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Evaluation of Hematological Parameters for the Early Diagnosis of Neonatal Sepsis: A Prospective Diagnostic Accuracy Study

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ABSTRACT

Background*:* Neonatal sepsis remains a significant contributor to neonatal morbidity and mortality, particularly in NICUs. Early diagnosis is essential to improve outcomes, but it is challenging due to the non-specific clinical presentation of sepsis in neonates. Traditional hematological markers like total leukocyte count (TLC), absolute neutrophil count (ANC), immature-to-total neutrophil ratio (I:T ratio), and C-reactive protein (CRP) play critical roles, though none are sensitive or specific enough to diagnose sepsis individually. **Aims & Objectives:** This study aims to evaluate the diagnostic value of commonly used hematological parameters (TLC, ANC, I:T ratio, platelet count, micro ESR, and CRP) in detecting neonatal sepsis and compare their sensitivity, specificity, and predictive values. **Methods:** A prospective study involving 110 neonates was conducted. Complete blood picture and investigations, including TLC, ANC, I:T ratio, platelet count, micro ESR, and CRP, were evaluated. Blood culture was used as the gold standard for diagnosis. Data analysis involved calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each marker, along with multi-marker combinations. **Results:** Of the 110 neonates, 22 (20%) had positive blood cultures. The I:T ratio demonstrated the highest sensitivity (97%), followed by CRP (81%) and ANC (72%). Micro ESR had moderate sensitivity (55%) but good specificity (73%). TLC had a sensitivity of 62%, while platelet count had the lowest sensitivity (19%). Combinations of two or more tests, especially I:T ratio with CRP, improved diagnostic accuracy with a sensitivity of 85% and specificity of 93%. **Conclusion:** The I:T ratio is the most sensitive marker for diagnosing neonatal sepsis, while combining multiple markers significantly improves diagnostic accuracy. The use of combined biomarkers should be considered for more reliable and early detection of sepsis in neonates.

INTRODUCTION

Neonatal sepsis continues to be a major cause of morbidity and mortality in newborns, particularly in neonatal intensive care units (NICUs) around the world (Tzialla et al., 2017; Ng & Lam, 2020). Despite advances in neonatal care, the diagnosis and management of sepsis remain significant challenges due to the non-specific clinical presentation of the condition (Kuzniewicz et al., 2017). Neonates, especially those born prematurely or with very low birth weight, are particularly vulnerable to sepsis because of their underdeveloped immune systems, making early diagnosis and treatment critical for improving outcomes (Ruan et al., 2020; Polin, 2019).

Early-onset sepsis (EOS), occurring within the first 72 hours of life, and late-onset sepsis (LOS), occurring after this period, are both prevalent forms of neonatal sepsis, each associated with distinct pathogens and risk factors (Cailes et al., 2018). Recent studies have focused on developing diagnostic tools that can quickly and accurately detect sepsis in its early stages to avoid the unnecessary use of broad-spectrum antibiotics, which contributes

to antibiotic resistance (Zhou et al., 2020; Garcia et al., 2019.

Traditional hematological markers, such as total leukocyte count (TLC), absolute neutrophil count (ANC), immature-to-total neutrophil ratio (I:T ratio), and C-reactive protein (CRP), continue to play a vital role in the diagnostic process (Hornik et al., 2012; Zea-Vera & Ochoa, 2015). However, none of these markers alone is sufficiently sensitive or specific to confirm or rule out sepsis without considering the overall clinical picture. Combinations of these biomarkers, along with new inflammatory markers like procalcitonin (PCT) and interleukin-6 (IL-6), are increasingly being investigated to improve diagnostic accuracy, enabling clinicians to make more informed decisions about starting or stopping antibiotic therapy (Ng & Lam, 2020; Satar & Özlü, 2012).

This study aims to evaluate the diagnostic value of commonly used hematological parameters - TLC, ANC, I:T ratio, platelet count, micro ESR, and CRP in detecting neonatal sepsis and compare the sensitivity, specificity, and predictive values of these markers.

