

# Early- vs. Late-Onset Neonatal Sepsis: The Predictive Role of Hemoglobin, Delivery Mode, and Inflammatory Indices

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## ABSTRACT

**Purpose:** To identify maternal, perinatal, and neonatal factors distinguishing early-onset sepsis (EOS) from late-onset sepsis (LOS).

**Methods:** This retrospective study included 74 neonates with sepsis (April 2022 and April 2025) with complete maternal laboratory data. EOS was defined as  $\leq 72$  h ( $n=34$ ) and LOS as  $> 72$  h ( $n=40$ ). Maternal/perinatal variables, neonatal laboratory parameters (including hemoglobin), and inflammatory indices [neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio, systemic immune-inflammation index (SII), systemic inflammation response index, pan-immune-inflammation value] were compared. Predictors were assessed using logistic regression and receiver operating characteristic (ROC) analysis.

**Results:** Cesarean delivery, in vitro fertilization, and maternal antibiotic use were more frequent in LOS ( $p<0.05$ ). EOS infants had lower gestational age (195.5 vs. 267 days,  $p<0.001$ ) and birth weight (1210 vs. 3200 g,  $p<0.001$ ). Maternal hemoglobin did not differ ( $p=0.140$ ), whereas neonatal hemoglobin was significantly lower in EOS (17.5 vs. 18.7 g/dL,  $p<0.001$ ). CRP, white blood cell count, and neutrophils were higher in LOS. Among indices, only NLR and SII were elevated in LOS ( $p=0.025$ ,  $p=0.009$ ). In multivariate analysis, neonatal hemoglobin [odds ratio (OR)=0.707, 95% confidence interval (CI): 0.553-0.904,  $p=0.006$ ] and vaginal delivery (OR=0.068, 95% CI: 0.007-0.632,  $p=0.018$ ) independently predicted EOS. ROC of neonatal hemoglobin showed moderate discrimination (AUC=0.741) with a cut-off of 17.5 g/dL (sensitivity 82.4%, specificity 50.0%).

**Conclusion:** Neonatal hemoglobin and delivery mode independently predicted EOS, whereas NLR and SII were higher in LOS. Simple clinical and hematologic parameters may help differentiate sepsis timing.

**Keywords:** Neonatal sepsis, early-onset, late-onset, hemoglobin, inflammatory indices

## INTRODUCTION

Neonatal sepsis remains an important health challenge worldwide and continues to result in poor outcomes, despite considerable advances in intensive care.<sup>1</sup> Clinically, it is typically categorized as early-onset sepsis (EOS), defined as infection within the first 72 hours of life, and late-onset sepsis (LOS), which develops thereafter.<sup>2</sup> EOS is commonly related to vertical transmission from the mother, premature rupture of membranes, or complications occurring around delivery, whereas LOS is generally attributed to hospital-acquired infections, invasive medical procedures, and prolonged stays in neonatal units.<sup>3,4</sup>

Recognized risk factors include prematurity, low birth weight, extended rupture of membranes, and maternal infections.<sup>5,6</sup> A wide range of biomarkers including C-reactive protein (CRP), procalcitonin (PCT), and various interleukins, have been extensively investigated for the early detection of sepsis.<sup>7,8</sup> However, most previous studies have focused primarily on differentiating septic neonates from healthy controls, with limited evidence addressing the temporal distinction between EOS and LOS.<sup>9,10</sup>

Recent studies have explored multiple hematologic and inflammatory parameters to improve diagnostic discrimination.<sup>11</sup> Demonstrated that CRP, PCT, and interleukin-6



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levels differ substantially between EOS and LOS, with higher inflammatory responses in LOS. Yin et al.<sup>12</sup> and Eichberger and Resch<sup>13</sup> further showed that indices derived from routine blood counts, including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) may serve as adjunctive indicators for sepsis subtype differentiation. Similarly, Gatseva et al.<sup>14</sup> reported that the combination of PCT with hematologic ratios improved accuracy in predicting sepsis onset timing. Collectively, these findings highlight growing interest in the use of accessible inflammatory indices for distinguishing sepsis subtypes, although results remain inconsistent and require further validation.

