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COMPARISON OF HEMATOLOGICAL PARAMETERS BETWEEN EARLY AND LATE-ONSET NEONATAL SEPSIS: A CROSS-SECTIONAL STUDY

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Abstract-
Introduction- Neonatal sepsis, a major cause of neonatal morbidity and mortality, is categorized into early-onset and late-onset based on timing. Hematological parameters serve as crucial diagnostic tools. This study compares hematological profiles in early- and late-onset neonatal sepsis to identify distinguishing features and support improved diagnosis and management strategies.
Material and method- This hospital-based cross-sectional study was conducted from January 2023 to December 2023 and included 120 neonates diagnosed with sepsis—70 with early-onset sepsis (EOS) and 50 with late-onset sepsis (LOS). Blood samples were collected aseptically and analyzed using automated hematology analyzers. Hematological parameters were compared between groups. Data were processed using SPSS version 20, and a p-value <0.05 was considered statistically significant.

Result- In present study neonates with EOS had significantly higher gestational age and birth weight. Hematologically, EOS was characterized by significantly lower total leukocyte and neutrophil counts, elevated immature-to-total neutrophil (I/T) ratio, and more frequent thrombocytopenia. Conversely, LOS presented with more leukocytosis. EOS was predominantly caused by Escherichia coli and Klebsiella pneumoniae, while LOS by Klebsiella pneumoniae, Staphylococcus aureus, and coagulase-negative staphylococci. Respiratory distress was more prevalent in EOS, while poor feeding was more common in LOS. Risk factors for EOS included prolonged rupture of membranes and maternal fever, while LOS was linked to low birth weight and invasive procedures.

Conclusion- This study underscores the hematological differences between EOS and LOS, highlighting their distinct etiologies and immune responses. Recognizing these profiles aids early diagnosis, supports targeted therapy, and informs screening and antibiotic stewardship for improved neonatal outcomes.

Keywords- Neonates, LOS, EOS, Hematological, Sepsis etc.

Introduction-

Neonatal sepsis is a significant cause of morbidity and mortality in neonates, particularly in low- and middle-income countries. It is defined as a systemic infection occurring in the neonatal period and is categorized into early-onset sepsis (EOS) and late-onset sepsis (LOS) based on the timing of onset, with EOS occurring within the first 72 hours of life and LOS after 72 hours. [1] The clinical manifestation of neonatal sepsis is often nonspecific, with symptoms such as poor feeding, lethargy, respiratory distress, and abnormal temperature regulation, which can overlap with other neonatal conditions, making diagnosis challenging.[2] EOS is typically acquired through vertical transmission during labor and delivery, with pathogens such as Group B Streptococcus, Escherichia coli, and Listeria monocytogenes being the most common culprits.[3] On the other hand, LOS is often a result of horizontal transmission, frequently associated with nosocomial infections acquired in neonatal intensive care units (NICU) or due to invasive medical procedures, and is commonly caused by organisms such as Staphylococcus aureus and coagulase-negative staphylococci.[1,4] Understanding the distinct mechanisms and clinical features of EOS and LOS is critical in tailoring effective management strategies.

Hematological parameters are frequently utilized to aid in the diagnosis of neonatal sepsis, as alterations in these indices can reflect systemic infection. Key hematological markers include total leukocyte count (TLC), absolute neutrophil count (ANC), platelet count, and red blood cell indices, which can provide valuable insights into the underlying pathophysiology of sepsis.[5] Studies have shown that EOS is often associated with an elevated white blood cell count, neutrophilia, and a high immature-to-total neutrophil (I/T) ratio, reflecting the body's acute immune response to infection.[2] In contrast, LOS may present with a more complex hematological profile, including thrombocytopenia, neutropenia, and low or normal white blood cell counts, indicating a delayed immune response or a chronic inflammatory state.[6] While there is significant literature on neonatal sepsis, comparative studies on hematological distinctions between EOS and LOS are relatively limited. Few studies have explored how hematological indices differ between these two categories of sepsis, with existing research focusing primarily on isolated markers or specific pathogens.[7,8] A deeper understanding of these distinctions may enhance diagnostic accuracy and enable clinicians to tailor interventions more effectively based on the timing of sepsis onset. Hence this study was planned to compare the hematological profiles of neonates with EOS and LOS to identify key differences that may help in making diagnostic and therapeutic strategies. By exploring these hematological markers in greater detail, we aim to improve early detection, reduce delays in treatment, and ultimately improve neonatal outcomes.

