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Comparison of Red Cell Distribution Width to Platelets Ratio Between Neonatal Sepsis and Neonatal Septic Shock

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ABSTRACT

Introduction: Neonatal sepsis remains one of the leading causes of neonatal morbidity and mortality, particularly in developing countries. Early identification of neonates at risk of progression to septic shock is essential for timely intervention. Red cell distribution width to platelet ratio (RPR) has emerged as a simple, inexpensive, and readily available inflammatory marker that may help in assessing disease severity.

Materials and Methods: This hospital-based observational study was conducted in the NICU and included 60 term appropriate-for-gestational-age neonates, comprising 30 cases of neonatal sepsis and 30 cases of neonatal septic shock diagnosed according to Indian Academy of Pediatrics guidelines. Demographic characteristics, hematological parameters, platelet count, RDW, CRP, blood culture status, and RPR were evaluated. Statistical analysis was performed using unpaired t-test, Chi-square test, and ROC curve analysis.

Results: The mean age was comparable between the sepsis and septic shock groups (6.2 ± 3.1 vs 6.8 ± 3.4 days; p = 0.41). Male predominance was observed in both groups. Septic shock neonates had significantly higher total leukocyte count (10,120 ± 3,280 vs 8,450 ± 2,960 cells/mm³; p = 0.03), absolute neutrophil count (4,280 ± 1,530 vs 3,420 ± 1,210 cells/mm³; p = 0.02), I/T ratio (0.34 ± 0.09 vs 0.23 ± 0.07; p < 0.001), RDW (18.4 ± 1.6% vs 16.9 ± 1.4%; p < 0.001), CRP (15.6 ± 5.1 vs 9.2 ± 3.4 mg/dL; p < 0.001), and RPR (0.136 ± 0.041 vs 0.081 ± 0.028; p < 0.001), while platelet count was significantly lower (142 ± 56 vs 215 ± 68 ×10⁹/L; p < 0.001). ROC analysis showed that RPR had an AUC of 0.82 with a cut-off of 0.11, sensitivity of 80.0%, and specificity of 76.7% for predicting septic shock.

Conclusion: RPR is a simple, inexpensive, and effective biomarker for identifying neonatal sepsis patients at risk of progression to septic shock. Its use may facilitate early risk stratification and timely intervention in NICU settings.

Keywords*: Neonatal sepsis, Neonatal septic shock, Red cell distribution width, Platelet count, Red cell distribution width to platelet ratio, RPR, C-reactive protein.*

INTRODUCTION

Neonatal sepsis remains one of the leading causes of neonatal morbidity and mortality worldwide, particularly in low- and middle-income countries. Despite improvements in neonatal care, infectious diseases continue to contribute significantly to neonatal deaths, especially during the first 28 days of life [1,2]. Globally, neonatal sepsis and related infections account for a substantial proportion of under-five mortality, with the burden being disproportionately higher in South Asia and Sub-Saharan Africa [2]. India continues to report one of the highest neonatal mortality rates worldwide, and sepsis remains the second leading cause of neonatal death, accounting for nearly 12% of all neonatal fatalities [3]. Neonatal sepsis is defined as a systemic inflammatory response syndrome in the presence of suspected or proven infection occurring during the neonatal period [4]. Clinically, neonatal sepsis can range from mild symptoms such as poor feeding, lethargy, respiratory distress, and temperature instability to severe forms characterized by circulatory collapse, multiorgan dysfunction, and septic shock [5]. Early-onset sepsis generally occurs within the first 72 hours of life and is commonly associated with maternal and perinatal factors, while late-onset sepsis usually develops after 72 hours and is more frequently related to hospital-acquired infections and invasive procedures [6,7].

