JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Prediction of mortality by nSOFA Score for late-onset sepsis in very low birth weight infants

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Abstract

Introduction: Sepsis is a major cause of morbidity and mortality in premature infants. Rapid diagnosis and initiation of treatment are of great importance. This study aims to evaluate the role of the Neonatal Sequential Organ Failure Assessment (nSOFA) score in predicting the causal agents and outcomes of late-onset sepsis in preterm neonates.

Methodology: In this single-center, retrospectively designed study, nSOFA scores of preterm infants born before 32 gestational weeks and weighing under 1500 g with a diagnosis of culture-proven late-onset sepsis (LOS) were compared at different timepoints in relation to mortality.

Results: Thirteen of 117 preterms included in the study died. At all the timepoints examined, the median nSOFA score was found to be higher in the mortality group (all $p < 0.001$). A 3.5 cutoff value of nSOFA showed the best differentiation, with AUC = 0.97 (95% CI: 0.94–1.00), 100% sensitivity, and 91.4% specificity. When nSOFA scores were compared in patients grouped as gram-positive sepsis and gram-negative sepsis, scores at T0, T6, T12, and T24 timepoints were determined to be significantly higher in the exitus group (all $p < 0.008$). In preterm infants born before 28 gestational weeks, mortality was predicted with the 3.5 cutoff value at T6, T12, T24, and T48 timepoints (AUC = 0.947, 0.943, 0.972, and 0.940, respectively, all $p < 0.001$).

Conclusions: The results showed that the nSOFA score is useful for predicting sepsis-related mortality in preterm infants and correlates with the severity of gram-negative sepsis.

Key words: Late onset sepsis; mortality; nSOFA; preterm.

J Infect Dev Ctries 2025; 19(12):1801-1808. doi:10.3855/jidc.21217

(Received 17 December 2024 – Accepted 04 June 2025)

Introduction

Sepsis is defined as "a life-threatening organ dysfunction caused by an irregular response of the host to infection" [1]. Late-onset sepsis (LOS) is defined as a clinical infection caused by specific micro-organisms, the clinical symptoms of which emerge at postnatal 3–30 days, and is a significant cause of morbidity and mortality in preterm infants [2,3]. The incidence of LOS has increased with the increase in survival of preterm infants, and it continues to be a global public health problem. Globally, infections are responsible for 40% of neonatal deaths [4]. LOS affects 20–30% of preterm infants and has a mortality rate of approximately 15% [5-7].

Preterm infants are at higher risk of LOS than term infants due to their insufficiently developed immune systems and the need for long-term care in the neonatal intensive care unit (NICU). However, as the clinical findings of sepsis in preterm infants are less distinctive, with limited sensitivity and specificity, diagnosis remains difficult [8,9]. When the long-term results are examined, LOS, prolonged hospitalization (average 3+ weeks), neurodevelopmental disorders, growth restriction, and very low birthweight (VLBW) lead to an increase of up to 24% in the mortality rate of newborns [10]. Therefore, a rapid diagnosis of sepsis is of critical importance to perform accurate interventions. The gold standard for diagnosis is confirmation of a pathogen by blood culture, but the inherent limitations in culture procedures cause delays in definitive diagnosis. The use of biomarkers (CRP, PCT, IL-6, etc.) may help the diagnosis, but despite previous research, an ideally definitive biomarker has not yet been established [11-13].

Moreover, as the survival rates of very small preterm infants have improved as a result of developments in the field of neonatal care, attempts have been undertaken to make more accurate and timely

diagnoses with different scoring systems that evaluate more than one parameter rather than a single biomarker. Although there are many scoring systems for the evaluation of mortality risk of sepsis, there are limitations to the existing scoring systems, and their ability to predict mortality has been shown to be insufficient in recent cohorts. Therefore, a new scoring system is needed [14].

The Sequential Organ Failure Assessment (SOFA) score, which evaluates the severity of organ dysfunction, has been used for a long time to evaluate the risk of ICU admission and mortality, with proven validity in both children and adults. In recent years, it has been adapted for newborn infants using hematological, cardiovascular, and respiratory parameters, but it has not yet been established in routine practice [1,15]. Studies on the use of nSOFA scores in neonatal practice are relatively recent [16-19]. This study aims to demonstrate the suitability of the nSOFA as a scoring system for predicting the septic agent and mortality in sepsis, a significant cause of morbidity and mortality in preterm infants born at < 32 weeks gestational age (GA) and weighing < 1500 g. Additionally, the predictive value of nSOFA for mortality in preterm infants born before 28 weeks of GA was examined separately.