Material and Method-

This study was a cross-sectional, hospital-based analysis conducted at Department of Pediatrics, Rama Medical College and Hospital, Hapur, India between January 2023 and December 2023. The primary aim was to compare the hematological profiles of neonates with early-onset sepsis (EOS) and late-onset sepsis (LOS), focusing on differences in hematological parameters to better understand the underlying pathophysiology of each condition. The study was conducted following ethical approval from the Institutional Ethics Committee (IEC) and informed written consent was obtained from the parents or guardians of the neonates enrolled in the study. Patient confidentiality was maintained, and all data were anonymized prior to analysis. A total of 120 neonates were included in the study, divided into two groups: 70 neonates with EOS (Group A) and 50 neonates with LOS (Group B). Neonates were categorized based on the onset of sepsis, with EOS diagnosed when symptoms of sepsis manifested within the first 72 hours of life and LOS diagnosed when symptoms occurred after 72 hours.[1]

Diagnosis of sepsis was based on clinical signs, laboratory findings, and positive blood culture for a pathogenic organism, with the identification of the causative pathogen done using standard microbiological techniques. The study focused on common pathogens associated with EOS, such as

Group B Streptococcus and Escherichia coli, and with LOS, including Staphylococcus aureus and coagulase-negative staphylococci.[2] Inclusion criteria for the study were neonates born at term (≥37 weeks gestation), admitted to the hospital within 24 hours of birth, and diagnosed with either EOS or LOS Exclusion criteria included neonates with congenital anomalies, perinatal asphyxia, multiple gestations, those requiring blood transfusions or receiving medications or any condition that could affect hematological indices. Mothers with any chronic systemic diseases, infections, hypertension, diabetes mellitus, or autoimmune disorders were excluded from the study.

Maternal and neonatal demographic and clinical data were collected using a pretested structured proforma. Maternal information included age, parity, gestational age at delivery, history of any complications, and mode of delivery (vaginal or cesarean). Neonatal data included birth weight, Apgar scores at 1 and 5 minutes, sex, need for neonatal intensive care unit (NICU) admission, and any associated comorbidities, such as intrauterine growth restriction (IUGR) or neonatal respiratory distress syndrome (RDS). Hematological analyses were performed on blood samples collected from the neonates immediately after birth, prior to the initiation of any antibiotic therapy. A blood sample of 2 mL was drawn aseptically from the umbilical vein and placed into an EDTA vial for complete blood count (CBC) analysis. Hematological parameters assessed included hemoglobin concentration (g/dL), hematocrit (%), total leukocyte count (TLC) (cells/mm^3), absolute neutrophil count (ANC) (cells/mm^3), platelet count (lakh/mm^3), red cell indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), reticulocyte count (%) and nucleated red blood cell (nRBC) count per 100 WBC. These parameters were chosen as they reflect the immune response and hematological status of the neonate during sepsis. Type of organisms isolated were also detected. The samples were processed within two hours of collection using an automated hematology analyzer, and the results were interpreted using gestation-appropriate reference ranges as outlined by Christensen and Henry.[9]

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20. Descriptive statistics were used to summarize maternal and neonatal characteristics, as well as hematological parameters. The independent sample t-test was employed to compare means of continuous variables between the two groups (EOS vs. LOS), and the chi-square test was used to analyze categorical variables. A p-value of <0.05 was considered statistically significant. Subgroup analyses were performed to evaluate any potential differences based on the severity of sepsis and the identified pathogens.