Recent evidence suggests that other hematological parameters may provide additional value. Lungu et al.<sup>15</sup> reported that septic neonates had significantly lower hemoglobin compared to healthy controls. Moreover, in adult sepsis populations, lower hemoglobin has been linked to adverse outcomes.<sup>16</sup> Despite these insights, the predictive role of neonatal hemoglobin and basic obstetric factors, such as mode of delivery in distinguishing EOS from LOS has not been adequately investigated.<sup>17,18</sup> Therefore, the aim of this study was to identify maternal, perinatal, and neonatal predictors that distinguish EOS from LOS in neonates, with particular emphasis on the roles of neonatal hemoglobin levels, delivery mode, and inflammatory indices.

## METHODS

### Study Design and Population

This study used a retrospective cohort design at Okan University Hospital and involved neonates admitted to the neonatal intensive care unit between April 2022 and April 2025. Newborns diagnosed with sepsis were included. Cases were classified into two groups: (EOS,  $\leq 72$  h of life) and (LOS,  $> 72$  h of life). Neonates with major congenital anomalies, chromosomal abnormalities, or incomplete medical records were excluded.

### Diagnostic Criteria for Sepsis

Sepsis was defined according to clinical signs (respiratory distress, temperature instability, feeding intolerance, lethargy, hypotonia, seizures) combined with at least one abnormal laboratory finding (abnormal white blood cell count, elevated CRP or PCT) and/or a positive blood culture, in line with international consensus definitions.<sup>1,2</sup>

### Maternal and Perinatal Data

Maternal variables included age, presence of preeclampsia, gestational diabetes mellitus, in vitro fertilization (IVF) pregnancy, prolonged premature rupture of membranes ( $\geq 18$  h), and intrapartum antibiotic use. Obstetric characteristics recorded were mode of delivery and gestational age at birth. Inflammatory indices were calculated as follows:

- $NLR = \text{neutrophil count} / \text{lymphocyte count}$
- $PLR = \text{platelet count} / \text{lymphocyte count}$

- $SII = (\text{platelet} \times \text{neutrophil}) / \text{lymphocyte}$
- Systemic inflammation response index (SIRI) =  $(\text{neutrophil} \times \text{monocyte}) / \text{lymphocyte}$
- Pan-immune-inflammation value (PIV) =  $(\text{neutrophil} \times \text{platelet} \times \text{monocyte}) / \text{lymphocyte}$ .

### Neonatal Data

Neonatal variables included birth weight, Apgar scores, hemoglobin levels, bilirubin, glucose, CRP, and PCT levels at admission. Based on established literature, CRP and PCT thresholds of  $>5$  mg/L and  $>2$  ng/mL, respectively, were considered clinically significant for neonatal sepsis.<sup>7,8</sup>

### Outcome Measures

The primary outcome was to identify independent predictors of EOS versus LOS. Secondary analyses included comparison of maternal, neonatal, and inflammatory indices between the two groups.

### Ethics Statement

The study was conducted at Okan University Hospital. However, at the time of study initiation, the Okan University Clinical Research Ethics Committee was not yet operational. Therefore, ethical approval was obtained from the Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 829, date: 17.07.2025) to ensure compliance with ethical standards. Data collection and analysis were entirely performed at Okan University Hospital. The study was conducted in accordance with the Declaration of Helsinki.

### Statistical Analysis

All analyses were performed using SPSS, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Data are presented as mean  $\pm$  standard deviation or median (interquartile range) as appropriate. Continuous variables were compared between EOS and LOS groups using either the Student's t-test or the Mann-Whitney U test, depending on distribution, whereas categorical variables were analyzed with chi-square or Fisher's exact tests.

To assess associations between clinical or laboratory factors and sepsis onset, univariate logistic regression was first applied. Variables meeting a significance threshold of  $p < 0.10$  were subsequently included in the multivariate regression model. Results are summarized as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). For significant laboratory predictors, receiver operating characteristic (ROC) curve analysis was performed, and the area under the curve (AUC), sensitivity, and specificity are presented. A  $p$ -value  $< 0.05$  was considered statistically significant.

### Sample Size and Power

This retrospective study was based on all eligible cases admitted during the study window; therefore, an a priori sample size calculation was not performed. Instead, we conducted a

post hoc sensitivity analysis to quantify the detectable effect with the available sample (EOS n=34 vs. LOS n=40; total n=74). For a two-sided  $\alpha=0.05$  and 80% power, this available sample provided sensitivity to detect a standardized mean difference of approximately  $d\approx0.65$  between groups (e.g., for hematologic variables such as neonatal hemoglobin). In line with our primary model, events-per-variable considerations also support parsimony in multivariable logistic regression ( $\approx34$  events for EOS), justifying inclusion of a limited number of independent predictors. We report this as a feasibility-driven retrospective cohort with post hoc sensitivity rather than a priori power (Software: G\*Power 3.1.).