Methodology

This retrospective, single-center, case-control study was approved by the Clinical Research Ethics Committee of a university hospital (protocol no: 2011-KAEK-25 2023/04-08). The study included premature infants born < 32 weeks GA and weighing < 1500 g who were diagnosed with LOS in the NICU of a tertiary-level university hospital between January 2019 and March 2023. The use of the nSOFA score in the prediction of sepsis agents and mortality in preterm infants was evaluated.

Infants born before 32 weeks of gestation with a birth weight of < 1500 g, a culture-proven diagnosis of sepsis at > 72 hours and < 30 days of age, and a CRP level higher than 10 mg/L (to exclude contamination in cases with gram-positive blood culture) were included in the study [20]. Patients with major congenital malformations, metabolic disease, genetic disease, or incomplete data were excluded. Sepsis was defined using EMA (European Medicines Agency) scores, but only culture-proven sepsis cases were included. For patients with more than one sepsis episode, the first episode was included in the study. The primary outcome of the study was the occurrence of death during treatment for LOS. The secondary outcome was the ability of the nSOFA score to predict the causal agent of sepsis.

The nSOFA score uses only objective and existing clinical care standard data to detect organ dysfunction, which facilitates the classification of mortality risk in VLBW infants with confirmed LOS. The nSOFA score points range from 0 to 15, where 0 is the best. The nSOFA score uses three subscores for respiratory, cardiovascular, and hematological components to define dynamic changes objectively: i) the need for invasive ventilation and oxygen treatment (score range, 0–8), ii) the need for inotropic support including the use of corticosteroids (for suspicion of adrenal failure or catecholamine-resistant shock) (score range, 0–4), and iii) the presence and severity of thrombocytopenia (score range, 0–3) (Table 1). The time of sepsis evaluation was defined as the time of blood culture collection before starting empirical treatment in the presence of a clinical suspicion of sepsis. The timepoints were defined as 6 (T−6), 12 (T−12), 24 (T−24), and 48 (T−48) hours before drawing blood culture, and the time of the culture (T0) and 6 (T6), 12 (T12), 24 (T24), and 48 (T48) hours after drawing the blood culture. The nSOFA score with clinical and laboratory data was calculated at nine timepoints, before and after the disease, during treatment, and at death.

Table 1. Neonatal Sequential Organ Failure Assessment (nSOFA) Components and Scoring.

Respiratory Score	**0**	**2**	**4**	**6**	**8**
Criteria	Not-intubated or intubated; $SpO_2/FiO_2 \geq 300$	Intubated $SpO_2/FiO_2 < 300$	Intubated $SpO_2/FiO_2 < 200$	Intubated $SpO_2/FiO_2 < 150$	Intubated $SpO_2/FiO_2 < 100$
Cardiovascular Score	**0**	**1**	**2**	**3**	**4**
Criteria [a]	No inotropes, no systemic steroids	No inotropes, systemic steroids treatment	One inotrope, no systemic steroids	At least two inotropes or one inotrope and systemic steroids	At least two inotropes and systemic steroids
Hematologic Score	**0**	**1**	**2**	**3**	
Criteria[b]	Platelet count ≥ 150 × 10^9/L	Platelet count 100-149 × 10^9/L	Platelet count < 100 × 10^9/L	Platelet count < 50 × 10^9/L	

FiO_2: fraction of inspired oxygen; SpO_2: oxygen saturation as measured bypulseoxymetry. [a] Medications considered asinotropic or vasoactive included dopamine, dobutamine, epinephrine, norepinephrine, vasopressin, milrinone, and phenylephrine; [b] Most recent platelet count available to the clinician.

Statistical Analysis

Differences between groups were compared using the Mann–Whitney U-test for continuous data and the chi-square test for categorical data. As the variables were non-parametric, median and interquartile range (IQR, 25th–75th percentile) values were used. In all the analyses, a value of $p < 0.05$ was accepted as the level of statistical significance. Receiver operating characteristic (ROC) curve analysis was used to calculate the cutoff points and the sensitivity and specificity values of the nSOFA scores in predicting mortality. The point at which sensitivity and specificity provided 95% confidence intervals was determined to be the optimal cutoff value. These analyses were performed using SPSS v. 23.0. In the comparisons of the ROC curves, MedCalc Statistical Software v. 19.2.6 was used, and for the violin plots visualization, the DATAtab Online Statistics Calculator was used.