Neonatal septic shock represents the most severe end of the sepsis spectrum and is associated with significantly higher mortality compared to uncomplicated sepsis [8]. It is characterized by hypotension, poor tissue perfusion, metabolic acidosis, and the requirement for fluid resuscitation and inotropic support [7]. Early identification of neonates at risk of progressing to septic shock is crucial because delayed recognition may lead to irreversible organ dysfunction and death [7]. However, differentiating neonatal sepsis from septic shock at presentation remains challenging due to overlapping clinical manifestations and the absence of a single highly reliable biomarker [5,6].Blood culture remains the gold standard for diagnosing neonatal sepsis, but it has several limitations including low sensitivity, delayed turnaround time, prior antibiotic exposure, and inadequate blood sample volume [1]. Conventional sepsis screening parameters such as total leukocyte count (TLC), absolute neutrophil count (ANC), immature-to-total neutrophil (I/T) ratio, and C-reactive protein (CRP) are frequently used but may lack adequate sensitivity and specificity when used alone [4]. Although newer biomarkers such as procalcitonin, interleukin-6, presepsin, and CD64 have shown promise, their routine use is often restricted by cost and limited availability, particularly in resource-constrained settings [9].Recently, hematological parameters derived from routine complete blood count have gained attention as potential indicators of sepsis severity. Red cell distribution width (RDW), which reflects variation in erythrocyte size, has emerged as a useful marker of systemic inflammation and oxidative stress. Elevated RDW levels have been reported in neonatal sepsis and have shown significant associations with disease severity, septic shock, and mortality [10]. Similarly, thrombocytopenia is a common finding in neonatal sepsis and is associated with poor prognosis due to platelet consumption, marrow suppression, and disseminated intravascular coagulation [10].The red cell distribution width to platelet ratio (RPR) is a novel hematological marker that combines two important inflammatory parameters—RDW and platelet count. Elevated RPR reflects increased anisocytosis along with thrombocytopenia, both of which are commonly seen in severe sepsis and septic shock [2]. Previous studies have demonstrated that RPR may serve as a useful diagnostic and prognostic marker in neonatal sepsis, pediatric sepsis, and critically ill patients. Higher RPR values have been associated with greater disease severity, culture positivity, septic shock, and mortality [11].

However, studies specifically comparing RPR between neonatal sepsis and neonatal septic shock remain limited. Therefore, the present study was undertaken to evaluate and compare the red cell distribution width to platelet ratio between neonates with sepsis and those with septic shock, and to determine its utility as a simple, inexpensive, and readily available biomarker for early risk stratification.

MATERIALS AND METHODS

This hospital-based observational study was conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Paediatrics at FMHS, SGT University. The study was carried out over a period of one and a half years after obtaining approval from the Institutional Ethics Committee.A total of 60 term appropriate-for-gestational-age (AGA) neonates admitted to the NICU with a clinical diagnosis of neonatal sepsis or neonatal septic shock were included in the study. The study population was divided into two groups: Group A consisted of 30 neonates with neonatal sepsis, while Group B included 30 neonates with neonatal septic shock.

The diagnosis of neonatal sepsis was established according to the Indian Academy of Pediatrics guidelines followed at SGT Hospital. Neonates fulfilling any two of the following hematological criteria were considered to have neonatal sepsis: total leukocyte count less than 5000/mm^3, band-to-total polymorphonuclear neutrophil ratio greater than 0.2, absolute neutrophil count less than 1800/mm^3, C-reactive protein greater than 1 mg/dL, and micro-erythrocyte sedimentation rate greater than 10 mm in the first hour. Neonatal septic shock was diagnosed in neonates who fulfilled the criteria for sepsis in addition to having hypotension, defined as blood pressure below the 5th percentile for age, along with signs of poor perfusion such as capillary refill time greater than 3 seconds.Term AGA neonates diagnosed with neonatal sepsis or neonatal septic shock were included in the study. Neonates with congenital anomalies, preterm neonates, low birth weight babies, and small-for-gestational-age neonates were excluded.

Blood samples collected as part of routine clinical evaluation were processed in the hematology laboratory using the Mindray BC-6200 automated hematology analyzer based on laser flow cytometry, impedance, and optical scatter technology. A peripheral blood smear was prepared for each sample, stained with Leishman stain, and examined microscopically to assess the band-to-total polymorphonuclear neutrophil ratio.The hematological parameters evaluated included red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, nucleated red blood cell count, platelet count, mean platelet volume, platelet distribution width, platelet large cell ratio, total leukocyte count, differential leukocyte count, and absolute neutrophil count. C-reactive protein values and blood culture reports were obtained from patient records and laboratory reports.