RESULTS

Baseline Characteristics

A total of 74 neonates with sepsis were included, of whom 34 (45.9%) had EOS and 40 (54.1%) had LOS. Maternal and obstetric characteristics are presented in Table 1. Cesarean delivery was more frequent in the LOS group compared with EOS (95.0% vs. 76.5%,  $p=0.037$ ). IVF pregnancies (20.0% vs. 0%,  $p=0.006$ ) and intrapartum maternal antibiotic use (30.0% vs. 5.9%,  $p=0.015$ ) were also more common in LOS. Maternal age, preeclampsia, and gestational diabetes did not differ significantly between groups.

Clinical and Laboratory Findings

Blood culture results were available in 56 neonates (75.7%). Among these, 25 (44.6%) had positive cultures. The most commonly isolated microorganisms were *Staphylococcus epidermidis* (n=12), *Klebsiella pneumoniae* (n=8), and *Escherichia coli* (n=5). The remaining 31 culture-negative

cases were diagnosed based on compatible clinical and laboratory findings, as per the study criteria. Neonatal clinical and laboratory parameters are shown in Table 2. Median gestational age (267 vs. 195.5 days,  $p<0.001$ ) and birth weight (3200 g vs. 1210 g,  $p<0.001$ ) were higher in EOS compared with LOS. White blood cell count ( $p=0.015$ ) and neutrophil count ( $p=0.002$ ) were higher in LOS. Neonatal hemoglobin levels were higher in EOS (18.7 vs. 17.5 g/dL,  $p<0.001$ ). CRP values were higher in LOS ( $p=0.037$ ). Length of hospital stay was longer in LOS (20 vs. 8 days,  $p<0.001$ ).

Inflammatory Indices

Among inflammatory indices, NLR and SII were higher in LOS ( $p=0.025$  and  $p=0.009$ , respectively), while PLR, SIRI, and PIV showed no significant differences between groups (Table 3).

Multivariate Logistic Regression

Variables entered into the multivariate logistic regression model included gestational age, birth weight, neonatal hemoglobin, and mode of delivery. Neonatal hemoglobin (OR=0.707, 95% CI: 0.553-0.904,  $p=0.006$ ) and vaginal delivery (OR=0.068, 95% CI: 0.007-0.632,  $p=0.018$ ) were identified as independent predictors of EOS. Gestational age and birth weight were not significant in the adjusted model. The model accuracy was 86.5% with a Nagelkerke  $R^2$  of 0.595, and the Hosmer-Lemeshow test yielded a  $p$  value of 0.018.

ROC Curve Analysis

ROC analysis of neonatal hemoglobin showed an AUC of 0.741 for predicting EOS. The optimal cut-off value was 17.5 g/dL, corresponding to a sensitivity of 82.4% and a specificity of 50.0% (Table 4).

Table 1. Maternal and obstetric characteristics of neonates with early- and late-onset sepsis			
Variable	Early-onset (n=34)	Late-onset (n=40)	p value
ASA use, n (%)	2 (5.9)	0 (0)	0.208
Mode of delivery (C/S), n (%)	26 (76.5)	38 (95.0)	0.037*
IVF pregnancy, n (%)	0 (0)	8 (20.0)	0.006**
Preeclampsia, n (%)	2 (5.9)	8 (20.0)	0.097
Gestational DM, n (%)	4 (11.8)	8 (20.0)	0.528
PPROM > 18 h, n (%)	4 (11.8)	12 (30.0)	0.088
Maternal antibiotic use, n (%)	2 (5.9)	12 (30.0)	0.015*
Discharge status (exitus), n (%)	6 (17.6)	14 (35.0)	0.119
* $p<0.05$ ; ** $p<0.01$ . Categorical variables were compared using the $\chi^2$ test or Fisher's exact test, as appropriate IVF: In vitro fertilization, PPRM: Preterm premature rupture of membranes, DM: Diabetes mellitus, ASA: Acetylsalicylic acid			