Result-

A total of 120 neonates diagnosed with sepsis were enrolled in the study, comprising 70 (58.3%) with early-onset sepsis (EOS) and 50 (41.7%) with late-onset sepsis (LOS). Table 1 shows the baseline characteristics of neonates and their mothers. The mean gestational age of neonates with EOS was significantly higher (36.2±2.4weeks) compared to those with LOS (34.8±3.1 weeks) (p=0.041). Similarly, birth weight was significantly greater in the EOS group (2,650±410 grams) than in the LOS group (2,480±460 grams) (p=0.038). However, there was no statistically significant difference in the male-to-female ratio between the two groups (1.3:1 in EOS vs. 1.4:1 in LOS; p=0.781). An Apgar score at 5minutes <7 was observed in 25.7% of EOS cases and 30.0% of LOS cases, with no significant difference (p=0.604). Regarding maternal characteristics, the mean maternal age was comparable between groups (25.8±4.3 years in EOS vs. 26.4±4.7 years in LOS; p=0.481). There were no significant differences between the groups in terms of urinary tract infection during pregnancy (20.0% vs. 14.0%; p = 0.412), hypertensive disorders of pregnancy (17.1% vs. 16.0%; p= 0.867), or gestational diabetes mellitus (7.1% vs. 6.0%; p=0.813). However, intrapartum antibiotic use was significantly more frequent among mothers of neonates with EOS (38.6%) compared to those with LOS (18.0%) (p=0.011)

Table 1-Neonatal and maternal baseline characteristics

Characteristic	Early-Onset Sepsis (n = 70)	Late-Onset Sepsis (n = 50)	p-value
Gestational Age (weeks)	36.2 ± 2.4	34.8 ± 3.1	0.041
Birth Weight (grams)	2,650 ± 410	2,480 ± 460	0.038
Male:Female Ratio	40:30 (1.3:1)	29:21 (1.4:1)	0.781
Apgar Score at 5 min < 7	18 (25.7%)	15 (30.0%)	0.604
Maternal Age (years)	25.8 ± 4.3	26.4 ± 4.7	0.481
UTI in Pregnancy	14 (20.0%)	7 (14.0%)	0.412
Hypertension in Pregnancy	12 (17.1%)	8 (16.0%)	0.867
Gestational Diabetes Mellitus	5 (7.1%)	3 (6.0%)	0.813
Intrapartum Antibiotic Use	27 (38.6%)	9 (18.0%)	0.011

A comparison of hematological parameters between early-onset sepsis (EOS) and late-onset sepsis (LOS) is shown in Table 2. The mean total leukocyte count was significantly lower in neonates with EOS (10,200±3,150/mm³) compared to those with LOS (13,400±3,670/mm³) ($p<0.001$). Similarly, the absolute neutrophil count was significantly reduced in the EOS group (3,800±1,250/mm³) compared to the LOS group (6,100±1,530/mm³) ($p<0.001$). Conversely, the immature-to-total neutrophil (I/T) ratio was significantly higher in EOS cases (0.29±0.08) than in LOS (0.22±0.06) ($p=0.013$). The mean platelet count was lower in the EOS group (143,500±42,800/mm³) compared to the LOS group (165,700±48,300/mm³), with statistical significant ($p=0.027$) difference. Thrombocytopenia was more frequent in EOS (41.4%) than LOS (26.0%) ($p=0.048$). There was no significant difference in hemoglobin levels (14.6±1.8 g/dL in EOS vs. 14.3±2.1g/dL in LOS; $p=0.418$) or mean corpuscular volume (MCV) (108.2±7.6 fL in EOS vs. 109.1±8.2fL in LOS; $p=0.581$). Blood culture positivity was observed in 44.3% of EOS cases and 54.0% of LOS cases, but the difference was not statistically significant ($p=0.292$).