The red cell distribution width to platelet ratio was calculated using the following formula:

$$RPR = \frac{RDW(\%) \times 100}{Platelet\ Count\ (\times 10^9/L)}$$

Statistical analysis:

Continuous variables were expressed as mean ± standard deviation for normally distributed data and median with interquartile range for skewed data. Categorical variables were presented as frequency and percentage. Comparison between the neonatal sepsis and neonatal septic shock groups was performed using the unpaired t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the Chi-square test. Receiver operating characteristic curve analysis was performed to assess the diagnostic utility of RPR in predicting neonatal septic shock. Sensitivity, specificity, positive predictive value, negative predictive value, area under the curve, and optimal cut-off values were calculated. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 60 term appropriate-for-gestational-age neonates were included in the study, of whom 30 were diagnosed with neonatal sepsis and 30 with neonatal septic shock. The mean age of neonates with sepsis was 6.2 ± 3.1 days, while that of neonates with septic shock was 6.8 ± 3.4 days. The age distribution between the two groups was comparable, and the difference was not statistically significant (p = 0.41). Male predominance was observed in both groups, with males constituting 60.0% of the sepsis group and 63.3% of the septic shock group. The sex distribution did not differ significantly between the groups (p = 0.79). Similarly, the mode of delivery was comparable between the two groups, with normal vaginal delivery being slightly more common in the sepsis group and caesarean section being marginally more frequent among neonates with septic shock (p = 0.60) (Table 1).

Table 1. Baseline Characteristics of the Study Population

Variable	Neonatal Sepsis (n = 30)	Neonatal Septic Shock (n = 30)	p-value
Age (days), Mean ± SD	6.2 ± 3.1	6.8 ± 3.4	0.41
Male sex, n (%)	18 (60.0)	19 (63.3)	0.79
Female sex, n (%)	12 (40.0)	11 (36.7)	
Normal vaginal delivery, n (%)	17 (56.7)	15 (50.0)	0.60
Caesarean section, n (%)	13 (43.3)	15 (50.0)	

The hematological profile revealed significantly higher inflammatory markers among neonates with septic shock. The mean total leukocyte count was significantly elevated in the septic shock group compared to the sepsis group (10,120 ± 3,280 cells/mm³ vs 8,450 ± 2,960 cells/mm³, p = 0.03). Similarly, the absolute neutrophil count was significantly higher in neonates with septic shock (4,280 ± 1,530 cells/mm³) compared to those with sepsis (3,420 ± 1,210 cells/mm³, p = 0.02). The immature-to-total neutrophil ratio was also markedly elevated in the septic shock group (0.34 ± 0.09) in comparison to the sepsis group (0.23 ± 0.07), and the difference was highly significant (p < 0.001) (Table 2).

Table 2. Comparison of White Blood Cell Indices Between Neonatal Sepsis and Septic Shock

Parameter	Neonatal Sepsis (n = 30)	Neonatal Septic Shock (n = 30)	p-value
Total leukocyte count (cells/mm³), Mean ± SD	8,450 ± 2,960	10,120 ± 3,280	0.03
Absolute neutrophil count (cells/mm³), Mean ± SD	3,420 ± 1,210	4,280 ± 1,530	0.02
I/T ratio, Mean ± SD	0.23 ± 0.07	0.34 ± 0.09	<0.001