**Table 2. Neonatal clinical and laboratory findings in early- and late-onset sepsis**

Variable	Early-onset sepsis (n=34) median (IQR)	Late-onset sepsis (n=40) median (IQR)	p value
Gestational age (days)	267 (236-268)	195.5 (182-236)	<0.001*
White blood cell ( $\times 10^3/\mu\text{L}$ )	11.4 (9.0-12.1)	13.0 (10.0-17.5)	0.015*
Neutrophil ( $\times 10^3/\mu\text{L}$ )	10.9 (8.8-12.0)	13.9 (10.8-17.3)	0.002*
Platelet ( $\times 10^3/\mu\text{L}$ )	216.9 (155-278)	218.3 (185-264)	0.862
Maternal hemoglobin (g/dL)	12.4 (10.9-13.0)	11.1 (10.0-12.4)	0.140
Prothrombin time (sec)	14.4 (13.6-15.0)	14.3 (12.8-16.5)	0.811
aPTT (sec)	27.8 (24.9-29.3)	24.7 (22.3-30.3)	0.233
INR	1.11 (1.02-1.20)	1.08 (0.95-1.27)	0.572
Infant weight (g)	3200 (2700-3400)	1210 (1000-2000)	<0.001*
Neonatal hemoglobin (g/dL)	18.7 (17.2-21.5)	17.5 (15.0-19.0)	<0.001*
Fetal bilirubin (mg/dL)	10.0 (6.7-12.1)	7.9 (5.6-11.0)	0.224
Fetal glucose (mg/dL)	56 (45-79)	64 (48-94)	0.460
Fetal CRP (mg/L)	3.7 (0.7-13.7)	10.9 (1.7-25.9)	0.037*
Procalcitonin (ng/mL)	2.8 (1.1-5.9)	2.4 (0.7-6.0)	0.508
Length of hospital stay (days)	8 (6-9)	20 (13-27)	<0.001*

\* $p < 0.05$  continuous variables are presented as median (interquartile range) and were compared using the Mann-Whitney U test  
CRP: C-reactive protein, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, IQR: Interquartile range

**Table 3. Comparison of inflammatory indices between early- and late-onset sepsis**

Variable	Early-onset sepsis (n=34) median (IQR)	Late-onset sepsis (n=40) median (IQR)	p value
Neutrophil-to-lymphocyte ratio (NLR)	4.5 (3.6-5.3)	8.2 (4.8-11.0)	0.025*
Platelet-to-lymphocyte ratio (PLR)	108.8 (93-132)	130.1 (97-214)	0.108
Systemic immune-inflammation index (SII)	977 (704-1277)	1224.5 (919-2735)	0.009*
Systemic inflammation response index (SIRI)	2.88 (1.8-3.9)	2.25 (1.3-4.8)	0.680
Pan-immune-inflammation value (PIV)	566.4 (372-809)	462.8 (298-811)	0.965

\* $p < 0.05$  continuous variables are presented as median (interquartile range) and were compared using the Mann-Whitney U test  
IQR: Interquartile range

**Table 4. ROC analysis of neonatal hemoglobin for predicting early-onset sepsis**

Cut-off (g/dL)	Sensitivity (%)	Specificity (%)	Youden index
14.95	94.1	15.0	0.09
17.15	82.4	45.0	0.27
17.75	76.5	60.0	0.37
18.55	52.9	75.0	0.28

ROC: Receiver operating characteristic

## DISCUSSION

By examining a cohort of septic neonates, we identified distinct maternal, perinatal, and laboratory patterns separating EOS from LOS cases. Our findings demonstrate that neonatal hemoglobin and mode of delivery were independent predictors of EOS, while gestational age and birth weight, though significant in univariate analyses, lost predictive value in the adjusted model. In addition, LOS was characterized by higher NLR and SII values, suggesting distinct inflammatory patterns.