Results

Throughout the defined study period, 457 preterm infants were admitted to the ICU and examined for eligibility. Following the implementation of the study inclusion and exclusion criteria, 117 preterm infants with a diagnosis of sepsis were included in the study. Thirteen of these cases died. The detailed flow chart of the patients included in the study is shown in Figure 1. The gestational age and birthweight of the cases with mortality were found to be lower than those of the survivors. The demographic characteristics of the patients are shown in Table 2.

When the clinical characteristics of the groups were compared, there was no significant difference in the duration of invasive mechanical ventilation ($p > 0.05$). The duration of non-invasive mechanical ventilation and total parenteral nutrition (TPN) was found to be longer in the survivors group ($p < 0.001$ for both). Renal failure was more frequent in the non-survivors ($p = 0.029$). Gram-negative sepsis was found in 9 (69.2%) and Candida in 1 (7.7%) of the cases that died. In the survivors group, gram-negative sepsis was determined in 15 (14.4%) cases and *Candida* in 2 (1.9%). The IVH (Intraventricular hemorrhage) rate was higher in the non-survivors group ($p < 0.001$), and PVL (Periventricular leukomalacia) was more frequent in the survivors group ($p = 0.047$). The length of stay in the NICU was longer in the survivors group ($p < 0.001$). The clinical characteristics of the patients are shown in Table 3.

Figure 1. Patients' Selection.

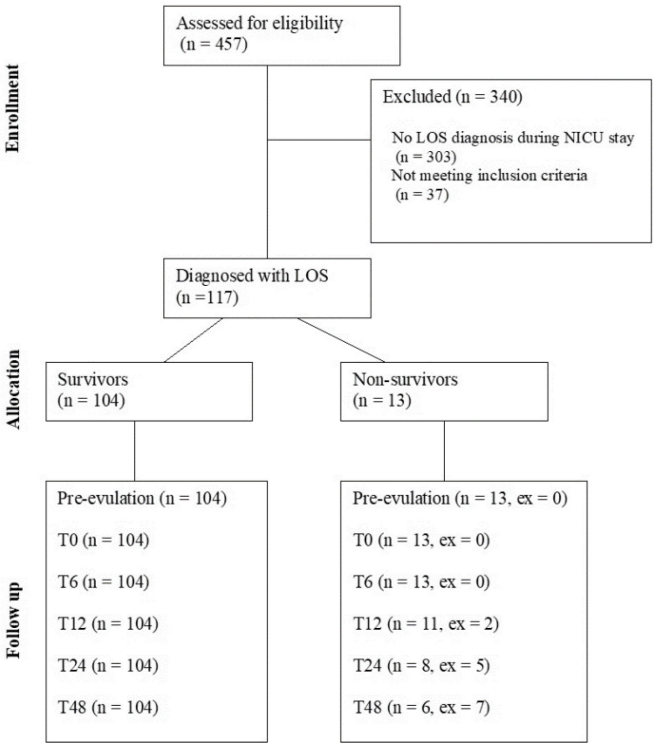


Table 2. Neonatal and Maternal Characteristics of the Study Groups.

	All infants (n = 117)	Survivors (n = 104)	Non-survivors (n = 13)	*p*
Birth weight, *median (IQR)*	870 (742-1070)	905 (755-1126)	780 (550-825)	**0.011**[b]
Gestational age, *median (IQR)*	27 (25-29)	27 (26-29)	24 (23-26)	**< 0.001**[b]
Female Gender *(n,%)*	50 (42.7)	44 (42.3)	6 (46.2)	> 0.99[a]
Cesarean delivery (n,%)	110 (94)	99 (95.2)	11 (84.6)	0.17[a]
Race, Refugee (n,%)	20 (17.1)	17 (16.3)	3 (23.1)	0.70[b]
Apgar Score 1 min, *median (IQR)*	6 (5-7)	6 (5-7)	5 (3-6)	**0.048**[b]
Apgar Score 5 min, *median (IQR)*	8 (6-8)	8 (7-9)	7 (6-8)	0.14[b]
IUGR *(n,%)*	36 (30.7)	34 (32.7)	2(15.4)	0.34[b]
Mother's age, *median (IQR)*	28 (24-33)	28 (24-33)	28 (24-33)	0.94[a]
Multiparity, *(n,%)*	71 (87)	64 (61.5)	7 (53.8)	0.76[b]
Twins, *(n,%)*	21 (17.9)	16 (15.4)	5 (38.5)	0.06[b]
Maternal disease, (n,%)	40 (34.2)	38 (36.5)	2 (15.4)	0.13[b]
PPROM, *(n,%)*	11 (9.5)	8 (7.8)	3 (23.1)	0.11[b]
Antenatal Steroids				
None (n,%)	25 (21.4)	20 (19.2)	5 (38.5)	
Single Course (n,%)	32 (27.4)	30 (28.8)	2 (15.4)	0.24[b]
Repeat Course (n,%)	60 (51.3)	54 (51.9)	6 (46.2)	