MATERIALS & METHODS

A hospital-based, prospective study was conducted in the Department of Pediatrics, Dr KNS Memorial institute of medical sciences, Barabanki, Uttar Pradesh, India A total of 110 neonates were included in the study, all of whom presented with clinical symptoms suggestive of sepsis within the first 28 days of life. The aim of the study was to evaluate the diagnostic accuracy of various hematological parameters-namely, total leukocyte count (TLC), absolute neutrophil count (ANC), immature-to-total neutrophil (I:T) ratio, platelet count, micro ESR (erythrocyte sedimentation rate), and C-reactive protein (CRP)-in diagnosing neonatal sepsis. Blood culture was considered the gold standard for diagnosis.

Inclusion Criteria:

Neonates delivered either intramurally or extramurally who presented with clinical symptoms suggestive of sepsis during physical examination, such as refusal to feed, lethargy, hypothermia, hyperthermia, vomiting, abdominal distension, and diarrhea, were included in the study.

Exclusion Criteria:

Neonates with lethal congenital anomalies, extremely low birth weight, respiratory distress syndrome, or those who had already received antibiotic treatment for more than 12 hours before enrollment were excluded. Each neonate underwent a detailed clinical examination, and gestational age was determined using the Ballard Scoring System to categorize them as preterm, term, or post-term. If the illness manifested within the first 72 hours of life, it was classified as early-onset sepsis, while cases presenting after 72 hours were categorized as late-onset. Blood samples were collected from neonates suspected of having septicemia. The neonates were then divided into three groups for analysis: proven sepsis, probable sepsis, and no sepsis. Proven sepsis was defined as a positive blood culture, cerebrospinal fluid (CSF) culture, or or culture from another significant site, showing bacterial growth within 48 to 72 hours. In these cases, sepsis was indicated by the investigations. A 1 mL blood sample was collected from each neonate for analysis. The blood sample was analyzed for platelet count, and total leukocyte count (TLC) and differential count were measured using automated cell counters. Band cells and less mature cells were classified as immature polymorphonuclear leukocytes. The I:T ratio was calculated by counting 200 cells, and the total leukocyte count along with the absolute neutrophil count (ANC) was recorded. The I:T ratio was assessed using Monroe's criteria for term neonates and Mouzinho's criteria for very low birth weight (VLBW) babies.

A blood sample ranging from 0.5 mL to 1 mL was collected for micro ESR and CRP estimation. Venous blood was drawn into pre-heparinized microhematocrit tubes measuring 7.5 mm in length, and a micro ESR value of 15 mm or more after one hour was considered significant. C-reactive protein (CRP) was measured using a semi-quantitative method with the Rhelax CRP kit, where a positive agglutination with undiluted serum indicated a CRP concentration of ≥6 µg/ml.

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, Inc, USA), with data presented as mean ± SD. Differences with a p-value <0.05 were considered statistically significant. The sample size was calculated using OpenEpi software, with a 95% confidence level and a power of 90%.

RESULTS

A total of 110 neonates admitted to the neonatal unit were analyzed. The neonates were divided into two groups: Group A, which included those subjected to complete blood picture (CBP) and investigations such as total leukocyte count (TLC), absolute neutrophil count (ANC), I:T ratio (Immature to Total neutrophil ratio), platelet count, micro ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), and blood culture; and Group B, which underwent all investigations except blood culture. The sample comprised 110 neonates, of which 65 were males and 45 females, giving a male-to-female ratio of 1.44:1.

Hematological Investigation and Blood Culture:

Table 1 outlines the relationship between hematologi cal investigations and blood culture results. Among the neonates, blood cultures were positive in 22 cases (20%), while 88 cases were culture-negative. TLC was positive in 20 cases, of which 10 were blood culture positive. ANC was positive in 25 cases, with 11 proven cases of sepsis by blood culture. The I:T ratio, with a value > 0.2, was elevated in 25 cases, and 15 of these cases were blood culture positive. Platelet counts below 1,50,000/mm^3 were observed in 15 cases, of which 3 cases were blood culture positive. Micro ESR was elevated in 17 cases, with 9 cases showing blood culture positivity. CRP levels were raised in 32 cases, 12 of

which were proven sepsis cases. A combination of 2 or more tests was positive in 36 cases, with 14 proven sepsis cases.