The predominance of cesarean delivery in LOS and the association of vaginal delivery with EOS in our study reflect differences in transmission routes. EOS is primarily linked to vertical maternal transmission at birth, whereas LOS typically reflects hospital-acquired infections and the influence of invasive procedures.<sup>19,20</sup> The association between mode of delivery and sepsis onset timing may be explained by differences in exposure pathways. EOS typically results from vertical transmission of maternal microorganisms during vaginal delivery or after membrane rupture, whereas LOS is



more often related to nosocomial pathogens acquired during hospitalization.<sup>20</sup> The higher frequency of cesarean births in the LOS group in our cohort supports this pattern. Previous studies have shown that *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are among the most frequent causative agents of late-onset, hospital-acquired sepsis following surgical deliveries and prolonged neonatal intensive care.<sup>21,22</sup> These findings collectively suggest that delivery mode may indirectly influence the timing and microbiological profile of neonatal sepsis.

Neonatal hemoglobin emerged as another key predictor, with lower levels associated with EOS. Lungu et al.<sup>15</sup> recently demonstrated that hemoglobin, together with ferritin and lactate dehydrogenase levels, could serve as predictive markers for neonatal sepsis in general. Our results extend this evidence, showing that hemoglobin also plays a role in distinguishing sepsis timing. In adult critical care, anemia has been consistently associated with poor outcomes in sepsis.<sup>16,23</sup> The mechanisms may involve impaired oxygen delivery, reduced host immunity, and bone marrow suppression. In neonates, lower hemoglobin at birth may reflect intrauterine stress, prematurity, or suboptimal erythropoiesis, all of which predispose to EOS.

Gestational age and birth weight, classical risk factors for sepsis, showed strong associations in univariate analyses but lost significance in multivariate models. This is likely due to collinearity between the two variables, as also reported in previous neonatal sepsis cohorts.<sup>9</sup> Importantly, our model retained high discriminative accuracy (86.5%), suggesting that hemoglobin and delivery mode provide sufficient independent predictive power.

Inflammatory indices, particularly NLR and SII, were elevated in LOS. Similar findings have been described in adult and pediatric sepsis, where elevated NLR and SII are markers of systemic inflammation and worse prognosis.<sup>24,25</sup> In neonates, however, the published evidence is limited, and our study contributes novel evidence linking these indices specifically to LOS. This suggests that LOS may involve a more pronounced systemic inflammatory response, potentially related to prolonged hospital exposure and nosocomial pathogens.

### Clinical implications

Our results have several implications. Recognizing hemoglobin levels and delivery route as predictors of EOS underlines the potential of basic, widely accessible parameters for early clinical risk assessment. The ROC-derived cut-off for hemoglobin (~17.5 g/dL), although falling within the normal range, provides a clinically applicable threshold for identifying neonates at higher risk of EOS. Third, the elevation of NLR and SII in LOS suggests that inflammatory indices may have adjunctive value in guiding differential diagnosis once sepsis is established.

### Study Limitations

Strengths of this study include the comprehensive evaluation of maternal, perinatal, and neonatal parameters within a single cohort and the use of multiple statistical approaches,

including both logistic regression and ROC analyses. However, several limitations should be acknowledged. The retrospective, single-center design and relatively small sample size limit the generalizability of our findings. Furthermore, although the multivariate logistic regression model achieved good discriminative accuracy, its calibration was suboptimal (Hosmer-Lemeshow  $p=0.018$ ), indicating a potential limitation in model fit. Blood culture confirmation was not available for all cases, and the diagnosis of sepsis was therefore based on a combination of clinical and laboratory findings. Future prospective multicenter studies with larger populations and microbiological validation are warranted to confirm these results.

## CONCLUSION

Neonatal hemoglobin level and delivery mode were identified as independent markers distinguishing EOS from LOS in neonates, whereas elevated NLR and SII values characterized LOS cases. These readily available parameters may provide clinicians with preliminary guidance for risk stratification and early management decisions. Nevertheless, given the limited sample size and retrospective design, these findings should be interpreted with caution and validated in larger prospective studies.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from the Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 829, date: 17.07.2025).

**Informed Consent:** Due to the retrospective nature of the study and the use of anonymized data obtained from routine medical records, the requirement for written informed consent was waived by the Ethics Committee.

### Authorship Contributions

Surgical and Medical Practices: G.K., E.C.N.K.Y., Ş.B., Concept: G.K., Design: G.K., E.C.N.K.Y., Data Collection or Processing: E.C.N.K.Y., Ş.B., Analysis or Interpretation: G.K., Literature Search: E.C.N.K.Y., Ş.B., Writing: G.K., E.C.N.K.Y., Ş.B.

### Footnotes

**Conflict of Interest:** No conflict of interest was declared by the authors.

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