

Clinical Utility of Platelet Indices in Predicting the Severity of Neonatal Sepsis

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ABSTRACT

Objective: To compare the effectiveness of platelet indices and other hematological parameters from a complete blood count (CBC) in the diagnosis of neonatal sepsis.

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Department of Haematology, Combined Military Hospital Lahore, Pakistan from Mar to Sep 2024.

Methodology: In total, 262 neonates were included in the study. Neonates without sepsis were 122 and neonates diagnosed with sepsis, either culture proven or clinically defined were 140. Haematological parameters including CBC values, platelet indices and C-reactive protein (CRP) levels were analyzed. Independent t-test and Mann-Whitney tests were used to assess significant differences. Chi-square test was applied to know the correlation for significant variables and ROC curve analysis were used to measure the diagnostic accuracy of the variables showing statistically significant differences in means.

Results: In this study, 262 patients were evaluated, comprising 60.3% males and 39.7% females. Sepsis was diagnosed in 53.4% of the cohort, with culture positivity was seen only in 16%. Abnormalities in haematological parameters included anemia (12.2%), leukopenia (1.5%), leukocytosis (12.2%), thrombocytopenia (17.6%), and thrombocytosis (13%). Neonates with sepsis exhibited significantly higher median values of TLC 13.9 (9.2-19.6), ANC 7.5 (5.0-11.5), AMC 1.5 (1.0-2.5), and CRP 28.0 (11.1-54.4) alongside significantly lower median Plt count 215 (157-372) and lower mean Hb ($p=0.001$). ROC curve analysis showed elevated CRP, TLC, ANC, and AMC had more AUC than that of PDW in diagnosing sepsis in neonates.

Conclusion: this study showed that neonates diagnosed with sepsis showed significantly higher PDW but other platelet indices had no significant differences between septic and non-septic neonates. Elevated levels of TLC, ANC, AMC and CRP showed better diagnostic accuracy as compared to the platelet indices (PDW).

Keywords: Complete blood count, Neonates, Neonatal sepsis, Platelets, Sepsis.

How to Cite This Article: Mian AW, Rober HM, Rana NA, Hafeez A, Mughal Z. Clinical Utility of Platelet Indices in Predicting the Severity of Neonatal Sepsis. *Pak Armed Forces Med J* 2026; 76(5): 730-734. DOI: <https://doi.org/10.51253/pafmj.v76i5.13034>

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INTRODUCTION

Sepsis, characterized by a maladaptive host immune response to infection, presents definitional challenges in pediatric populations, with a notably high incidence observed in neonates, combined with the absence of reliable biomarkers, hinder consensus. Platelets, known for their role in haemostasis and thrombosis, are now recognized for their involvement in both innate and adaptive immunity.¹

Platelet indices, including platelet count, mean platelet volume (MPV), plateletcrit (PCT), and immature platelet fraction (IPF), may be valuable predictors in cases of neonatal illness. As acute-phase reactants, these parameters can fluctuate in response to inflammation and alterations in platelet consumption and production.² Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), and Platelet Large Cell Ratio (P-LCR) are hematological

indices reflecting platelet size and variability and help identify thrombocytopenia causes but aren't widely used in routine.³

Blood culture and sepsis screening are costly and delayed, while platelet indices like PLT, MPV, PDW, and P-LCR, accessible via routine tests, may improve neonatal sepsis diagnosis. Early detection is critical due to subtle and non-specific symptoms and the need of critical therapeutic decisions.^{4,5,6}

Maternal and neonatal factors contribute to neonatal sepsis. Markers like CRP, IL-6, IL-8, TNF-alpha, and procalcitonin aid in diagnosis. While no global consensus exists, CRP with total leukocyte count (TLC), and blood culture is valuable for screening.^{7,8}

Platelet indices, like MPV, are accessible tests with potential prognostic value in septic shock remains underexplored. Studies have showed that patients with low platelets and high mean platelet volume (MPV had) more severe illness. Additionally,

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Received: 28 Dec 2024; revision received: 05 Sep 2026; accepted: 09 Sep 2026

reduced platelets and elevated MPV had shorter survival.^{9,10}

The objective of this study is to identify the clinical effectiveness of platelet indices (relatively newer and less used parameter) in diagnosis of neonatal sepsis and to compare their diagnostic accuracy with other laboratory parameters including routine CBC and CRP levels.

METHODOLOGY

This cross-sectional analytical study was done at Neonatal Intensive Care Unit of Combined Military Hospital Lahore Pakistan for the period of 6 months starting March 2024. Ethical approval was given by the Research Institutional Review Board, Combined Military Hospital Lahore, dated February 2024 (IRB number 504/2024). Sample size was calculated via WHO calculator. It came out to be 262 based on prevalence of neonatal sepsis 12.3% in Pakistan,¹¹ 95% CI, and 3.98% margin of error. Patient induction was carried out by non-probability consecutive sampling.