Table 2: Comparison of hematological parameters between early-onset and late-onset neonatal sepsis

Parameter	Early-Onset Sepsis (n = 70)	Late-Onset Sepsis (n = 50)	p-value
Total Leukocyte Count (/mm³)	10,200 ± 3,150	13,400 ± 3,670	<0.001
Absolute Neutrophil Count (/mm³)	3,800 ± 1,250	6,100 ± 1,530	<0.001
I/T Neutrophil Ratio	0.29 ± 0.08	0.22 ± 0.06	0.013
Platelet Count (/mm³)	143,500 ± 42,800	165,700 ± 48,300	0.027
Thrombocytopenia (%)	41.4%	26.0%	0.048
Hemoglobin (g/dL)	14.6 ± 1.8	14.3 ± 2.1	0.418
MCV (fL)	108.2 ± 7.6	109.1 ± 8.2	0.581
Blood Culture Positivity (%)	44.3%	54.0%	0.292

Figure 1 depicts the distribution of organisms isolated from blood cultures in early-onset and late-onset sepsis. Among neonates with early-onset sepsis (EOS), gram-negative organisms were predominant. Escherichia coli (17.1%) and Klebsiella pneumoniae (14.3%) were the most frequently isolated pathogens, followed by Pseudomonas aeruginosa (4.3%). Gram-positive organisms such as Staphylococcus aureus (5.7%), coagulase-negative staphylococci (2.9%), and Group B Streptococcus (8.6%) were less common. No fungal isolates were found in EOS cases. In LOS, Klebsiella pneumoniae (24.0%) remained the most common isolate, followed by Staphylococcus aureus (18.0%), coagulase-negative staphylococci (14.0%), and Pseudomonas aeruginosa (10.0%). Escherichia coli accounted for 8.0% of isolates, while Group B Streptococcus was identified in only 2.0% of cases. Notably, fungal pathogens (Candida spp.) were isolated in 6.0% of LOS cases but were absent in EOS. Overall, 58 out of 120 neonates (48.3%) had a positive blood culture, with slightly higher positivity in LOS (54.0%) compared to EOS (44.3%).

