RESEARCH PAPER

Diagnostic Accuracy of CRP, Total Leucocyte Count, and Platelet Count as Predictors of Blood Culture Positivity in Neonatal Sepsis: A Cross-Sectional Study

Saladi Mounika Ratnam[1], Navreet Kaur[2], Suddapalli Sivaram Prasad[3], Yammanuru Pavan Kumar Reddy[4]

[1]PG 3rd Year, MD Paediatrics, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala District, Haryana, India

[2]Assistant Professor, MD Paediatrics, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala District, Haryana, India

[3]Professor, MD Paediatrics, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala District, Haryana, India

[4]PG 3rd Year, MD Paediatrics, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala District, Haryana, India

Corresponding Author:
Saladi Mounika Ratnam
PG 3rd Year, MD Paediatrics, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala District, Haryana, India
Email: mounikasaladi.bn16@gmail.com

Abstract

Background: Neonatal sepsis is a leading cause of morbidity and mortality in developing countries. Blood culture, the gold standard, is time-consuming and yields false-negative results in up to 30–40% of cases. Rapid, cost-effective biomarkers such as C-reactive protein (CRP), total leucocyte count (TLC), and platelet count are increasingly utilised for early detection and empirical antibiotic decision-making.

Aim: To evaluate the diagnostic accuracy of CRP, TLC, and platelet count as individual and combined predictors of blood culture positivity in neonatal sepsis.

Methods: A cross-sectional observational study was conducted in the NICU of a tertiary care centre. A total of 190 neonates with clinical suspicion or risk factors for neonatal sepsis were enrolled. Blood samples were collected under aseptic precautions for CRP estimation (quantitative turbidimetric immunoassay), haematological analysis, and aerobic blood culture. Diagnostic accuracy parameters — sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) — were computed against blood culture as the reference standard. Statistical analysis used SPSS software; $p < 0.05$ was considered significant.

Results: Blood culture positivity was noted in 122 (64.2%) neonates. Early onset sepsis (EOS) constituted 60% of cases. *Klebsiella pneumoniae* (25.3%) was the most frequently isolated organism. CRP (>1 mg/dL) demonstrated the best diagnostic performance: sensitivity 89.3%, specificity 77.9%, PPV 87.9%, NPV 80.3% ($\chi^2 = 87.196$, $p < 0.001$). Thrombocytopenia (<1.5 lakhs/μL) showed sensitivity 68.0%, specificity 75.0%, PPV 83.0%, NPV 56.7% ($\chi^2 = 32.432$, $p < 0.001$). TLC (<5,000 cells/cumm) demonstrated low sensitivity (46.7%) but high specificity (88.2%) ($\chi^2 = 23.706$, $p < 0.001$). Mean CRP was significantly higher in culture-positive neonates (8.657 ± 5.488 vs 0.988 ± 1.252 mg/dL; $p < 0.001$). A weak but significant negative correlation was found between CRP and platelet count ($r = -0.182$; $p = 0.012$).

Conclusion: CRP is the most reliable individual biomarker for predicting blood culture positivity in neonatal sepsis. TLC, though of low sensitivity, contributes high specificity when leukopenia is present. Thrombocytopenia serves as an important supplementary marker. A combined multi-parameter approach using CRP, TLC, and platelet count

alongside blood culture and clinical assessment optimises early detection and supports rational antimicrobial stewardship, particularly in resource-limited settings.

Keywords: Blood culture; C-reactive protein; Neonatal sepsis; Platelet count; Total leucocyte count

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Introduction

The neonatal period — defined as the first 28 days of life — represents a phase of extreme physiological vulnerability. Neonates are especially predisposed to infections owing to immature innate and adaptive immune defences, frequent invasive procedures during critical care, and exposure to nosocomial pathogens.(1) This vulnerability is particularly pronounced in preterm and low birth weight infants. In developing nations, risks are amplified by malnutrition, poor socioeconomic conditions, unhygienic delivery practices, and limited access to skilled neonatal care.(1)