[a] Chi-square test; [b] Mann Whitney-U test (IQR: Inter Quantile Range; IUGR: Intrauterine growth restriction; PPROM: Preterm premature rüptüre of membranes).

Table 3. Clinical Characteristics of the Infants.

	All infants (n = 117)	Survivors (n = 104)	Non-survivors (n = 13)	*p*
Mechanical Ventilation (PTV, HFOV), *median (IQR)*	10 (4-30)	10 (3-39)	9 (7-16)	0.83[b]
Non-invasive Mechanical Ventilation, *median (IQR)*	14 (4-30)	17 (7-31)	0 (0-1)	**< 0.001**[b]
TPN, *median (IQR)*	22 (16-38)	26 (17-41)	10 (8-17)	**< 0.001**[b]
Oliguria/anuria, *(n,%)*	7 (6)	4 (3.8)	3 (23.1)	**0.029**[a]
Pathogens				
Gram positives (n,%)	90 (76.9)	87 (83.7)	3 (23.1)	
Gram negatives (n,%)	24 (20.5)	15 (14.4)	9 (69.2)	**< 0.001**[a]
Fungi (n,%)	3 (2.6)	2 (1.9)	1 (7.7)	
RDS, *(n,%)*	91 (77.8)	79 (76)	12 (92.3)	0.29[a]
PDA, *(n,%)*	72 (61.5)	63 (60.6)	9 (69.2)	0.55[a]
IVH, *(n,%)*	20 (17.1)	12 (11.5)	8 (61.5)	**< 0.001**[a]
Hidrocefalia*, *(n,%)*	11 (9.4)	10 (9.6)	1 (7.7)	> 0.99[a]
PVL, *(n,%)*	47 (40.9)	45 (44.1)	2 (15.4)	**0.047**[a]
NEC, *(n,%)*	12 (10.3)	10 (9.6)	2 (15.4)	0.52[a]
NICU, *median (IQR)*	63 (43-88)	67 (49-91)	11 (8-17)	**< 0.001**[b]

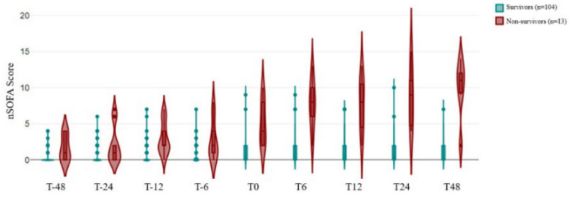
[a] Chi-square test; [b] Mann Whitney-U test; * Posthemorrhagic hydrocephalus. PTV Patient-triggered Ventilation; HFOV: High Frequency Oscillatory Ventilation; IQR: Inter Quantile Range; TPN: Total parenteral nutrition; RDS: Respiratory distress syndrome; PDA: Patent ductus arteriosus; IVH: Intraventricular hemorrhage; PVL: Periventricular leukomalacia; NEC: Necrotizing enterocolitis; NICU: Neonatal Intensive Care Unit.

The median values of the total nSOFA score at all time points before and after LOS evaluation were found to be significantly higher in the non-survivors group [T−48: 0 (quartiles 0, 0) vs. 1 (0, 4); T−24: 0 (0, 0) vs. 1 (0, 4); T−12: 0 (0, 0) vs. 2 (0, 5);T−6: 0 (0, 2) vs. 2 (0, 6); T0: 0 (0, 2) vs. 4 (2, 8); T6: 1 (0, 2) vs. 8 (5, 10); T12: 1 (0, 2) vs. 8 (4, 11); T24: 1 (0, 2) vs. 9 (4, 13); T48: 1 (0, 3) vs. 11 (7, 13); all $p < 0.001$]. In the nSOFA subscores, the pulmonary nSOFA score was found to be significantly higher in the non-survivors group at all timepoints ($p < 0.001$ for all). The predictive power of the nSOFA scores for mortality was examined at all timepoints with ROC curve analysis, and the best differentiation was seen at T24 ($p < 0.001$).