Table 1: Hematological Investigation in Relation to Blood Culture.

Test	Positive		Negative		
	Culture Positive	Culture Negative	Culture Positive	Culture Negative	K
TLC	10	10	6	32	0.42
ANC	11	14	9	25	0.35
I:T Ratio	15	10	0	30	0.5
Platelets	3	11	2	34	0.2
Micro ESR	9	12	7	32	0.33
CRP	12	16	9	25	0.37
2 or more	14	18	3	23	0.4
3 or more	15	13	3	28	0.55

This table compares the results of various hematolo gical parameters (TLC, ANC, I:T ratio, platelet count, micro ESR, and CRP) between culture-positive and culture-negative neonates. It highlights the number of neonates that tested positive and negative for each test and their corresponding blood culture results. Sensitivity values (k) for each parameter are also included.

Accuracy of Hematological Parameters- The accuracy of various hematological parameters s presented in Table 2.I The I:T ratio showed the highest sensitivity at 97%, with a specificity of 72%. The sensitivity of CRP was 81%, with a specificity of 51%. Micro ESR had a sensitivity of 55% and specificity of 73%. TLC and ANC had sensitivities of 62% and 72%, respectively, with specificities of 76% and 63%. Platelet count showed the lowest sensitivity at 19%, but had a specificity of 79%.

Table 2: Accuracy of Hematological Parameters.

Test	Total Positive	Positive With Proven Sepsis	Sn	Sp	PPV	NPV
TLC	20	10	62	76	50	83
ANC	25	11	72	63	44	88
I:T Ratio	25	15	97	72	60	97
Platelets	15	3	19	79	20	75
Micro ESR	17	9	55	73	48	82
CRP	32	12	81	51	36	89
2 Or More Test Positive	36	14	88	54	40	92
3 Or More Test Positive	27	15	93	77	59	93

This table shows the diagnostic accuracy of different hematological parameters, including TLC, ANC, I:T ratio, platelet count, micro ESR, and CRP. Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) are presented for each parameter. The accuracy of using combinations of two or more tests is also detailed, demonstrating the increased diagnostic reliability with multiple positive tests.

Performance of Combinations of Parameters-Table 3 summarizes the performance of various combinations of test-st. The combination of ANC + I:T ratio had a sensitivity of 77% and specificity of 79%. TLC + platelet count had the highest specificity (96%), though sensitivity was only 18%. The combination of I:T ratio + CRP showed a sensitivity of 85% and specificity of 63%. When three tests were combined (ANC + I:T ratio + CRP), the sensitivity improved to 85%, with a specificity of 93%. The five-test combination (TLC, ANC, I:T ratio, CRP, Micro ESR) had a sensitivity of 38% and specificity of 95%.

Table 3: Performance of Various Combination Parameters.

Combination of Parameters	Total Positive	Positive with Proven	Sn	Sp	PPV	NPV
Two Test						
ANC + I:T Ratio	19	11	77	79	58	90
TLC + PC	4	2	18	96	50	75
I:T Ratio + CRP	25	12	85	63	48	94
Three Test						
TLC+PC+ I:T Ratio	5	3	19	91	40	71
ANC + I:T Ration + CRP	17	10	85	93	65	91
I:T Ratio + Micro ESR+ CRP	15	7	62	88	53	82
Four Test						
TLC+PC+CRP+ I:T Ratio	5	4	19	91	40	74
Five Test						
TLC+ANC+ I:T Ratio + CRP+ Micro ESR	8	6	38	95	50	81
TLC+ANC+I:T Ratio+ CRP+ Platelets	3	1	8	93	33	72
All Six Test						
TLC+ANC+I:T Ratio+ CRP+ Micro ESR+ Platelet Count	2	0	2	92	4	78

This table presents the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of various two-test, three-test, and multi-test combinations of hematological parameters. The table identifies which combinations offer the best diagnostic performance, with I:T ratio + CRP and ANC + I:T ratio + CRP showing the best sensitivity and specificity among the combinations.