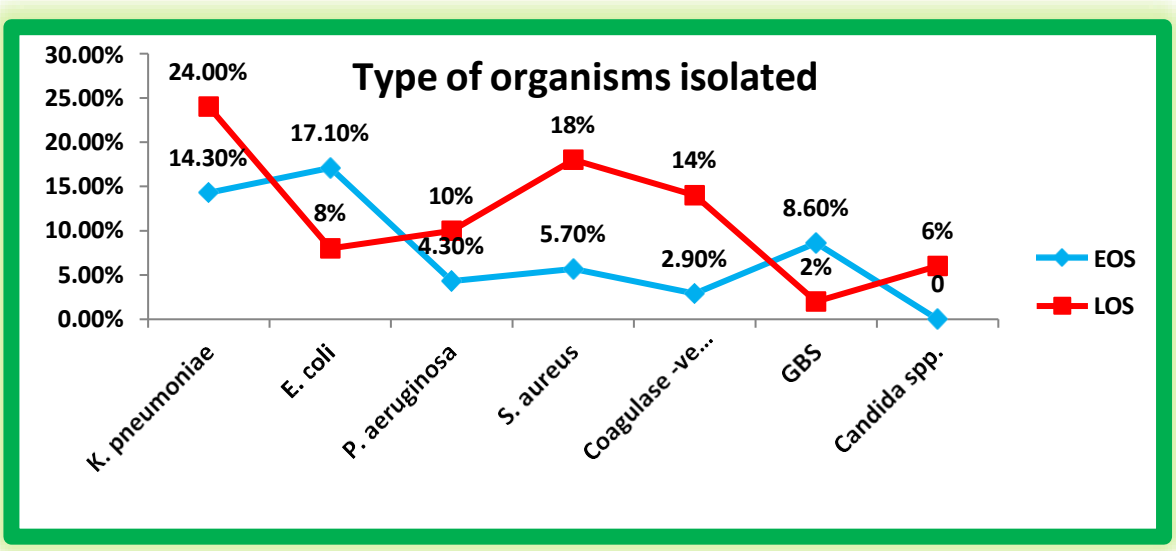

Figure 1- Type of organisms isolated in EOS and LOS

The distribution of hematological abnormalities between early-onset sepsis (EOS) and late-onset sepsis (LOS) is presented in figure 2. Leukopenia, defined as a total leukocyte count <5,000/mm³, was significantly more frequent in the EOS group (25.7%) compared to the LOS group (12.0%) (p=0.048). In contrast, leukocytosis (>20,000/mm³) was more prevalent in neonates with LOS (28.0%) than in those with EOS (12.9%) (p=0.037). Neutropenia (absolute neutrophil count <1,500/mm³) occurred in 14.3% of EOS cases and 6.0% of LOS cases, but the difference was not statistically significant (p=0.139). An elevated immature-to-total neutrophil (I/T) ratio (>0.2) was observed significantly more often in EOS (57.1%) than in LOS (38.0%) (p=0.038). Thrombocytopenia (platelet count <150,000/mm³) was also more commonly observed in EOS cases (41.4%) compared to LOS (26.0%), reaching statistical significance (p = 0.048). The prevalence of anemia (hemoglobin <13 g/dL) did not differ significantly between the groups, being 17.1% in EOS and 22.0% in LOS (p=0.504). These results suggest distinct hematological profiles in EOS and LOS, with EOS showing a higher frequency of leukopenia, elevated I/T ratio, and thrombocytopenia, while LOS demonstrated more cases of leukocytosis.