Neonatal sepsis is defined as a clinical syndrome of systemic infection accompanied by positive blood culture occurring within the first 28 days of life.(2) The disease presents with subtle, non-specific, and heterogeneous manifestations — including poor feeding, lethargy, respiratory distress, hypothermia, or fever — making early clinical recognition challenging, and delays in treatment potentially fatal.(2,3) Globally, neonatal sepsis is the third leading cause of neonatal death after prematurity and intrapartum-related complications, accounting for approximately 42% of fatalities in the first week of life and roughly 13% of all neonatal mortality.(3) Worldwide incidence is estimated at 2,800–3,000 cases per 100,000 live births, with a case fatality rate of 15–20%; the burden is disproportionately concentrated in low- and middle-income countries.(4,5) In India, the incidence approximates 25–30 per 1,000 live births, making neonatal sepsis one of the most significant contributors to neonatal mortality alongside prematurity and birth asphyxia.(5,6)

Neonatal sepsis is classified by timing: early-onset sepsis (EOS), presenting within the first 72 hours, is typically associated with organisms from the maternal genital tract; late-onset sepsis (LOS), occurring after 72 hours, is generally linked to nosocomial or community-acquired pathogens.(7,8) Risk factors for EOS include low birth weight, maternal febrile illness, prolonged rupture of membranes (>24 hours), meconium-stained amniotic fluid, prolonged labour, and perinatal asphyxia.(9,10) In NICU settings across India and South Asia, gram-negative pathogens — particularly *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter* species — predominate, while gram-positive organisms such as *Staphylococcus aureus* and coagulase-negative staphylococci (CONS) are also frequently encountered.(11,12)

A confirmed diagnosis requires positive blood or cerebrospinal fluid culture, typically taking 24–72 hours and yielding false-negative results in up to 30–40% of clinically apparent cases due to prior antibiotic use, low inoculated blood volumes, or intermittent bacteraemia.(13,14) The National Neonatology Forum (NNF) sepsis screen comprises TLC, absolute neutrophil count (ANC), immature-to-total neutrophil (I/T) ratio, micro-erythrocyte sedimentation rate (m-ESR), and CRP; a screen is considered positive when two or more parameters are abnormal.(15)

C-reactive protein (CRP), first described in 1930 by Tillet and Francis at Rockefeller University, is a hepatic acute-phase reactant synthesised in response to pro-inflammatory cytokines — interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α).(16) CRP levels rise up to 1,000-fold within 4–6 hours of an inflammatory stimulus, with a plasma half-life of approximately 19 hours.(17) Since minimal CRP crosses the placenta, any elevation in a neonate reflects endogenous production rather than passive maternal transfer.(18,19) CRP enhances natural killer cell activity, neutrophil activation, platelet degranulation, and cell-mediated cytotoxicity, making it physiologically relevant in the setting of bacterial sepsis.(17,18)

TLC is readily available but non-specific; it may remain normal in up to 30% of culture-proven sepsis cases. Leukopenia (TLC <5,000 cells/mm³) is more specific for bacterial infection than leukocytosis.(20) Platelet count, although commonly perturbed in sepsis — with up to 50% of bacteraemic neonates developing thrombocytopenia — is an insensitive standalone

marker but significantly increases diagnostic accuracy when combined with other sepsis screen parameters.(21) The present study was designed to determine the diagnostic accuracy of CRP, TLC, and platelet count against blood culture findings in neonatal sepsis, and to evaluate their individual and collective utility for early prediction of culture-confirmed sepsis.

Materials and Methods

Study Design and Setting

A cross-sectional observational study was conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Paediatrics, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, Haryana — a tertiary care centre with established diagnostic and microbiological facilities. The study was conducted over a duration of one and a half years from the date of approval by the Institutional Ethics Committee.

Study Population and Sample Size

The study enrolled neonates admitted to the NICU presenting with clinical features suggestive of sepsis or with identifiable risk factors for neonatal sepsis, covering both EOS and LOS. Sample size was calculated based on an anticipated blood culture positivity rate of 10% at the institution and a reported CRP sensitivity of 90% from prior literature, yielding a required sample of 190 neonates.