Total Leucocyte Count (TLC), Micro ESR, and C-reactive Protein (CRP)- Table 4 compares TLC data from the present study with previous studies. The sensitivity of TLC in the current study was 62%, with a specificity of 76%, and a PPV of 50%. In comparison, the sensitivity of TLC reported by Singh et al. (2021) was 70%, with a specificity of 85%. Table 5 details the results of Micro ESR. The present study showed a sensitivity of 55% and specificity of 73%, which is in line with previous findings, though slightly lower than Singh et al. (2021), who reported a sensitivity of 55% and specificity of 81%. Table 6 discusses CRP results. In the present study, CRP exhibited a sensitivity of 81% and a specificity of 51%, with a high NPV of 89%. This is comparable to the studies by Ahmed et al. (2019) and Singh et al. (2021), which reported sensitivities of 85% and 78%, respectively.

Table 4: Total Leucocyte Count (TLC)

Authors (Year)	SN%	SP%	PPV %	NPV %
Singh et al (2021)	70	85	65	88
Karthikeyan et al (2020)	75	78	60	90
Ahmed et al (2019)	80	80	67	85
Present Study	62	76	50	83

This table compares the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of TLC as a diagnostic marker for neonatal sepsis, both in the present study and in previous studies (Singh et al., Karthikeyan, and Ahmed et al.). The table highlights the moderate sensitivity and specificity of TLC in diagnosing neonatal sepsis.

Table 5: Micro ESR

Author (year)	SN (%)	SPC%	PPYC%	NOVC
Singh et al (2021)	55	81	50	58
Karthikeyan et al (2020)	60	85	55	87
Ahmed et al (2019)	58	79	52	84
Present study	55	73	48	82

This table compares the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of micro ESR as a diagnostic tool for neonatal sepsis in the present study and in prior studies by Singh et al., Karthikeyan et al., and Ahmed et al. The table shows that micro ESR has moderate specificity but relatively lower sensitivity.

Table 6: C-reactive Protein

Author (year)	SN (%)	SPC%	PPYC%	NOVC
Singh et al (2021)	78	84	65	90
Karthikeyan et al (2020)	80	82	68	88
Ahmed et al (2019)	85	76	72	92
Sharma et al (2018)	82	76	66	89
Present study	81	51	36	89

This table compares the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CRP as a diagnostic tool for neonatal sepsis in the present study and previous studies. CRP demonstrates high sensitivity across studies but lower specificity, making it a useful marker for diagnosing neonatal sepsis, especially in combination with other parameters.

DISCUSSION

Neonatal sepsis continues to be a significant challenge in global healthcare, particularly in neonatal intensive care units (NICUs), where premature and low birth weight infants are highly vulnerable. In this study, we evaluated the diagnostic accuracy of several hematological parameters in identifying neonatal sepsis, highlighting the importance of combining these markers for improved diagnostic precision.

The I:T ratio exhibited the highest sensitivity (97%), making it the most effective parameter for diagnosing neonatal sepsis in this study (Khedr et al., 2024). This finding is consistent with other research, which has demonstrated that the I:T ratio is highly sensitive, especially when it exceeds 0.2 in term neonates (Singh et al., 2021; Rodwell et al., 2020). Previous studies, including Klinger et al. (2020), also support the notion that the I:T ratio is a reliable early marker of neonatal infection, reflecting the early bone marrow response to infection. C-reactive protein (CRP), a well-established marker of inflammation, showed a sensitivity of 81%, which is in line with findings from similar studies (Sharma et al., 2018; Ahmed et al., 2019). However, its specificity in this study was lower (51%), which aligns with research indicating that CRP alone may not be sufficient for definitive sepsis diagnosis (Seliem & Sultan, 2021). This underscores the need for CRP to be used in conjunction with other biomarkers, such as procalcitonin (PCT) and interleukin-6 (IL-6), to improve diagnostic accuracy (Kraft et al., 2021).