Inclusion Criteria: Neonates both male and female aged up to 28 days, suspected of sepsis, were included in the study and taken as positive cases following the provision of written informed consent by their parents. Neonates not fulfilling the criteria for sepsis as defined earlier and had CRP levels below 6 µg/L were taken as negative controls.

Exclusion Criteria: Neonates with low APGAR (score <5) at birth, presence of congenital malformations, metabolic disorders and congenital cardiac abnormalities were excluded.

International consensus definition was used to define neonatal sepsis. Culture proven sepsis included cases with positive growth on blood, urine or cerebrospinal fluid (CSF) culture and clinical signs of tachycardia, tachypnea, hyperthermia / hypothermia. Clinical/suspected sepsis was defined as cases with negative cultures showing clinical signs of sepsis as mentioned earlier along with leukocytosis (TLC > 20x10⁹/L), leukopenia (TLC < 5x10⁹/L), raised CRP (>6 µg/L) or presence of predisposing factors including maternal fever. Severe sepsis was defined as a patient with sepsis showing signs of multiorgan failure or septic shock.¹⁰

For the patients included in this study, detailed history with complete physical examination was done and relevant laboratory parameters were recorded. For all neonates, samples taken included blood/urine/CSF (for culture and sensitivity in

culture media), Complete blood count (in EDTA tube), CRP (in serum tubes). Culture was performed on BACTALERT. CBC was done on XN-1000 automated haematology analyzer and CRP was analyzed on COBAS-501 automated chemistry analyzer. Leukopenia was defined as TLC below 4x10⁹/L, leukocytosis as TLC above 20x10⁹/L, anaemia as Hb <12g/dL, thrombocytopenia as Plt < 150x10⁹/L, and thrombocytosis as Plt >450x10⁹/L. A low PDW was defined as value <9.4fL and high PDW as >17.1fL. Absolute neutrophil count (ANC) <3x10⁹/L was considered as neutropenia and >7x10⁹/L as neutrophilia. Absolute monocyte count (AMC) below 0.1x10⁹/L as monocytopenia and >1.7x10⁹/L as monocytosis.

Statistical analysis was done with the use of Statistical Package for Social Sciences version 26. Normality was checked using Kolmogorov-Smirnov test, a *p*-value of >0.05 was considered significant. Quantitative variables with normal distribution pattern were presented as Mean±SD and included haemoglobin (Hb), hematocrit (Hct), and platelet-large cell ratio (P-LCR) showing *p*-values of 0.2, 0.2, and 0.55 respectively; other variables that did not show normal distribution were TLC, RBC, MCV, MCH, RDW, PDW, PCT, ANC, ALC, AMC, AEC, age, CRP (each with *p*-value 0.001), Plt (*p*-value 0.004), and MPV (*p*-value 0.008) these were expressed as median and interquartile ranges (IQR). Qualitative data was presented as frequencies and percentages. Independent t-test and Mann-Whitney tests were used to assess the statistical significance of quantitative variables. For variables showing statistically significant values, ROC curve was used to measure diagnostic accuracy along with sensitivity, specificity and optimal cutoff values. A *p*-value of <0.05 and area under the curve (AUC) >0.5 were employed as statistically significant.

RESULTS

In this study a total of 262 patients were included in the assessment process. Males were 60.3% (158/262) and females were 39.7% (104/262). Patients diagnosed with sepsis made up 53.4% (140/262). Culture positivity was seen in 16% (42/262) of the patients. Mean age of the patients with and without sepsis was 4.8±4.3 days and 4.7±4.1 days respectively. Anaemia was seen in 12.2% (32/262), leukopenia in 1.5% (4/262), leukocytosis in 12.2% (32/262), thrombocytopenia in 17.6% (46/262) and thrombocytosis in 34.13% (34/262) of patients. Low

ANC was seen in 23.7% (62/262), high ANC in 35.9% (94/262), and monocytosis in 35.1% (92/262).

The mean Hb ($p=0.001$) and Hct ($p=0.001$) were significantly lower in patients with sepsis (Table-I).

Table-I: Comparison of Different Variables Between Neonates with and Without Sepsis (n=262)

Variables	Mean±SD		p-value
Hb (g/ dL)	16.4±2.3	No sepsis	0.001
	14.5±3.0	Sepsis	
Hematocrit (%)	48.9±7.08	No sepsis	0.001
	43.8±8.8	Sepsis	
P-LCR	29.3±5.9	No sepsis	0.08
	30.8±8.1	Sepsis	

Haemoglobin (Hb), platelet large cell ratio (P-LCR)

The median levels of variables in neonates with sepsis showed TLC 13.9(9.2-19.6) $\times 10^9/L$, Plt 215 (157-372) $\times 10^9/L$, ANC 7.5 (5.0-11.5) %, AMC 1.5 (1.0-2.5) %, and PDW 12.8 (10.3-14.4) fL. Levels of Hb, TLC, Plt count, ANC, AMC and PDW showed strong association with diagnosis of sepsis (Table-II).