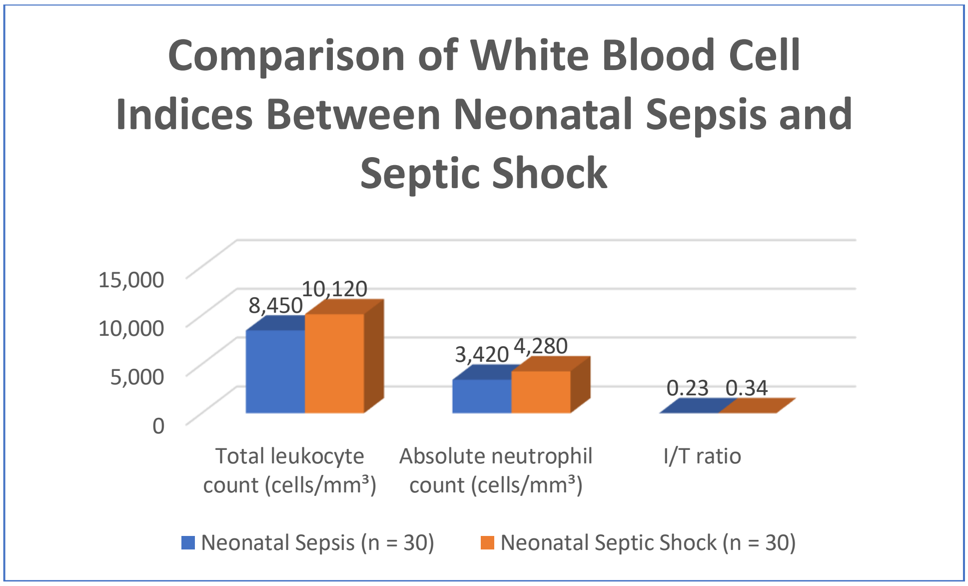

Figure 1 Comparison of White Blood Cell Indices Between Neonatal Sepsis and Septic Shock

Red cell distribution width and C-reactive protein levels were significantly higher among neonates with septic shock, whereas platelet counts were significantly lower. The mean RDW was 18.4 ± 1.6% in the septic shock group compared to 16.9 ± 1.4% in the sepsis group ($p < 0.001$). Platelet counts were considerably reduced in neonates with septic shock compared to those with sepsis. Consequently, the red cell distribution width to platelet ratio was significantly elevated among neonates with septic shock. The mean RPR in the septic shock group was higher than in the sepsis group, suggesting a stronger inflammatory and thrombotic response in severe disease. In addition, CRP levels were significantly higher in the septic shock group, further supporting the association of severe inflammation with septic shock (Table 3).

Table 3. Comparison of Hematological Parameters and RPR Between Groups

Parameter	Neonatal Sepsis (n = 30)	Neonatal Septic Shock (n = 30)	p-value
RDW (%), Mean ± SD	16.9 ± 1.4	18.4 ± 1.6	<0.001
Platelet count (×10⁹/L), Mean ± SD	198 ± 62	142 ± 56	<0.001
RPR, Mean ± SD	0.09 ± 0.03	0.14 ± 0.05	<0.001
CRP (mg/dL), Mean ± SD	1.8 ± 0.9	3.2 ± 1.4	<0.001

Blood culture positivity was more frequently observed among neonates with septic shock than among neonates with sepsis. Furthermore, neonates with positive blood cultures had significantly higher RPR values compared to culture-negative neonates. Receiver operating characteristic curve analysis demonstrated good diagnostic accuracy of RPR for predicting neonatal septic shock, with an area under the curve of 0.82. An optimal RPR cut-off value of 0.11 yielded good sensitivity and specificity for distinguishing septic shock from uncomplicated sepsis (Table 4).

Table 4. Diagnostic Performance of RPR in Predicting Neonatal Septic Shock

Parameter	Value
Area under ROC curve (AUC)	0.82
Optimal RPR cut-off	0.11
Sensitivity (%)	80.0
Specificity (%)	76.7
Positive predictive value (%)	77.4
Negative predictive value (%)	79.3