The scores at the T−24 and T−6 timepoints were not significantly predictive ($p = 0.13$ and $p = 0.22$,

Figure 2. Neonatal sequential organ failure assessment (nSOFA) total scores survivors and nonsurvivors. **A.** Total nSOFA scores; **B.** ROC curves of nSOFA scores at time points with a difference in mortality; **C.** Sensitivity, specificity and cut-off scores of nSOFA scores predicting mortality.

A.



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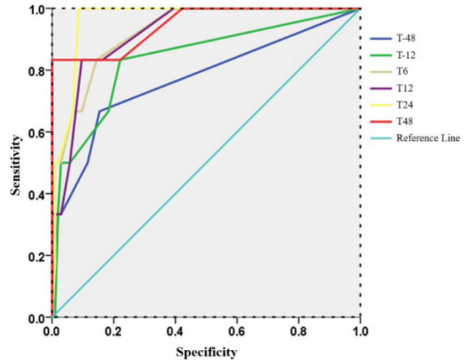
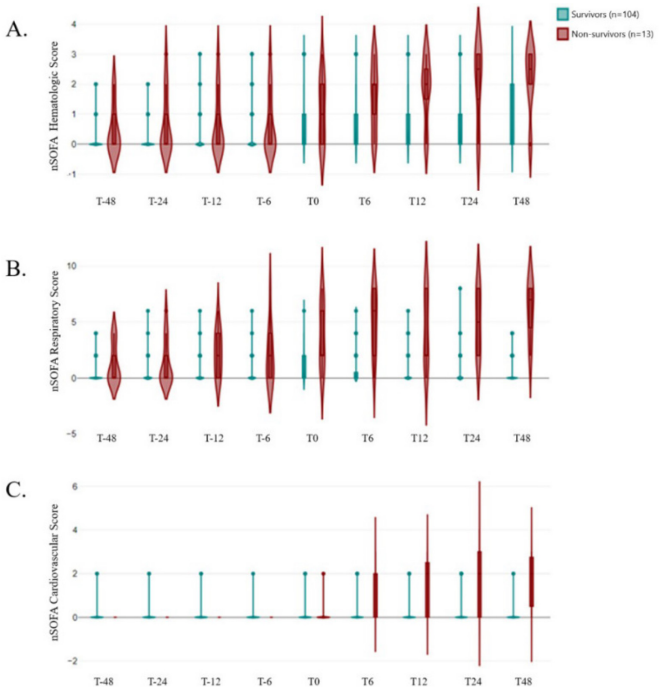


C.

	Cut-off	Sensitivite	Specificity	p value	AUC (95% CI)
T-48	0.5	0.615	0.846	0.027	0.74 (0.58-0.91)
T-12	0.5	0.923	0.779	<0.001	0.87 (0.77-0.97)
T0	2.5	0.692	0.865	<0.001	0.90 (0.82-0.97)
T6	3.5	0.923	0.856	<0.001	0.96 (0.91-1.00)
T12	3.5	0.909	0.904	0.001	0.96 (0.90-1.00)
T24	3.5	1.000	0.913	<0.001	0.97 (0.94-1.00)
T48	3.5	0.833	0.885	<0.001	0.95 (0.85-1.00)

Figure 3. Components of nSOFA score for survivors and nonsurvivors. **A.** Hematologic component; **B.** Respiratory component; **C.** Cardiovascular component.



respectively). At the T24 timepoint, a 3.5 cutoff value of the nSOFA score predicted mortality with 100% sensitivity, 91.3% specificity, and an AUC of 0.97 (95% 0.94–1.00, $p < 0.001$) (Figure 2). In the nSOFA subscores, the hematological nSOFA score was found to be significantly higher at all timepoints in the non-survivors group ($p < 0.05$ for all). The nSOFA cardiological subscore was not significantly different before and at the time of sepsis evaluation (all $p > 0.05$). Scores after the diagnosis of sepsis (T6, T12, T24, T48) were significantly higher in the non-survivors group ($p < 0.001$ for all timepoints). The changes in the nSOFA subscores are shown in Figure 3. The most significant subscore with respect to mortality was the pulmonary subscore. When the differences between the timepoints (delta-Δ) were examined, the most significant difference with respect to mortality was found to be between T–12 and T12 (Figure 4) ($p < 0.001$). The changes in the nSOFA scores before, after, and during sepsis evaluation are shown in Table 3. The mortality rate was found to be higher as the nSOFA scores increased (Figure 5).