Table-II: Comparing Medians of Values in Neonates with and without Sepsis (n=262)

Parameters	Study Groups		p-value
	No Sepsis (n=122) Median (IQR)	Sepsis (n=140) Median (IQR)	
TLC ($\times 10^9/L$)	10.9 (7.8-12.8)	13.9 (9.2-19.6)	0.001
RBC ($\times 10^{12}/L$)	4.7 (4.2-5.1)	4.4 (3.7-5.1)	0.003
MCV (fL)	103.3 (100.1-106.9)	101.9 (95.7-105.8)	0.003
MCH (pg)	34.6 (33.5-36.2)	33.9 (31.7-35.1)	0.003
PLT ($\times 10^9/L$)	311 (210.0-386.0)	215.0 (157.0-372.0)	0.001
RDW-SD (fL)	62.2 (56.6-66.2)	60.3 (56.7-66.6)	0.522
PDW (fL)	11.9 (10.9-13.2)	12.8 (10.3-14.4)	0.181
MPV (fL)	10.7 (10.1-11.1)	10.7 (9.9-11.6)	0.356
PCT (%)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.438
ANC (%)	3.6 (2.6-5.4)	7.5 (5.0-11.5)	0.001
ALC (%)	3.6 (2.6-5.5)	3.7 (2.5-5.3)	0.680
AMC (%)	1.4 (1.0-1.7)	1.5 (1.0-2.5)	0.015
AEC (%)	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.192
Age (years)	3.0 (1.0-7.0)	3.0 (1.0-8.0)	0.984
CRP (mg/L)	1.1 (0.6-2.4)	28.0 (11.1-54.4)	0.001

Total leukocyte count (TLC), red blood-cells count (RBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelet count (Plt), red-cell distribution width-standard deviation (RDW-SD), platelet distribution width (PDW), mean platelet volume (MPV), fL, plateletcrit (PCT), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute eosinophil count (AEC), C-reactive protein (CRP)

Area under the curve (AUC) was calculated with value <0.5 was considered non-discriminating, 0.5-0.6 as poorly discriminating, 0.6-0.7 as acceptable, 0.7-0.8 excellent, and >0.9 as outstanding in discriminating septic from non-septic neonates. AUC for CRP was 0.962 (95% confidence interval 0.91-1.44, $p=0.001$), ANC 0.758 (95% confidence interval 0.72-0.79, $p=0.001$), and TLC 0.689 (95% confidence interval 0.65-0.72, $p=0.001$) showed good diagnostic accuracy (Table III).

Table-III: Area under the curve (AUC) in Descending Order with Sensitivity and Specificity (n=262)

Variable	AUC	Cutoff Value	Sensitivity	Specificity
CRP	0.962	5.95	91.4%	99.9%
ANC	0.758	4.85	80.0%	67.2%
TLC	0.689	15.4	44.3%	93.4%
AMC	0.587	2.41	28.6%	98.4%
PDW	0.548	12.95	50.0%	70.5%
Plt	0.380	-	-	-
Hb	0.317	-	-	-

Area under the curve (AUC), C-reactive protein (CRP), absolute neutrophil count (ANC), total leukocyte count (TLC), absolute monocyte count (AMC), platelet distribution width (PDW), platelet count (Plt), haemoglobin (Hb)

AMC 0.587(95% confidence interval 0.56-0.62, $p=0.015$), and PDW 0.584 (95% confidence interval 0.52-0.58, $p=0.181$) showed poor diagnostic accuracy with AUC of >0.5 , whereas Hb and Plt had lower (<0.5) AUC values (Figure).

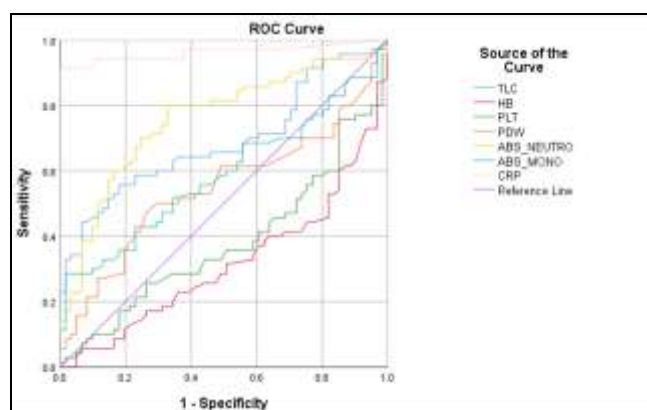


Figure: ROC curve analysis of CRP (light-pink), ANC (yellow), TLC (blue), AMC (green), PDW (orange), Hb (red), and Plt (dark green)