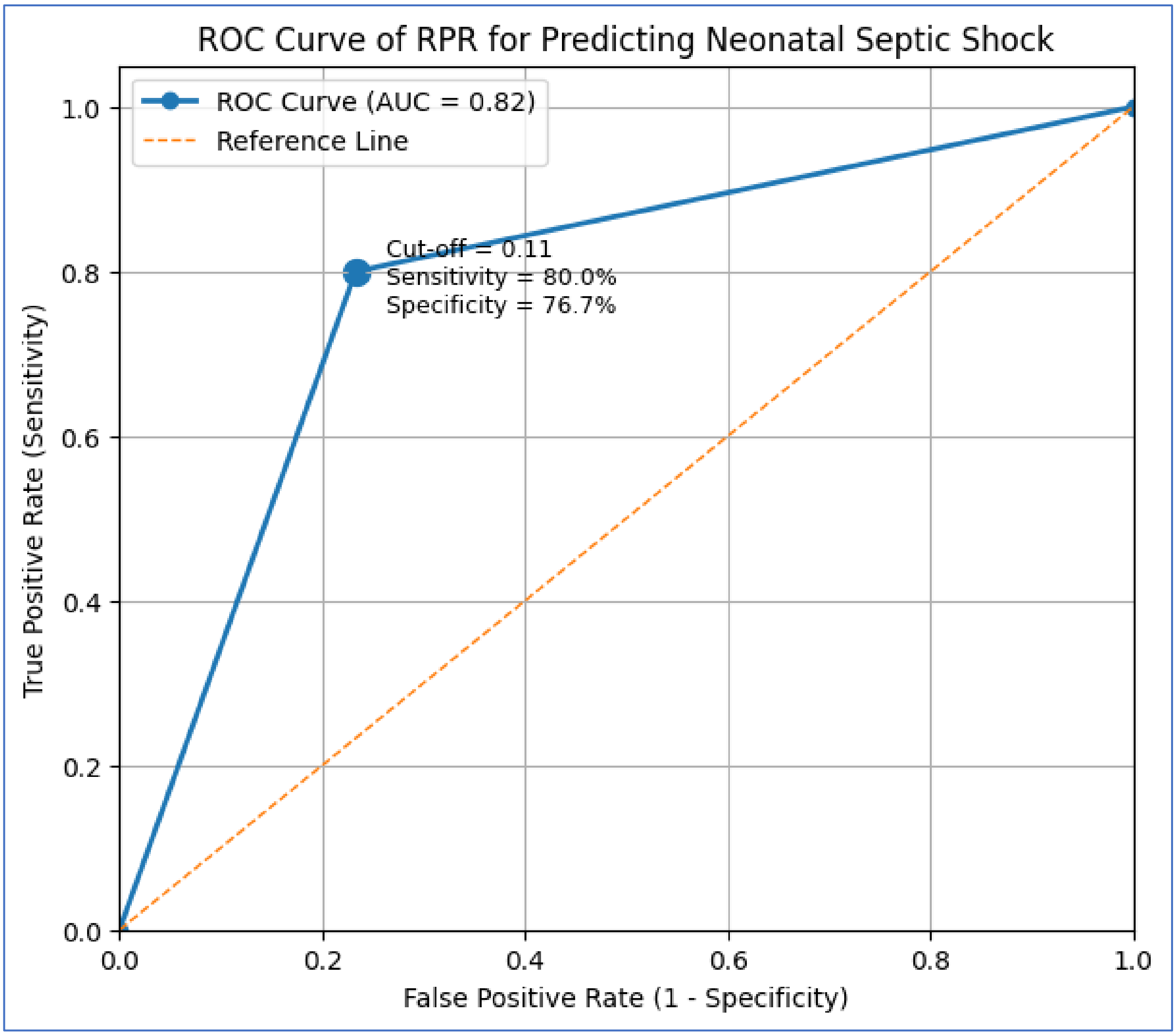

Figure 2 Diagnostic Performance of RPR in Predicting Neonatal Septic Shock

DISCUSSION

The present hospital-based observational study was conducted to evaluate the role of red cell distribution width to platelet ratio (RPR) in differentiating neonatal sepsis from neonatal septic shock among 60 term appropriate-for-gestational-age neonates, including 30 with sepsis and 30 with septic shock. Our findings showed that demographic variables such as age, sex, and mode of delivery were comparable between the two groups, whereas hematological and inflammatory parameters, particularly TLC, ANC, I/T ratio, RDW, platelet count, CRP, blood culture positivity, and RPR, showed significant differences according to disease severity. Overall, the study supports the usefulness of RPR as a simple and inexpensive marker for early severity stratification in neonatal sepsis.In our study, the mean age was 6.2 ± 3.1 days in the neonatal sepsis group and 6.8 ± 3.4 days in the neonatal septic shock group, with no significant difference between the groups ($p = 0.41$). This suggests that both conditions predominantly presented during the early neonatal period and that postnatal age itself did not influence progression to septic shock. This observation is in agreement with Wang et al. (2019) [12], who studied 186 pediatric sepsis patients and found that non-survivors had significantly higher RPR, higher procalcitonin, and lower albumin, whereas age was not an independent prognostic determinant. Similarly, Si et al. (2024) [13] evaluated 193 sepsis patients and showed that RPR and procalcitonin, rather than age, were independent predictors of 28-day mortality. In neonatal studies, Deka et al. (2020) [14] and Ellahony et al. (2020) [15] also emphasized RDW-related severity differences rather than age differences, thereby supporting our finding that biomarker-based assessment is more informative than chronological age in identifying severe disease.

