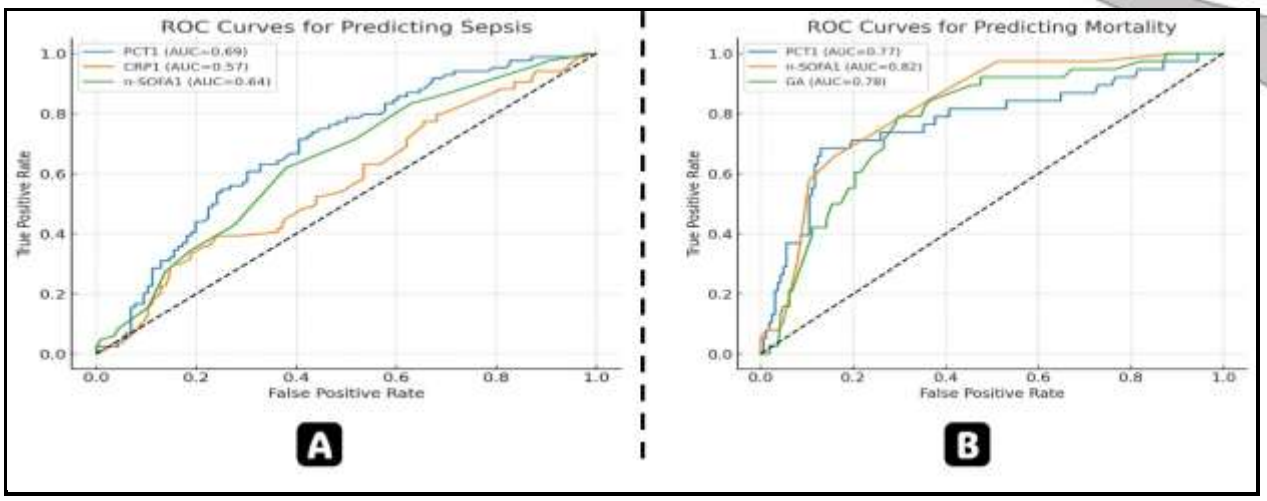

Figure 2: ROC curve analysis was performed for PCT1, CRP1, and n-SOFA1 to predict A) culture-confirmed LOS and B) 7-day mortality in preterm neonates

Among neonates without sepsis, PCT1 showed a significant positive correlation with n-SOFA1 (r = 0.45, P < 0.001), while gestational age showed a significant negative correlation with n-SOFA1 (r = -0.42, P < 0.001). Similarly, among neonates with sepsis, PCT1 was significantly positively correlated with n-SOFA1 (r = 0.47, P < 0.001), whereas gestational age was significantly negatively correlated with n-SOFA1 (r = -0.45, P < 0.001). **Table 3**

Among survivors, PCT1 also revealed a significant positive correlation with n-SOFA1 (r = 0.46, P < 0.001), and gestational age revealed a significant negative correlation with n-SOFA1 (r = -0.37, P < 0.001). Among deaths, PCT1 showed a significant negative correlation with CRP1 (r = -0.34, P = 0.036), and gestational age showed a significant negative correlation with n-SOFA1 (r = -0.35, P = 0.031). **Table 3**

Table 3: Correlation of procalcitonin, C-reactive protein, gestational age, and nSOFA score according to sepsis and mortality outcomes

	No Sepsis (n=116)		Sepsis (n=84)	
Pair	**r**	**P-value**	**r**	**P-value**
PCT1 vs n-SOFA1	0.45	**<0.001***	0.47	**<0.001***
PCT1 vs CRP1	0.01	0.9	-0.02	0.87
GA vs n-SOFA1	-0.42	**<0.001***	-0.45	**<0.001***
	Survivors (n=162)		**Deaths (n=38)**	
Pair	**r**	**P-value**	**r**	**P-value**
PCT1 vs n-SOFA1	0.46	**<0.001***	0.22	0.19
PCT1 vs CRP1	0.1	0.22	-0.34	**0.036***
GA vs n-SOFA1	-0.37	**<0.001***	-0.35	**0.031***

PCT1: Procalcitonin, n-SOFA1: Neonatal Sequential Organ Failure Assessment, CRP1: C-reactive protein, GA: Gestational age, r: Correlation coefficient, *: Significant P-value.