DISCUSSION

Septicemia is a serious condition/disease causing widespread damage and is a major contributor to neonatal mortality. It typically occurs within the first 28 days of life, a critical period for development. The incidence is rising due to various factors, affecting 1 in 8 out of every 1,000 live births, and significantly increases newborn morbidity and mortality.⁷

Serum levels of acute-phase reactants, including CRP, leukocyte activation markers, interleukins, tumor necrosis factor-alpha, and procalcitonin, rise during infection and serve as non-specific indicators of bacterial sepsis. While no global consensus exists on neonatal sepsis screening, CRP is widely recognized as an inflammatory marker. Its measurement, alongside

TLC, DLC, and blood culture, aids in diagnosing or ruling out sepsis.⁸

Platelet indices, like mean platelet volume (MPV), are simple and widely available blood tests. However, their ability to predict outcomes in septic shock isn't well understood. More research is needed to determine their real impact on patient care.⁹

Platelets (Plt) are essential for blood clotting, immune response, and keeping blood vessels intact.^{1,2,3} Platelet indices help assess platelet count, size, and how they function in the body. Common measures include platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT). A drop in platelet count can be a serious and has been established as an independent risk factor for critically ill patients.⁶ The APACHE II system recognizes thrombocytopenia as an independent risk factor for mortality. However, the link between other platelet indices and disease severity or patient outcomes is still being studied.¹⁰

Recent studies have explored inflammatory markers for diagnosing neonatal sepsis, but their high cost limits routine use, especially in resource-poor settings. Hematological parameters offer a practical, affordable alternative, though study results vary possibly due to differences in study populations, methodologies, and cut-off values. Still, they remain useful for screening and may help reduce unnecessary antibiotic use.¹²

This study showed mean age of the neonates diagnosed with sepsis of 4.7 days with males making up 60.3%, Talat *et al.* reported in their study about males to be 58.5%.¹³ Culture positivity was seen in 16% of neonates diagnosed, Choudhary *et al.* reported a much higher culture positivity of 35.2%, and Mayuga *et al.* reported culture positivity in 3-8% of neonates with sepsis. Moreover, Marks *et al.* showed that culture positivity was seen within 24 hours in more than 90% of cases.^{4,12,14}

This study showed that 12.2% of the patients had anaemia, 17.7% thrombocytopenia, and 12.2% had leukocytosis. Talat *et al.* quoted anaemia to be seen in 27.4% and thrombocytopenia in 51.8% neonates diagnosed with sepsis. Ahmad *et al.* reported thrombocytopenia in 27.7% and Akarsu *et al.* reported thrombocytopenia in 20% of cases. Adane *et al.* reported incidence of leukocytosis in septic neonates of 7.7%. Morag *et al.* have reported that incidence of leukocytosis was seen in 6.1% neonates with proven

infection out of 22% of patients manifesting raised TLC.^{15,16,17}

This study showed PDW out of platelet indices to be significantly higher in neonates with sepsis as well as positive correlation with diagnosis of sepsis (*p*-value 0.03). ROC curve analysis showed other variables (CRP, ANC & TLC) to be more accurate in diagnosing neonatal sepsis than PDW. Other platelet indices did not show any statistically significant difference among neonates in two groups. Talat *et al.*¹³ in their study published similar findings of platelet indices exhibiting no significant difference in culture positive and culture negative neonates. In contrast Nadeem *et al.* reported that platelet indices (MPV, P-LCR & PDW) were significantly higher in neonates admitted and had strong correlation with neonatal mortality. Nadeem showed sensitivity of PDW and MPV in culture positive case to be 14% and 26.4% respectively and specificity of 62% and 62.5%. Both PDW and MPV had *p*-values of >0.05.¹⁸

LIMITATIONS OF STUDY

The study focuses on diagnostic markers for neonatal sepsis but doesn't address long-term outcomes like development or survival outcomes after the diagnosis of sepsis. As a cross-sectional/point-in-time analysis, it only provides a snapshot of sepsis at one point, missing how it progresses over time. A longitudinal approach would better track changes in markers throughout the disease.

CONCLUSION

This study showed platelet distribution width (PDW) to be notably elevated in sepsis cases and correlated with the diagnosis, though other platelet indices showed no significant difference. ROC analysis indicated that CRP, ANC, and TLC were more accurate than PDW in diagnosing sepsis, which aligns with other studies suggesting minimal significance of platelet indices in neonatal sepsis outcomes.

Conflict of Interest: None.

Funding Source: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

AWM & HMR: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

NAR & AH: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ZM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

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