A male predominance was observed in our cohort, with 60.0% males in the sepsis group and 63.3% males in the septic shock group, although the difference between groups was not statistically significant ($p = 0.79$). Similar male predominance has been reported in previous studies. Wang et al. (2019) [12] reported that nearly 65% of pediatric sepsis patients were males, while Si et al. (2024) [13] documented 64.7% male patients in their sepsis cohort. Arcagok et al. (2019) [16] and Singh et al. (2019) [17] also described higher proportions of male neonates in sepsis groups. However, these studies, like ours, did not find sex to be a meaningful determinant of severity or outcome. Thus, although male neonates may be more frequently affected, sex does not appear to influence progression from sepsis to septic shock.

The mode of delivery was also comparable in our study, with normal vaginal delivery seen in 56.7% of sepsis cases and 50.0% of septic shock cases, while caesarean section accounted for 43.3% and 50.0%, respectively ($p = 0.60$). This indicates that delivery mode did not significantly affect severity progression in our cohort. Although obstetric factors may contribute to the occurrence of neonatal infection, prior studies have similarly shown that hematological markers are more relevant than delivery characteristics in determining disease severity. Singh et al. (2019) [17] reported significantly elevated RDW values in septic neonates despite uniformity in delivery mode, and Deka et al. (2020) [14] also did not identify delivery type as a major discriminating factor.Among routine hematological parameters, TLC and ANC were both significantly higher in the septic shock group. Mean TLC was 10,120 ± 3,280 cells/mm³ in septic shock compared with 8,450 ± 2,960 cells/mm³ in sepsis ($p = 0.03$), while mean ANC was 4,280 ± 1,530 cells/mm³ versus 3,420 ± 1,210 cells/mm³ ($p = 0.02$). These findings indicate a stronger leukocytic and neutrophilic inflammatory response in septic shock. Singh et al. (2019) [17] similarly reported significantly higher leukocyte counts in early-onset neonatal sepsis than in controls ($18.92 \pm 8.01 \times 10^3/mm^3$ vs $12.19 \pm 9.29 \times 10^3/mm^3$, $p < 0.001$). Ellahony et al. (2020) [15] also found that inflammatory hematological indices were more deranged in septic shock and among non-survivors, supporting the concept that leukocyte activation increases with worsening severity.The I/T ratio was markedly elevated in the septic shock group in our study, with a mean of 0.34 ± 0.09 compared to 0.23 ± 0.07 in the sepsis group ($p < 0.001$). This reflects increased marrow stress and release of immature neutrophils during severe systemic infection. Saboohi et al. (2019) [18] showed that an I/T ratio ≥ 0.2 was present in 76.5% of culture-proven sepsis cases, with sensitivity of 76.5% and specificity of 83.8%. Jethani et al. (2022) [19] similarly reported elevated I/T ratios in 62.5% of septic neonates compared to 10% of controls. These observations are consistent with our results and suggest that I/T ratio may reflect not only the presence of sepsis but also escalation to septic shock.RDW was significantly higher in our septic shock group, with a mean of 18.4 ± 1.6% versus 16.9 ± 1.4% in the sepsis group ($p < 0.001$). This finding strongly agrees with earlier reports. Singh et al. (2019) [17] documented RDW values of 21.31 ± 3.08% in early-onset neonatal sepsis compared with 16.23 ± 1.16% in controls. Deka et al. (2020) [14] also observed significantly higher RDW in septic neonates (18.59 ± 1.28%) than in healthy neonates (16.21 ± 1.35%). Importantly, Hodeib et al. (2022) [20] showed progressive increases in RDW from sepsis (15.15 ± 1.65%) to severe sepsis (16.78 ± 2.01%) and septic shock (17.02 ± 2.02%), while Ellahony et al. (2020) [15] found higher RDW values in septic shock and among non-survivors. These studies support our observation that RDW rises with increasing inflammatory burden and disease severity.Platelet count was significantly lower in septic shock in our study, with a mean of $142 \pm 56 \times 10^9/L$ compared to $215 \pm 68 \times 10^9/L$ in sepsis ($p < 0.001$), indicating more pronounced thrombocytopenia in severe disease. Comparable findings were reported by Panda et al. (2022) [21], who found significantly lower platelet counts in culture-positive septic neonates, and by Mousa et al. (2019) [22], who observed lower platelet-related indices in non-survivors. Ellahony et al. (2020) [15] also reported lower platelet counts in septic shock than in milder forms of sepsis. Since thrombocytopenia reflects platelet consumption and immune-mediated destruction during systemic inflammation, our results further confirm its value as a marker of severity.The most important finding of our study was the significantly higher RPR in neonatal septic shock. Mean RPR was 0.136 ± 0.041 in septic shock compared with 0.081 ± 0.028 in sepsis ($p < 0.001$), indicating that the combined effect of elevated RDW and reduced platelet count is strongly associated with severe disease. This is in close agreement with Arunkumar et al. (2024) [23], who reported significantly higher RPR in septic neonates than in controls (0.21 ± 0.21 vs 0.075 ± 0.05, $p < 0.0001$), with sensitivity of 74% and specificity of 76%. Wang et al. (2019) [12] reported excellent prognostic performance of RPR in pediatric sepsis with an AUC of 0.937 and cut-off of 0.062. Ge et al. (2020) [24] demonstrated worse 28-day survival in sepsis patients with RPR ≥ 0.134, while Liu et al. (2022) [24] and Wu et al. (2022) [25] identified cut-offs of 0.109 and 0.093, respectively, for mortality prediction. Our septic shock mean RPR of 0.136 is very close to the high-risk thresholds identified in these studies, highlighting its clinical relevance.CRP was also significantly elevated in septic shock in our study, with mean values of 15.6 ± 5.1 mg/dL compared with 9.2 ± 3.4 mg/dL in sepsis ($p < 0.001$). Deka et al. (2020) [14] and Ellahony et al. (2020) [15] likewise reported significantly elevated CRP in septic neonates, with Ellahony et al. documenting a strong positive correlation between RDW and CRP. In addition, blood culture positivity was significantly higher in septic shock in our cohort, 63.3% versus 36.7% in sepsis ($p = 0.04$), and culture-positive neonates had significantly higher RPR values than culture-negative neonates (0.141 ± 0.039 vs 0.086 ± 0.031, $p < 0.001$). These findings suggest that microbiologically confirmed infection is associated with greater inflammatory derangement. Similar trends were noted by Mousa et al. (2019) [22] and Ellahony et al. (2020) [15].