The logistic regression analysis demonstrated that procalcitonin (lnPCT1) was a significant independent predictor of sepsis among preterm neonates (OR = 1.56, 95% CI: 1.17–2.09, P = 0.003), indicating that each unit increase in lnPCT1 was associated with 56% higher odds of sepsis. **Table 4**

For mortality prediction, lower gestational age, higher n-SOFA score, and elevated lnPCT1 were all significant independent predictors. Specifically, lower gestational age was associated with lower odds of survival (OR = 0.75, P = 0.006), whereas both higher n-SOFA score (OR = 1.32, P = 0.001) and elevated lnPCT1 (OR = 1.80, P = 0.005) were associated with higher odds of death. Sepsis status itself was not an independent predictor of mortality after adjustment for these variables. **Table 4**

Table 4: Multivariable logistic regression analysis of predictors of culture-confirmed sepsis and 7-day mortality

	OR (95% CI)	P-value
Predictors of sepsis		
GA (weeks)	0.92 (0.79 - 1.08)	0.321
lnPCT1	1.56 (1.17 - 2.09)	**0.003***
lnCRP1	1.47 (0.84 - 2.58)	0.174
n-SOFA	1.06 (0.95 - 1.18)	0.316
Predictors of mortality		
GA (weeks)	0.75 (0.61 - 0.92)	**0.006***
n-SOFA 1	1.32 (1.12 - 1.55)	**0.001***
lnPCT1	1.80 (1.20 - 2.71)	**0.005***
Sepsis	0.83 (0.34 - 2.02)	0.686

OR: Odds ratio, CI: Confidence interval, GA: Gestational age, lnPCT1: Natural logarithm of procalcitonin, lnCRP1: Natural logarithm of C-reactive protein, n-SOFA 1: Neonatal Sequential Organ Failure Assessment, *: Significant P-value.

Kaplan–Meier survival curve shows the probability of survival over time among preterm neonates in the NICU. The survival probability declined sharply within the first two weeks, with most deaths occurring before day 15 of admission. Beyond this period, the survival curve plateaued, indicating that infants who survived the initial critical phase had a high chance of continued survival. the figure highlights that early mortality was concentrated in the first 10–15 days.

Figure 3: Kaplan–Meier survival curve according to mortality outcome among preterm neonates during NICU stay

Discussion

This study evaluated serum PCT and the neonatal Sequential Organ Failure Assessment score at the time of suspected LOS in preterm infants. PCT showed better diagnostic performance for culture-confirmed sepsis than C-reactive protein and was an independent predictor of confirmed infection, whereas nSOFA had a weaker diagnostic role for sepsis itself. In contrast, nSOFA was the strongest predictor of short-term mortality, outperforming both gestational age and PCT. Non-survivors had higher PCT levels and higher nSOFA scores than survivors, and both markers remained independent predictors of death after adjustment.

Our findings were consistent with those of Liu et al. [10], who found that PCT had strong diagnostic value in neonatal bacterial sepsis and performed better than CRP. They reported higher diagnostic accuracy than we observed, but the direction of the association was similar. Also, Beaumont et al. [11], found that PCT is a sensitive marker for neonatal infection, although its specificity varies across studies.

Likewise, Sofouli et al. [3] found that PCT is useful in neonatal sepsis assessment, but not sufficient as a standalone tool. This was in line with our finding that higher PCT values were independently associated with higher odds of culture-confirmed sepsis. Bianco et al. [12] also supported this interpretation, as they found that preterm infants require higher PCT cutoffs than term neonates. Tuoni et al. [13] further showed that even healthy very-low-birth-weight infants may have physiologically elevated PCT levels, which may partly explain the moderate diagnostic performance observed in our preterm cohort. Dongen et al. [14] also found that PCT was useful for identifying neonatal infection, supporting its overall diagnostic value.

In contrast, Park et al. [15] found that CRP outperformed PCT in their cohort, whereas in our study PCT performed better than CRP. This difference may be related to variation in patient characteristics or timing of sampling. Nguyen et al. [16] reported moderate diagnostic performance of PCT in early-onset sepsis that was closer to our findings, although their study differed in setting and sample type. The lower diagnostic accuracy in our study compared with some previous reports may also reflect differences in gestational age, baseline physiological PCT levels in preterm infants, and whether PCT was measured dynamically or at a single time point.