Inclusion criteria: (i) Neonates with signs and symptoms suggestive of neonatal sepsis as per the AIIMS Protocol (3rd edition); (ii) Neonates with major predisposing factors for early-onset neonatal sepsis.

Exclusion criteria: (i) Neonates with congenital malformations; (ii) Neonates with inborn errors of metabolism; (iii) Neonates who had received antibiotics prior to admission; (iv) Cases where informed consent was not obtained.

Data Collection

A standardised pre-structured proforma recorded comprehensive maternal history (gravida status, mode of delivery, antenatal complications) and neonatal data (gestational age, birth weight, APGAR scores at 1 minute, clinical features, and type of sepsis). Perinatal risk factors assessed included maternal fever, foul-smelling or meconium-stained liquor, rupture of membranes >24 hours, >3 vaginal examinations, prolonged labour >24 hours, and perinatal asphyxia.

Sample Collection and Laboratory Investigations

Blood samples were collected under strict aseptic conditions. The venipuncture site was disinfected with 70% isopropyl alcohol, followed by povidone-iodine and a second alcohol application in concentric circular motion, allowed to dry before puncture.

- **Haematological analysis:** Approximately 1 mL blood in an EDTA vial; automated haematology analyser for TLC, differential leucocyte count, platelet count, ANC, I/T ratio, and peripheral blood film examination.
- **CRP estimation:** Approximately 1 mL blood for quantitative serum CRP by turbidimetric immunoassay on an automated biochemistry analyser.
- **Blood culture:** Approximately 1 mL blood inoculated into appropriate culture medium; incubated and monitored for a minimum of 72 hours before reporting as sterile.

Diagnostic Criteria

Abnormal values were defined as: TLC <5,000 cells/cumm; serum CRP >1 mg/dL; platelet count <1.5 lakhs/µL; I/T ratio >0.2; ANC <1,800/cumm. Blood culture positivity served as the reference standard for confirmed neonatal sepsis.

Statistical Analysis

Data were compiled in Microsoft Excel and analysed using SPSS software (latest version). Chi-square (χ^2) tests assessed associations between categorical variables. Independent samples t-tests evaluated continuous variable differences between culture-positive and culture-negative groups. Pearson correlation coefficients (r) quantified relationships between continuous parameters. Sensitivity, specificity, PPV, and NPV were derived from 2×2 contingency tables against blood culture. A p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Profile

A total of 190 neonates were enrolled. Male neonates constituted 51.6% (n = 98) and females 48.4% (n = 92), yielding a male-to-female ratio of approximately 1.07:1. The mean birth weight was 2,699.96 ± 910.35 grams (range: 828–3,995 g); 67 (35.3%) neonates were low birth weight (<2,500 g) and 123 (64.7%) had normal birth weight. Mean head circumference was 33.15 ± 3.15 cm and mean length was 47.11 ± 4.76 cm.

The gestational age distribution showed: 40–42 weeks (36.8%), 36–39 weeks (32.1%), 28–31 weeks (16.8%), and 32–35 weeks (14.2%), with term neonates comprising the majority of the study population. Mode of delivery was normal vaginal delivery (NVD) in 90 (47.4%), lower segment caesarean section (LSCS) in 86 (45.3%), and assisted delivery in 14 (7.4%) cases. Mean APGAR score at 1 minute was 6.19 ± 2.664 (range: 0–9).