The patients were grouped as gram-negative and gram-positive, and no significant difference was determined in the nSOFA scores before the sepsis evaluation (all $p > 0.05$). At the T0, T6, T12, and T24 timepoints, the scores were significantly higher in the non-survivors group [T0: 0 (0, 2) vs. 2 (0, 5); T6: 0 (0, 2) vs. 2 (0, 7); T12: 0 (0, 2) vs. 2 (0, 7); T24: 0 (0, 2) vs. 2 (0, 5); all $p < 0.05$].

When examined according to gestational age, 63.2% of the patients were born at < 28 weeks, and 16.2% of these died during LOS treatment. As the mortality rate was significantly higher in those born at < 28 weeks ($p < 0.05$), the differences in nSOFA scores were examined in these patients as a subgroup. The nSOFA scores were found to be significantly higher in the mortality group at all timepoint [T−48: 0 (0, 0) vs. 2 (0, 4); T−24: 0 (0, 0) vs. 2 (0, 5); T−12: 0 (0, 1) vs. 2 (2, 6); T−6: 0 (0, 2) vs. 2 (0,6); T0: 0 (0, 2) vs. 4 (2, 8); T6: 1 (0, 2) vs. 8 (5, 10); T12: 1 (0, 2) vs. 8 (4, 11); T24: 1 (0, 2) vs. 9 (4, 13); T48: 1 (0, 3) vs. 11 (7, 13); all $p < 0.05$]. When this subgroup was evaluated with ROC curve analysis, the nSOFA score with a cutoff point of 3.5 predicted mortality at the timepoints of T6, T12, T24, and T48 (AUC = 0.947, 0.943, 0.972, and 0.940, respectively, all $p < 0.001$.

Figure 4. Change in nSOFA score infection episode survivors and nonsurvivors. **A.** Change in nSOFA pre-evaluation; **B.** Change in nSOFA post-evaluation; **C.** Change in nSOFA peri-evaluation (all p>0.005).

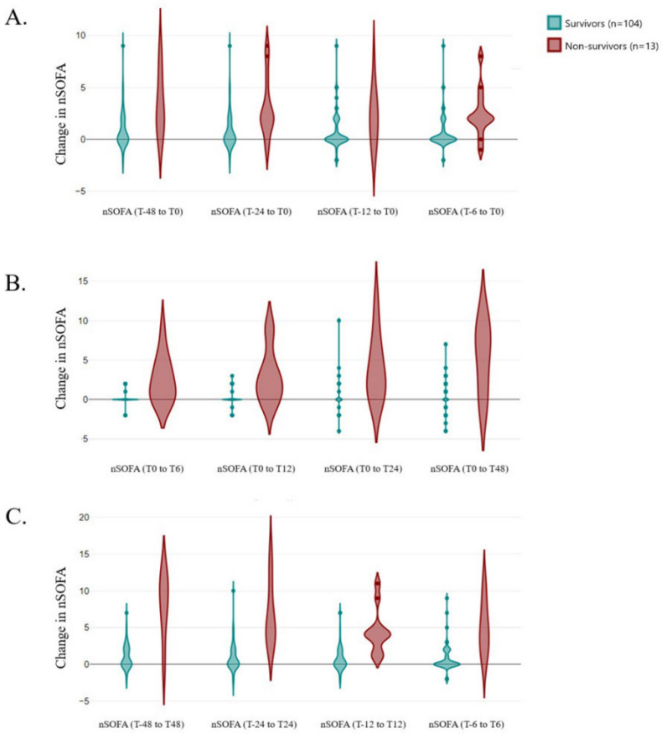
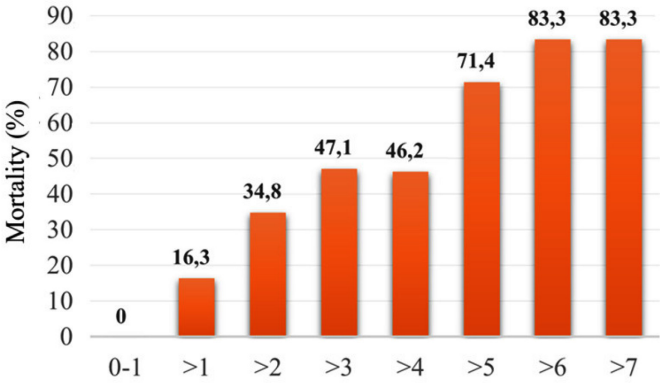


Figure 5. Mortality risk based on the nSOFA score at T24 hours.