Our findings on mortality prediction were consistent with those of Wynn and Polin [17], who first showed that nSOFA at the time of LOS evaluation predicts death in very-low-birth-weight preterm infants. Their reported AUC at evaluation was close to that observed in our study, supporting the prognostic value of nSOFA at the time of clinical assessment. Our results were also in line with Fleiss et al. [6], who found that nSOFA had good to excellent discrimination for LOS-related mortality across multiple centers, and with Wynn et al. [5], who reported strong prognostic performance of nSOFA for NICU mortality in a large cohort. In our cohort, nSOFA showed the highest AUC for 7-day mortality and remained an independent predictor of death after adjustment, indicating that it captured the severity of organ dysfunction beyond gestational age alone. This interpretation was also supported by Flannery et al. [18], who found that LOS was associated with reduced survival in very preterm infants, a relationship likely mediated by the degree of organ dysfunction.

Our findings on PCT were also consistent with those of Rüetsch et al. [19], who found that higher PCT levels in preterm infants with LOS were associated with poor survival and showed useful prognostic discrimination for mortality. Similarly, in our study, non-survivors had higher PCT levels than survivors, and lnPCT remained an independent predictor of death. These findings support the prognostic relevance of early PCT elevation in preterm neonatal sepsis. Sofouli et al. [3] also emphasized that combining selected parameters may improve prediction in LOS, which is consistent with our observation that PCT and nSOFA provided complementary prognostic information.

In contrast, Wynn and Polin [17] focused on nSOFA without evaluating PCT as a mortality predictor. Our findings suggest that, in addition to organ dysfunction scoring, inflammatory biomarkers may add prognostic value during early assessment. Regarding sepsis diagnosis, our results differed from those of Park et al. [15], who found CRP to outperform PCT, whereas PCT performed better than CRP in our cohort. Liu et al. [10] reported higher diagnostic accuracy for PCT than we observed, which may reflect differences in pathogen classification or sampling strategy. Bianco et al. [12] and Tuoni et al. [13] showed that preterm infants have higher physiological PCT levels and may require higher thresholds than term neonates, which may explain the more modest diagnostic performance of PCT in our study.

Our findings on mortality prediction were consistent with those of Fleiss et al. [20] and Wynn and Polin [17], who reported good to excellent discrimination of nSOFA for mortality in preterm infants with LOS. The AUC observed in our study was within the range reported in these studies, supporting the value of nSOFA at the time of sepsis evaluation. Wynn et al. [5] also found that nSOFA predicted NICU mortality with high accuracy, which agrees with our

finding that nSOFA was the strongest predictor of short-term death. Our results were also consistent with Rüetsch et al. [19], who found that elevated PCT levels were associated with poor survival in preterm infants with LOS. In our cohort, non-survivors had higher PCT levels than survivors, and PCT remained an independent predictor of mortality.

In contrast, studies of early-onset sepsis and term neonates, such as Dongen et al. [14], reported lower PCT cutoffs and different diagnostic performance. These differences are likely related to differences in gestational age, baseline physiological PCT levels, timing of sampling, and the use of cord blood rather than peripheral samples obtained at the time of LOS evaluation. Differences in pathogen profile and maternal factors may also limit direct comparison between EOS studies and our preterm LOS cohort. In addition, our single-center design may have contributed to variation in observed thresholds and performance measures.

Our findings also build on previous work examining the clinical use of PCT and sepsis scoring systems. Stocker et al. [21] showed that PCT-guided strategies can safely reduce antibiotic exposure, while Sofouli et al. [3] concluded that no single LOS score is sufficient on its own. In the same context, our results suggest that PCT and nSOFA provide complementary information.

Our study had several strengths in comparison with previous reports. PCT and nSOFA were assessed in real time at the moment of sepsis evaluation, allowing both biomarkers to be examined simultaneously in the same clinical setting. In addition, unlike earlier studies that focused mainly on very-low-birth-weight infants, our cohort included a broader preterm population of less than 34 weeks' gestation. This wider inclusion supports the applicability of nSOFA and PCT beyond the most extreme degrees of prematurity.

However, the study also had also limitations to be acknowledged. The sample size was modest relative to large multicenter studies, which may limit generalizability. In addition, the single-center design may have introduced center-specific practice and laboratory effects.

Conclusions

At sepsis evaluation in preterm neonates, PCT was the strongest individual predictor of culture-confirmed LOS, whereas nSOFA was the best predictor of 7-day mortality. Combined assessment of inflammatory response and organ dysfunction may improve early bedside stratification in suspected LOS.

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