Table 1: Baseline Demographic and Clinical Characteristics (n = 190)

Variable	Category	n	%
Sex	Male	98	51.6
	Female	92	48.4
Birth Weight	Low (<2,500 g)	67	35.3
	Normal (≥2,500 g)	123	64.7
Gestational Age	28–31 weeks	32	16.8
	32–35 weeks	27	14.2
	36–39 weeks	61	32.1
	40–42 weeks	70	36.8
Mode of Delivery	NVD	90	47.4
	LSCS	86	45.3
	Assisted	14	7.4
Type of Sepsis	Early Onset	114	60.0
	Late Onset	76	40.0

Maternal and Perinatal Risk Factors

Among maternal risk factors, PROM and related conditions were the most prevalent (27.4%), followed by gestational diabetes mellitus (7.4%), fetal distress (6.4%), and chorioamnionitis (5.3%). A total of 83 (43.7%) neonates had no identifiable maternal risk factor. Among the specific perinatal variables, rupture of membranes >24 hours was present in 52 (27.4%), foul-smelling or meconium-stained liquor in 49 (25.8%), maternal fever in 44 (23.2%), >3 vaginal examinations in 40 (21.1%), perinatal asphyxia in 33 (17.4%), and prolonged labour >24 hours in 33 (17.4%) cases.

Table 2: Maternal and Perinatal Risk Factors (n = 190)

Risk Factor	Present n (%)	Absent n (%)
Rupture of membranes >24 hours	52 (27.4)	138 (72.6)
Foul-smelling/meconium-stained liquor	49 (25.8)	141 (74.2)
Maternal fever	44 (23.2)	146 (76.8)
>3 vaginal examinations	40 (21.1)	150 (78.9)
Perinatal asphyxia	33 (17.4)	157 (82.6)
Prolonged labour >24 hours	33 (17.4)	157 (82.6)

Clinical Features

Poor feeding was the most common presentation (71.6%), followed by lethargy or weak cry (64.2%), respiratory distress or apnoea (53.2%), fever (43.2%), jaundice (36.8%), abdominal distension (26.8%), hypothermia (21.1%), skin findings (21.1%), seizures (17.9%), bulging fontanelle (14.7%), and meconium aspiration (12.1%).

Table 3: Distribution of Clinical Features Among Enrolled Neonates (n = 190)

Clinical Feature	Present n (%)	Absent n (%)
Poor feeding	136 (71.6)	54 (28.4)
Lethargy/Weak cry	122 (64.2)	68 (35.8)
Respiratory distress/Apnoea	101 (53.2)	89 (46.8)
Fever	82 (43.2)	108 (56.8)
Jaundice	70 (36.8)	120 (63.2)
Abdominal distension	51 (26.8)	139 (73.2)
Hypothermia	40 (21.1)	150 (78.9)
Skin findings	40 (21.1)	150 (78.9)
Seizures	34 (17.9)	156 (82.1)
Bulging fontanelle	28 (14.7)	162 (85.3)
Meconium aspiration	23 (12.1)	167 (87.9)

Blood Culture Results and Bacteriological Profile

Blood culture was positive in 122 (64.2%) neonates and negative in 68 (35.8%). Early onset sepsis accounted for 60% of all cases. Among culture-positive neonates, gram-negative organisms predominated. *Klebsiella pneumoniae* was the most frequently isolated pathogen (25.3%), followed by *Acinetobacter baumannii* (16.8%), *Candida* species (9.5%), and *Escherichia coli* (6.3%).

Table 4: Distribution of Isolated Organisms Among Culture-Positive Neonates (n = 122)

Organism	n	%
Klebsiella pneumoniae	31	25.3
Acinetobacter baumannii	21	16.8
Candida species	12	9.5
Escherichia coli	8	6.3
Other organisms	50	42.1

Haematological and Biomarker Parameters

Mean serum CRP was significantly higher in blood culture-positive neonates compared to culture-negative neonates (8.657 ± 5.488 vs 0.988 ± 1.252 mg/dL; t = 11.346; p <0.001). Mean platelet count was significantly lower in culture-positive neonates (1.628 ± 1.180 vs 2.438 ± 1.209 lakhs/µL; t = −4.491; p <0.001). Mean TLC did not differ significantly between culture-positive and culture-negative groups (12,200.89 ± 10,946.82 vs 11,857.18 ± 6,465.02 cells/cumm; t = 0.237; p = 0.813).

No statistically significant differences in CRP, TLC, or platelet count were observed across sex, mode of delivery, or between EOS and LOS groups (p >0.05 for all), indicating these biomarkers were not confounded by these demographic variables.