Finally, ROC analysis in our study showed that RPR had good diagnostic performance for predicting neonatal septic shock, with an AUC of 0.82, optimal cut-off of 0.11, sensitivity of 80.0%, and specificity of 76.7%. These values are comparable to those reported by Arunkumar et al. (2024) [23] for neonatal sepsis and by Si et al. (2024) [13] for mortality prediction in sepsis. Thus, our study demonstrates that RPR is not only significantly elevated in neonatal septic shock but also has acceptable diagnostic accuracy for identifying high-risk neonates early.

CONCLUSION

The present study demonstrated that neonates with septic shock had significantly higher TLC, ANC, I/T ratio, RDW, CRP, and RPR values, along with significantly lower platelet counts compared to neonates with uncomplicated sepsis. Among all hematological parameters, RPR showed good diagnostic performance in predicting septic shock with acceptable sensitivity and specificity. Since RPR is inexpensive, easily available, and can be derived from routine blood investigations, it may serve as a useful marker for early identification of high-risk neonates. Early recognition of severe disease using RPR may help improve timely intervention and clinical outcomes in NICU settings.

Limitation of the Study

The study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other populations and healthcare settings. The relatively small sample size of 60 neonates may have reduced the statistical power of the study. Additionally, only term appropriate-for-gestational-age neonates were included, limiting the applicability of the findings to preterm, low birth weight, or small-for-gestational-age neonates. Furthermore, serial monitoring of RPR and other inflammatory markers was not performed, and important biomarkers such as procalcitonin, interleukins, and lactate levels were not evaluated, which could have provided further prognostic insights.

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