Discussion

As a result of developments in NICU practices, very low birth weight preterm infants can now survive, but despite all these advances and innovations, sepsis remains one of the leading causes of morbidity and mortality [11]. Although microorganism proliferation in culture remains the gold standard for the diagnosis of sepsis, attempts have been made to perform more accurate and timely diagnoses with various scoring systems that evaluate several parameters rather than a single biomarker. There are many scoring systems for evaluating the risk of mortality in sepsis, but there are limitations related to the available scoring systems, and according to recent studies, these methods are insufficient. Thus, a new scoring system is needed [14].

This study aimed to establish the role of the nSOFA score, which is a new scoring system, in the prediction of mortality and the causal agent of sepsis, which is a significant problem in newborn infants. The study showed that at all the timepoints examined, the nSOFA score was higher in the preterm infants diagnosed with LOS who died, and that a cutoff value of 3.5 predicted mortality at the timepoints of T6, T12, T24, and T48. The majority of the non-survivors died within the first 48 hours, so predicting mortality risk quickly after diagnosis is crucial. Among these findings, the T24 timepoint was determined to have the greatest accuracy. The clinical characteristics of the patients are compared in Table 3. The duration of hospitalization and TPN was significantly longer in surviving patients. However, the shorter duration of these parameters in deceased patients reflects early mortality and not clinical well-being. Therefore, a comparison of these parameters may not accurately reflect clinical status or prognosis and should be interpreted with caution. In addition, the nSOFA score could predict gram-negative sepsis with a cutoff value of 3.5 at the T12 and T24 timepoints.

In a recent study that used the nSOFA score for the first time in VLBW preterm infants, except for 6 hours before sepsis, the nSOFA score was found to be significantly higher at all the other timepoints in cases with mortality [19]. Another study with preterm infants diagnosed with sepsis showed that the nSOFA scores were found to be higher in the mortality cases at all the timepoints except 24 hours before sepsis [21]. A higher nSOFA score in patients who developed mortality was also reported at all timepoints in another study [16,18].

Some researchers have also used the nSOFA score to predict mortality for causes other than sepsis. When the maximum nSOFA scores were compared throughout the first 28 days for all infants in the NICU, the maximum nSOFA score was determined to be higher in patients with all-cause mortality [22]. Another study evaluated nSOFA scores in patients who died due to necrotizing enterocolitis (NEC) and found that the scores of the patients who died were higher from the time of NEC diagnosis until 48 hours after, but there was no difference before the evaluation [23]. While previous studies mostly reported high nSOFA scores only at or near the time of death, our study showed that nSOFA scores were significantly higher at all time points evaluated in patients with exitus. This finding suggests that the nSOFA score can be used as a strong and consistent prognostic indicator throughout the entire sepsis process.

In the current study, the ROC curve analysis was used to calculate cutoff values for the risk of mortality at timepoints where the score was found to be significantly higher in exitus cases. Wynn *et al.* reported that mortality was higher in preterm infants with an nSOFA score > 4 at the T6 and T12 timepoints [19]. Fleiss *et al.* found the highest AUC value of 0.86 at T12 in a study of preterm infants diagnosed with sepsis [16]. Poggi *et al.* compared the SIRS and nSOFA scores and determined the highest AUC value of 0.91 at T12, and the cutoff value was calculated as 4 [17]. One single-center study reported 0.92 as the highest AUC value at the T48 timepoint [21]. Another study found the highest AUC value to be 0.92 at T24, and a cutoff value of 3.5 [18]. In a study by Lewis *et al.* of preterm infants diagnosed with NEC, it was reported that, similar to studies of premature infants with sepsis, there was an increased risk of surgery and mortality in preterm infants with NEC with an nSOFA score ≥ 4 at 12 hours after NEC diagnosis (AUC = 0.96) [23]. Unlike previous studies, which have usually reported cutoff values around 4, this study showed that a lower cutoff value of 3.5 effectively predicted mortality at early time points, such as T6, T12, T24, and T48. The highest prognostic accuracy was obtained at time point T24 (AUC = 0.97, $p < 0.001$). This AUC value is higher than the values reported in previous literature, emphasizing the higher predictive power and clinical relevance of our findings and supporting and extending the existing evidence on the prognostic value of the nSOFA score. Given that the majority of deaths occur within the first 48 hours, this earlier and sensitive threshold offers an important advance for timely clinical intervention and risk stratification in very low birth weight premature infants with sepsis.