Table 5: Comparison of Biomarker Levels Between Blood Culture-Positive and Culture-Negative Neonates

Parameter	Culture-Positive (Mean ± SD)	Culture-Negative (Mean ± SD)	t-value	p-value
Serum CRP (mg/dL)	8.657 ± 5.488	0.988 ± 1.252	11.346	<0.001*
Platelet Count (lakhs/µL)	1.628 ± 1.180	2.438 ± 1.209	−4.491	<0.001*
TLC (cells/cumm)	12,200.89 ± 10,946.82	11,857.18 ± 6,465.02	0.237	0.813

*Statistically significant (p <0.05)

Association of Biomarkers with Blood Culture Positivity

CRP levels >1 mg/dL showed a highly significant association with blood culture positivity ($\chi^2 = 87.196$; $p < 0.001$); 109 of 124 neonates with elevated CRP were culture-positive, while 53 of 66 neonates with normal CRP were culture-negative. Thrombocytopenia (<1.5 lakhs/µL) was significantly associated with blood culture positivity ($\chi^2 = 32.432$; $p < 0.001$); 83 of 100 thrombocytopenic neonates were culture-positive. Leukopenia (TLC <5,000 cells/cumm) was also significantly associated with culture positivity ($\chi^2 = 23.706$; $p < 0.001$); 57 of 65 leukopenic neonates were culture-positive.

Table 6: Association of CRP, Platelet Count, and TLC with Blood Culture Positivity

Biomarker (Cut-off)	Culture-Negative (n)	Culture-Positive (n)	χ^2	p-value
CRP >1 mg/dL (Positive)	15	109	87.196	<0.001*
CRP ≤1 mg/dL (Negative)	53	13		
Platelet <1.5 L/µL (Thrombocytopenia)	17	83	32.432	<0.001*
Platelet ≥1.5 L/µL (Normal)	51	39		
TLC <5,000/cumm (Leukopenia)	8	57	23.706	<0.001*
TLC ≥5,000/cumm (Normal)	60	65		

*Statistically significant ($p < 0.05$)

Diagnostic Accuracy of Biomarkers

CRP demonstrated the highest sensitivity (89.3%) and a clinically useful balance of specificity (77.9%), PPV (87.9%), and NPV (80.3%) against blood culture as the gold standard. TLC had the highest specificity (88.2%) but the lowest sensitivity (46.7%), confirming its role as a confirmatory rather than screening marker. Platelet count showed intermediate performance (sensitivity 68.0%; specificity 75.0%; PPV 83.0%; NPV 56.7%).

Table 7: Diagnostic Accuracy Parameters of CRP, TLC, and Platelet Count Against Blood Culture

Parameter (Cut-off)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP (>1 mg/dL)	89.3	77.9	87.9	80.3
TLC (<5,000 cells/cumm)	46.7	88.2	87.7	48.0
Platelet Count (<1.5 lakhs/µL)	68.0	75.0	83.0	56.7

Correlation Analysis

Serum CRP demonstrated a weak but statistically significant inverse correlation with platelet count ($r = -0.182$; $p = 0.012$), indicating that higher systemic inflammation was associated with lower platelet levels. A weak positive correlation was observed between platelet count and APGAR score at 1 minute ($r = 0.184$; $p = 0.011$). TLC showed no significant correlation with serum CRP ($r = 0.028$; $p = 0.704$) or platelet count ($r = 0.011$; $p = 0.881$). CRP did not correlate significantly with gestational age ($r = -0.013$; $p = 0.855$) or birth weight ($r = 0.031$; $p = 0.675$).