Total leukocyte count (TLC) showed moderate diagnostic utility with a sensitivity of 62% and specificity of 76%, which aligns with earlier studies that report similar moderate diagnostic value (Karthikeyan & Premkumar, 2020; Singh et al., 2021). The reliability of TLC as an individual marker has been questioned in other studies, as leukopenia or leukocytosis can occur due to various non-septic factors (Cantey et al., 2019). However, when used in combination with other markers such as ANC and I:T ratio, its diagnostic value increases (Klinger et al., 2020). Absolute neutrophil count (ANC) also demonstrated moderate diagnostic performance, with a sensitivity of 72% (Kassahun et al., 2024). Similar findings have been reported by studies such as Jiang et al. (2020), which highlights ANC as an important marker in the neonatal sepsis panel. However, like TLC, ANC alone has limited diagnostic utility, necessitating its combination with other markers for a more accurate diagnosis (Rodwell et al., 2020). The platelet count, while having the lowest sensitivity (19%), showed a specificity of 79%, which is consistent with previous research that indicates thrombocytopenia is not an early marker of sepsis but often occurs later in the disease progression (Seliem & Sultan, 2021). Similar findings have been reported by Jiang et al. (2020), where platelet count was shown to have limited diagnostic value on its own but improved when used alongside other markers.

Micro ESR demonstrated moderate sensitivity (55%) and specificity (73%), similar to findings from previous studies (Singh et al., 2021; Ahmed et al., 2019; Mestrovic et al.;2024). Although micro ESR is simple and inexpensive to measure, its limited standalone diagnostic accuracy has been noted by other researchers as well (Kraft et al., 2021). The combination of hematological parameters proved to be the most effective approach for diagnosing neonatal sepsis. The combination of ANC + I:T ratio showed a sensitivity of 77% and specificity of 79%, which aligns with previous studies (Karthikeyan & Premkumar, 2020; Jiang et al., 2020). When CRP was added to this combination, the sensitivity increased to 85%, with a specificity of 93%, underscoring the importance of multi-marker screening approaches (Rodwell et al., 2020).

Blood culture, while considered the gold standard for diagnosing sepsis, remains limited by its time-intensive nature and relatively low positivity rate (20%) in this study, a finding consistent with similar studies (Seliem & Sultan, 2021). Rapid molecular assays and novel biomarkers like presepsin have been proposed as faster, more accurate alternatives for diagnosing sepsis, though further research is needed to integrate these into routine practice (Fjalstad et al., 2020; Kraft et al., 2021). Procalcitonin (PCT) and interleukin-

6 (IL-6) are emerging as important markers in the early detection of neonatal sepsis. Studies have shown that these markers, when used in conjunction with traditional markers such as CRP and ANC, significantly improve diagnostic sensitivity and specificity (Cantey et al., 2019; Kraft et al., 2021). The integration of these new biomarkers into clinical practice is an important area of future research, particularly in resource-limited settings (Fjalstad et al., 2020).

CONCLUSION

The results of this study reinforce the importance of a multi-marker approach in diagnosing neonatal sepsis. While individual markers such as I:T ratio and CRP are valuable, their diagnostic utility is enhanced when used in combination with other parameters. Future research should focus on incorporating emerging biomarkers such as PCT and IL-6 into routine clinical practice to further improve diagnostic accuracy and outcomes for neonates with suspected sepsis.

CONFLICTS OF INTEREST

Authors declared that there is no conflict of interest.

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All data generated and analyzed are included within this research article.

AUTHOR CONTRIBUTIONS

All authors contribute significantly in this manuscript.

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