The diagnosis of sepsis is a challenging process, even in term infants. As the clinical condition of sepsis is more difficult to diagnose in preterm infants, this makes clinical management more difficult [8,9]. Moreover, sepsis mortality increases as the GA decreases [11]. It is important to find markers that can detect sepsis and predict the clinical course in very small preterm infants. In a study that compared the usability of the nSOFA score in preterm infants of different GAs, sub-analyses of the < 25-week GA preterm infants showed that the nSOFA score was higher in those who did not survive [16]. To examine whether the nSOFA could be used safely in extremely preterm infants, a subgroup was formed in the current study with patients < 28 weeks GA, and the nSOFA scores were compared again between the surviving and non-surviving patients in this group. Furthermore, mortality was predicted with high accuracy, with a cutoff value of 3.5. To our knowledge, this is one of the

few studies to demonstrate the prognostic value of the nSOFA score with such sensitivity in this vulnerable subgroup of extremely preterm patients, supporting and extending previous findings with stronger evidence.

In a previous study that examined the change in nSOFA according to the sepsis agent, it was shown that nSOFA could predict mortality regardless of the agent [16]. When the sepsis agents were examined in the current study, gram-negative sepsis was observed more frequently in the patients who died. In evaluating the efficacy of the nSOFA score, the scores were found to be significantly higher in gram-negative sepsis at the timepoints of T0, T6, T12, and T24. These results show for the first time that the nSOFA score correlates with severity in gram-negative sepsis in infants with LOS. These findings suggest that the nSOFA score is not only a prognostic tool; it also has the potential to help differentiate between gram-negative and gram-positive agents.

In the current study, separate evaluations were performed for pulmonary, hematological, and cardiovascular scores, which are the subscores of the nSOFA scoring system. Wynn *et al.* reported that the most significant changes occurred in the pulmonary subscore [19]. In a study by Husain *et al*., it was seen that all the subscores increased over time, but the most important change for the cases that did not survive occurred in the pulmonary and cardiovascular subscores [24]. In another study, the pulmonary score was found to be the most determinant marker, and the cardiovascular score was seen to increase continuously from beginning to end [25]. The results of the current study showed that the pulmonary and hematological subscores were higher at every time point, and the cardiovascular subscore was higher at T6, T12, T24, and T48. In addition, the most significant change in the nSOFA score was in the pulmonary subscore at the T12, T24, and T48 timepoints.

Thrombocytopenia is an important component of the nSOFA score and has been identified in the literature as an independent and strong risk factor for sepsis-related mortality in VLBW neonates. Thrombocytopenia in neonatal sepsis is associated with systemic inflammation, endothelial activation, and coagulopathy. Immaturity of the immune and coagulation systems in neonates may predispose them to the rapid progression of these processes. Pulmonary dysfunction is an early sign of sepsis-related organ failure, leading to respiratory failure due to capillary leakage, surfactant dysfunction, and inflammatory lung injury [26]. The prominence of these two parameters in our findings supports the fact that they are early markers of systemic deterioration in sepsis and explains their prognostic value in the nSOFA score.

There were some limitations to this study, primarily the single-center, retrospective design with a relatively low number of patients. Although the number of patients with mortality was low relative to the patient population, the results were consistent with those of many other studies, and this provides a certain amount of reliability with respect to generalizability, despite the low numbers. To reduce uncertainty about the deaths of the patients, as the study was retrospective, only patients with a positive culture were examined. However, recurrent infections per patient were excluded to avoid confusion. Due to the low number of patients, the nSOFA scores could not be compared according to the infection's region of origin.

As a strength, only preterm infants diagnosed with culture-positive LOS were included, so other prematurity-associated morbidities to which suspected infection could be attributed were excluded, and only preterm infants with a cause of death secondary to infection were evaluated. That all the patients were in the same center and followed up with the same protocols and similar care and treatment also ensured that the study group was more homogenous and that the nSOFA score was evaluated clearly.

Conclusions

The study results showed that the nSOFA score is a significant marker of sepsis-related mortality in preterm infants. To the best of our knowledge, this is the first study in the literature to have shown that the nSOFA score correlates with severity in gram-negative sepsis in infants with LOS. It was also shown that it can be safely used in extremely preterm infants.

Authors' Contributions

SY, IGV, AO, and GT participated in the planning of this study. SY, IGV participated in the data collection and reporting, reading, and approving the final manuscript. EGG, OB, participated in the data analysis.

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Conflict of interest

No conflict of interest is declared.

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