Table 8: Correlation of Serum CRP and Platelet Count with Key Clinical and Haematological Parameters

Correlation Pair	r	p-value	Inference
CRP vs Platelet Count	−0.182	0.012*	Significant (weak negative)
CRP vs TLC	0.028	0.704	Non-significant
CRP vs Gestational Age	−0.013	0.855	Non-significant
CRP vs Birth Weight	0.031	0.675	Non-significant
CRP vs APGAR Score at 1 min	−0.016	0.825	Non-significant
Platelet Count vs TLC	0.011	0.881	Non-significant
Platelet Count vs APGAR Score at 1 min	0.184	0.011*	Significant (weak positive)
TLC vs Gestational Age	0.087	0.232	Non-significant
TLC vs Birth Weight	0.003	0.964	Non-significant

*Statistically significant ($p < 0.05$)

Discussion

The present study evaluated the diagnostic accuracy of CRP, TLC, and platelet count as predictors of blood culture positivity in 190 neonates admitted to a tertiary care NICU with suspected sepsis.

Blood culture positivity and bacteriological profile. A blood culture positivity rate of 64.2% was observed in this study — higher than rates reported by Jatsho et al. (2020) and Mohakud et al. (2022) — likely attributable to the stringent NICU-based inclusion criteria, higher acuity of admitted neonates, and the study centre's referral burden.(22,23) *Klebsiella pneumoniae* (25.3%) was the most prevalent isolate, consistent with its well-established predominance in South Asian tertiary NICUs.(11,12) The notable isolation of *Candida* species (9.5%) underscores the emerging burden of fungal sepsis in critically ill and preterm neonates. Siddiqui et al. (2023) documented 76.5% amikacin resistance among *Klebsiella* isolates, reinforcing the need for institution-specific antibiotic stewardship.(24)

CRP as a diagnostic marker. CRP demonstrated the best individual diagnostic performance: sensitivity 89.3% and specificity 77.9%. These results align with and, in several instances, exceed prior published findings. Chandar et al. (2022) reported CRP sensitivity of 93.33% and diagnostic accuracy of 74% at the >1 mg/dL threshold in a comparable cohort of 100 neonates.(25) Loni et al. (2016) observed CRP sensitivity of 73% and specificity of 86.1%, with CRP positivity in 79% of culture-positive cases.(26) Monga et al. (2018) found CRP sensitivity of 85.11% and specificity of 43.40% in 100 suspected neonates.(27) Hassan et al. (2016) noted the highest sensitivity (95.2%) and NPV (89.3%) for CRP among all sepsis screen parameters across 100 neonates.(28) Shabuj et al. (2017), in a meta-analysis of 11 studies (n = 1,557 neonates), reported pooled CRP sensitivity of 71% and specificity of 86%, with an AUC of 0.8535 and diagnostic odds ratio of 19.10.(29) Liu et al. (2019) pooled data from 10 trials (n = 1,819) and reported sensitivity 70%, specificity 89%, and AUC 0.90, reflecting strong discriminatory performance.(30) The higher sensitivity in the current study may reflect a higher pre-test probability in an exclusively NICU-based population and inclusion of both EOS and LOS. Dubey et al. (2025) confirmed CRP's high sensitivity (87.1%) and strong NPV (91.7%) for excluding sepsis, while cautioning that CRP specificity was relatively low (50.6%) due to false positivity in non-infectious inflammation.(31)

The biological basis of CRP's diagnostic superiority is well established: as a hepatic acute-phase protein induced by IL-1, IL-6, and TNF-α, CRP levels can

increase 1,000-fold within 4–6 hours of infection, and its plasma half-life of approximately 19 hours allows reliable single-time-point estimation.(16,17) Since negligible CRP crosses the placenta, neonatal CRP elevations represent genuine endogenous synthesis.(18,19) However, Memar et al. (2019) cautioned that CRP sensitivity may be attenuated in the very early phase of EOS due to a lag between bacterial invasion and peak hepatic synthesis, recommending serial CRP measurements to maximise accuracy.(32) Sharma et al. (2025) confirmed moderate CRP-blood culture agreement ($\kappa = 0.58$), reinforcing that CRP should be interpreted alongside clinical assessment rather than as a standalone replacement for blood culture.(33)