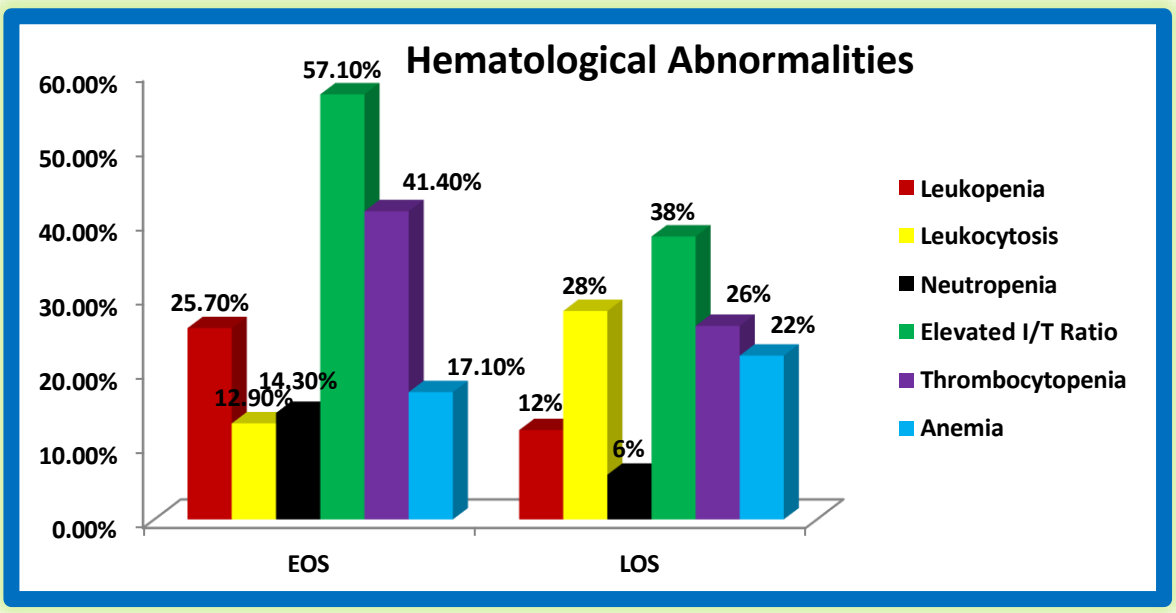

Figure 2- Comparison of hematological abnormalities in EOS and LOS

Table 3 shows the distribution of clinical features and associated risk factors among neonates with early-onset sepsis (EOS) and late-onset sepsis (LOS). Among the clinical presentations, respiratory distress was significantly more common in EOS cases (68.6%) compared to LOS (44.0%) (p=0.006). Poor feeding was more frequently observed in LOS (60.0%) than EOS (41.4%), and this difference was statistically significant (p=0.041). Other symptoms such as lethargy (45.7% vs. 52.0%), temperature instability (35.7% vs. 42.0%), seizures (14.3% vs. 16.0%), and jaundice (25.7% vs. 20.0%) did not differ significantly between the two groups. Regarding risk factors, low birth weight (<2500g) was more prevalent in LOS (62.0%) compared to EOS (40.0%), with statistical significance (p=0.017). Prolonged rupture of membranes (>18hours) and maternal fever during labor were significantly associated with EOS, occurring in 30.0% and 27.1% of cases, respectively, compared to 12.0% and 10.0% in LOS (p=0.016 and p=0.017, respectively). Use of invasive devices, such as central lines or endotracheal tubes, was significantly more frequent in LOS (38.0%) than EOS (8.6%) (p<0.001). Birth asphyxia was observed in both groups without a significant difference (22.9% in EOS vs. 16.0% in LOS, p=0.347). These findings suggest that while EOS is more closely linked to perinatal factors such as maternal fever and membrane rupture, LOS is more commonly associated with postnatal interventions and low birth weight

Table 3: Distribution of clinical presentation and risk factors in EOS and LOS

Variable	Early-Onset Sepsis (n = 70)	Late-Onset Sepsis (n = 50)	p-value
Clinical Presentation			
– Respiratory Distress	48 (68.6%)	22 (44.0%)	0.006
– Lethargy	32 (45.7%)	26 (52.0%)	0.478
– Poor Feeding	29 (41.4%)	30 (60.0%)	0.041
– Temperature Instability	25 (35.7%)	21 (42.0%)	0.472
– Seizures	10 (14.3%)	8 (16.0%)	0.790
– Jaundice	18 (25.7%)	10 (20.0%)	0.465
Risk Factors			
– Low Birth Weight (<2500 g)	28 (40.0%)	31 (62.0%)	0.017
– Prolonged Rupture of Membranes >18h	21 (30.0%)	6 (12.0%)	0.016
– Maternal Fever During Labor	19 (27.1%)	5 (10.0%)	0.017
– Birth Asphyxia	16 (22.9%)	8 (16.0%)	0.347
– Use of Invasive Devices	6 (8.6%)	19 (38.0%)	<0.001

Discussion-

This study highlights the significant hematological and clinical differences between early-onset sepsis (EOS) and late-onset sepsis (LOS) among neonates, underlining the influence of both perinatal and postnatal factors on the onset and progression of neonatal sepsis. Our findings provide insight into the diagnostic utility of hematological markers and the evolving microbiological patterns of neonatal sepsis. Present study observed that neonates with EOS had significantly higher gestational age and birth weight compared to those with LOS. This finding aligns with the report by Hornik et al., who noted that LOS is more common among preterm and low birth weight infants due to prolonged hospital stays and frequent invasive procedures.[10] Similarly, our study found a significantly greater use of invasive devices in LOS cases (38%), echoing the findings of Sharma et al., who attributed LOS in part to nosocomial sources and interventions like central lines and mechanical ventilation.[11] Blood culture positivity was slightly higher in LOS (54.0%) than EOS (44.3%), although this difference was not statistically significant. This trend is consistent with the findings of Camacho-Gonzalez et al., who reported increased culture positivity in LOS, potentially due to higher bacterial loads associated with hospital-acquired infections.[12] The predominant pathogens in EOS were gram-negative organisms, especially Escherichia coli and Klebsiella pneumoniae, while LOS was characterized by a broader range including gram-positive bacteria such as Staphylococcus aureus and coagulase-negative staphylococci (CONS), as well as fungal infections. These patterns corroborate prior studies by Bizzarro et al. and Dong et al., which emphasized the predominance of gram-negative sepsis in EOS and the increasing significance of CONS and fungal pathogens in LOS.[13,14]

Hematological parameters were distinctly different between EOS and LOS. EOS was significantly associated with lower total leukocyte and neutrophil counts, and higher immature-to-total (I/T) neutrophil ratios. The elevated I/T ratio observed in EOS (mean 0.29 vs. 0.22 in LOS, p=0.013) is a well-recognized early marker of infection, as supported by the work of Manroe et al., who developed reference ranges for interpreting neonatal neutrophil indices in sepsis.[15] In contrast, leukocytosis was significantly more common in LOS (28%) compared to EOS (12.9%), which may reflect a more robust bone marrow response to prolonged or nosocomial infections in LOS, consistent with observations by Schlapbach et al.[16] Thrombocytopenia was more frequent in EOS (41.4%) than LOS (26.0%), a finding that supports earlier reports by Guida et al., which suggested that platelet consumption during early systemic inflammatory responses is more pronounced in EOS.[17] Anemia prevalence was not significantly different between the groups, paralleling results from studies such as those by Klinger and Jelkmann, which noted that anemia in neonatal sepsis is multifactorial and not exclusive to the timing of infection onset.[18]

Clinical manifestations also varied: respiratory distress was significantly more common in EOS (68.6%), while poor feeding was more prominent in LOS (60.0%). These results are consistent with the findings of Simonsen et al., who emphasized that EOS often presents with rapid-onset respiratory symptoms due to perinatal insults, while LOS tends to have more subtle signs like feeding intolerance.[19] Risk factors diverged between the groups. EOS was significantly associated with perinatal risk factors such as prolonged rupture of membranes (>18 hours) and maternal fever during labor. These associations are in line with the CDC's guidelines for EOS risk evaluation, which emphasize intrapartum factors as key predictors.[20] On the other hand, LOS was strongly associated with low birth weight and the use of invasive devices, reinforcing its nosocomial origin. Similar conclusions were drawn by Stoll et al. in their multicenter neonatal network study.[21] This study adds to the growing body of evidence highlighting the diagnostic value of hematological parameters in neonatal sepsis. The I/T ratio, leukocyte count, and platelet levels can serve as supportive tools in distinguishing between EOS and LOS, aiding clinicians in tailoring early management strategies. Our findings echo the work of Rodwell et al., who developed the hematologic scoring system incorporating these variables to predict sepsis.[6] Additionally, the moderate culture positivity rate (48.3%) underscores the need for improved diagnostic tools, such as molecular assays, which could provide faster and more accurate identification of pathogens. Nonetheless, our study provides important clinical correlations and supports the distinct pathophysiological profiles of EOS and LOS.

Conclusion

This study reveals significant hematological and clinical distinctions between early-onset sepsis (EOS) and late-onset sepsis (LOS) in neonates, reflecting their differing etiologies and risk exposures. EOS was primarily associated with perinatal factors, likely contributing to early microbial transmission, The hematological profile in EOS reflects an immature or overwhelmed bone marrow response to acute infection. LOS showed more robust inflammatory response and was often influenced by postnatal environmental exposures and invasive interventions, which may indicate a matured immune activation or nosocomial nature of the infections. These findings underscore the importance of timely recognition of hematological patterns and associated risk factors to guide early diagnosis and appropriate management. The distinct hematological parameters can serve as supportive diagnostic tools for differentiating EOS and LOS in resource-limited settings where blood culture turnaround is delayed. Incorporating hematological profiling into the sepsis evaluation algorithm may improve the clinical differentiation of EOS and LOS, ultimately contributing to better outcomes in affected neonates. Recognizing these patterns may allow for earlier initiation of targeted therapy and preventive measures tailored to the timing and likely source of sepsis. Additionally, these results can inform neonatal sepsis screening protocols and antibiotic stewardship programs to minimize unnecessary antimicrobial use and improve neonatal outcomes.

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