Platelet count as a supplementary marker. Thrombocytopenia (<1.5 lakhs/μL) showed a significant association with blood culture positivity ($\chi^2 = 32.432$; $p < 0.001$) with sensitivity 68.0%, specificity 75.0%, and PPV 83.0%. Mean platelet counts were significantly lower in culture-positive neonates (1.628 ± 1.180 vs 2.438 ± 1.209 lakhs/μL; $p < 0.001$). These findings align with Ree et al. (2017), who documented thrombocytopenia in 49% of 460 culture-confirmed septic neonates, with severe thrombocytopenia in 20%, and identified gram-negative sepsis as an independent predictor of more severe platelet reduction.(34) Karne et al. (2017) similarly found 57.5% severe thrombocytopenia in culture-proven cases.(35) Polin (2012) noted that nearly 50% of neonates with bacterial sepsis develop thrombocytopenia — often as a relatively late haematological manifestation — but that thrombocytopenia combined with other abnormal screen parameters substantially enhances diagnostic accuracy.(21) Das et al. (2024) reported 75.5% thrombocytopenia among 94 culture-confirmed neonates, with a stronger association in gram-negative and fungal sepsis.(36) The inverse CRP-platelet correlation observed in the current study ($r = -0.182$; $p = 0.012$) reflects concurrent cytokine-mediated platelet consumption and acute-phase reactant synthesis during systemic infection, a finding also reported by Chavhan et al. (2024).(37) Can et al. (2018) reported that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) offer additional diagnostic value alongside CRP, with NLR cut-off 6.76 achieving sensitivity 97.4% and specificity 100% for EOS.(38)

TLC as a confirmatory marker. TLC demonstrated the highest specificity (88.2%) but the lowest sensitivity (46.7%), consistent with the well-established biological heterogeneity of neonatal leucocyte responses dependent on gestational age, bone marrow reserve, pathogen virulence, and timing of sampling. Mean TLC did not differ significantly between culture-positive and culture-negative groups ($p = 0.813$). These findings are concordant with Bharathi et al. (2021), who reported WBC sensitivity of only 21.43% in 127 neonates.(39) Sorsa (2018) reported WBC sensitivity of 59.5% and specificity of 79.6%.(40) Khurram et al. (2016) similarly found TLC and platelet count provided the highest specificity among all parameters, while the I/T ratio and CRP constituted the most sensitive combination.(41) Polepalli et al. (2025) reported TLC had low sensitivity and specificity in 100 neonates, whereas CRP showed high sensitivity (83.3%), reinforcing their complementary roles.(42) Leukopenia, however, when present (57 of 65 leukopenic neonates were culture-positive), strongly corroborates sepsis, supporting TLC's role as a confirmatory parameter in the diagnostic algorithm.

Combined biomarker strategies. A multi-parameter approach consistently outperforms any single marker. Shahid et al. (2025) demonstrated that combined CRP and TLC achieved sensitivity 92.04%, specificity 94.64%, PPV 94.55%, NPV 92.18%, and overall accuracy 93.33% in 225 neonates.(43) Sorsa (2018) found that the CRP + WBC combination raised sensitivity to 78.5% and specificity to 83%, superior to either parameter alone.(40) Bharathi et al. (2021) reported that combined CRP and WBC sensitivity improved to 78.57% and specificity to 81.81%, compared with 71.4% and 21.43% for CRP alone and WBC alone, respectively.(39) Li et al. (2021) demonstrated that the CRP-to-platelet ratio (CPR) was an independent predictor of neonatal sepsis severity (OR: 1.015; $p < 0.001$), with AUC 0.68, reflecting the additive value of combining these two parameters.(44) Manvitha et al. (2023) found that the Haematological Scoring System (HSS) with score ≥4 demonstrated sensitivity 92.24% and specificity 71.73%, suggesting that formally combining all haematological parameters into a composite score is clinically advantageous.(45) These findings collectively support a multi-parameter diagnostic framework for neonatal sepsis rather than reliance on any single biomarker.

Novel and emerging biomarkers. While the present study focused on CRP, TLC, and platelet count — the parameters most universally available in resource-limited settings — emerging evidence supports the diagnostic contribution of advanced biomarkers. Sethi et al. (2023) found high-sensitivity CRP (hs-CRP) achieved sensitivity of 100% with NPV markedly superior to standard CRP.(46) Goyal et al. (2024) demonstrated that point-of-care CRP correlated strongly with laboratory CRP ($r = 0.80$; $p < 0.001$) and required only 12 ± 3 minutes compared to 366 ± 61 minutes for standard methods.(47) Sharma et al. (2024) found POC-serum amyloid A (SAA) diagnostically equivalent to procalcitonin and hs-CRP for neonatal sepsis.(48) Sankar et al. (2022) identified differential microRNA expression (miR-21, miR-181b, miR-223) as potential sepsis diagnostic and prognostic adjuncts, reflecting immune dysregulation beyond conventional parameters.(49) Goswami et al. (2022) demonstrated that neutrophil CD64 expression achieved sensitivity of 92% for culture-positive neonatal sepsis in preterm infants, outperforming CRP in this specific subgroup.(50) These advances suggest that future diagnostic algorithms may incorporate molecular and cellular biomarkers alongside conventional parameters.

Demographic findings. The slight male preponderance (51.6% vs 48.4%) is consistent with prior literature. Mohakud et al. (2022) found 53% male predominance among culture-positive neonates, and Jatsho et al. (2020) reported 52.3% male infants, with the sex difference attributed to immune and genetic variations.(22,23) However, no statistically significant differences in CRP, TLC, or platelet count were observed between sexes, modes of delivery, or between EOS and LOS groups in the current study ($p > 0.05$ for all), confirming that the diagnostic utility of these biomarkers is independent of these demographic variables.

Strengths and Limitations

Strengths: This study enrolled a relatively large sample ($n = 190$) with simultaneous collection of CRP, TLC, platelet count, and blood culture from the same venepuncture episode, minimising pre-analytical variability. Both EOS and LOS were included, providing a comprehensive clinical spectrum. Blood culture was rigorously used as the reference standard. Detailed clinical and laboratory profiling enabled multiple subgroup and correlation analyses. The study was conducted in an NICU setting representative of tertiary care centres in North India, with clinically relevant microbiology.

Limitations: The single-centre design may limit generalisability to other institutions with different patient populations, microbial profiles, and antibiotic resistance patterns. Biomarkers were assessed at a single time point, precluding evaluation of dynamic changes that serial measurements might reveal — particularly important for CRP in early EOS. Blood culture sensitivity in neonates is inherently constrained by small collectible blood volumes (approximately 1 mL), potentially misclassifying true sepsis cases as culture-negative. Newer biomarkers — including procalcitonin, interleukins, immature platelet fraction, and hs-CRP — were not evaluated. Long-term neurodevelopmental and mortality outcomes were not followed.

Conclusion

In this cross-sectional study of 190 neonates with suspected sepsis, serum CRP was the most accurate individual biomarker for predicting blood culture positivity, with sensitivity 89.3% and specificity 77.9%. Thrombocytopenia served as an important supplementary diagnostic marker, with a significant inverse CRP-platelet correlation ($r = -0.182$; $p = 0.012$) reflecting shared inflammatory pathophysiology. TLC, though of limited sensitivity, contributed high specificity when leukopenia was present, supporting its role as a confirmatory parameter. The microbiological profile was dominated by *Klebsiella pneumoniae* and *Acinetobacter* species, reflecting the persistent gram-negative burden in tertiary NICU settings, with a notable proportion of *Candida* infections emphasising the growing importance of fungal sepsis among critically ill neonates.

A combined multi-parameter approach using CRP, TLC, and platelet count, interpreted in conjunction with clinical assessment and blood culture findings, optimises early diagnosis of neonatal sepsis and supports rational antimicrobial stewardship — particularly in resource-limited settings where advanced diagnostics are unavailable. Future multicentre studies incorporating serial biomarker measurements, procalcitonin, hs-CRP, and immature

platelet fraction are warranted to further refine neonatal sepsis diagnostic algorithms.

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