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Investigating the role of red cell and platelet distribution width-to-platelet ratios in diagnosing early-onset neonatal sepsis

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Abstract:

BACKGROUND: Early and accurate diagnosis of early-onset neonatal sepsis (EONS) is vital in improving survival and outcome in affected neonates. To date, no single inflammatory biomarker has demonstrated both high sensitivity and specificity for the diagnosis of EONS.

OBJECTIVES: The objective of this study was to explore the role of the red cell distribution width-to-platelet ratio (RPR) and the platelet distribution width-to-platelet ratio (PPR) in the diagnosis of EONS.

MATERIALS AND METHODS: A case–control study was conducted at a tertiary hospital in Baghdad, Iraq, over 10 months. Cases included neonates with culture-positive EONS, while healthy controls were selected from the outpatient clinic in a ratio of case to control of 1:1. Sepsis screening was performed for all neonates within 12–24 h of life and composed of complete blood count, C-reactive protein, and bacterial culture and sensitivity. The results of complete blood counts, along with PPR and RPR values, were compared between cases and controls.

RESULTS: A total of 352 neonates (176 cases and 176 controls) were included. There was no statistically significant difference in demographical characteristics between groups. The univariate analysis revealed that RPR was higher in the case group than the control group, $P = 0.02$. In contrast, PPR failed to show a statistically significant difference between cases and controls, $P = 0.77$. On the receiver operating characteristic analysis, RPR had a sensitivity of 88.4% and specificity of 36.4% for predicting sepsis. PPR had a sensitivity of 77.9% and specificity of 27.3% for predicting sepsis.

CONCLUSION: RPR and PPR exhibit high sensitivity, making them useful as initial screening tools for EONS. However, their low specificity limits their reliability as standalone diagnostic markers.

Keywords:

Neonatal sepsis, platelet distribution width, red cell distribution width

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Introduction

Early-onset neonatal sepsis (EONS), defined as sepsis that arises within the first 72 h of life, represents a global health concern due to its high morbidity and mortality among newborns.[1] Early and accurate diagnosis of EONS is vital in improving survival and outcome in affected neonates.[2,3] Since the gold standard diagnostic method for EONS is isolating the causative agent by blood culture which takes at least 48 h, more rapid inflammatory markers are being increasingly used.[4]

The traditional biomarkers currently in use for EONS offer valuable diagnostic insights stemming from wide availability, high specificity, and relatively low cost.[5,6]

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On the other hand, they exhibit several limitations that constrain their standalone diagnostic utility including delayed kinetics, and their level is affected by maternal and perinatal factors.[4,7] In addition, in resource-limited settings, particularly in low- and middle-income countries (LMICs), biomarkers incorporated in the diagnostic algorithm for neonatal sepsis had unclear discriminatory value.[8,9]

In neonatal sepsis, both red cell distribution width (RDW) and platelet distribution width (PDW) are elevated, reflecting the hematologic impact of systemic inflammatory mediators that induce anisocytosis through the premature release of immature hematopoietic cells from the bone marrow. Concurrently, platelet counts are typically reduced due to a combination of increased peripheral consumption and impaired marrow production.[10] These pathophysiological alterations collectively contribute to elevated values of the red cell distribution width-to-platelet ratio (RPR) and the platelet distribution width-to-platelet ratio (PPR), underscoring their potential utility as composite markers of sepsis-related hematologic dysregulation.[11]

In recent years, both RPR and PPR have gained increasing attention as potential diagnostic and prognostic biomarkers in the neonatal period, particularly in the context of inflammatory and infectious conditions such as neonatal sepsis.[12,13] Based on the literature, RPR had an established reference interval in neonates, while PPR was inadequately studied in this population. The utility of both ratios in diverse neonatal populations needs to be addressed.[14,15]

Given the limited availability of comprehensive tests for EONS in LMICs, there is an urgent need for accessible, cost-effective, and reliable markers. This study evaluates the potential utility of RPR and PPR in the prediction of EONS in a sample of Iraqi neonates as an example of LMICs, with the goal of assessing their efficacy and establishing a diagnostic threshold in EONS.

Materials and Methods

This case–control study was conducted to evaluate the diagnostic value of RPR and PPR in EONS. The study was conducted at the neonatal intensive care unit of Central Child Teaching Hospital, a tertiary hospital in Baghdad, Iraq, over a 10-month period, from October 1, 2024, to July 1, 2025. Cases included neonates with culture-positive EONS, defined as sepsis with onset at ≤3 days of age according to the American Academy of Pediatrics guidelines.[16,17] Healthy controls were selected from outpatient clinics during the same study period in a ratio of a case to control of 1:1. Controls were matched to cases based on gestational age (±1 week), birth weight (±250 g), to minimize the influence of these potential confounding variables on hematologic parameters.

Neonates with a known health condition incompatible with life were excluded from both cases and control groups in addition to those with severe congenital birth defects, cyanotic congenital heart disease were excluded.

Sepsis screening was conducted for all enrolled neonates within 12–24 h of life which was composed of complete blood count, C-reactive protein, and blood culture and sensitivity. Lumbar punctures were offered only to neonates with seizure or positive blood culture.[16,18] Demographics and perinatal characteristics (sex, gestational age, birth weight, and mode of delivery) were reported and compared between both groups.

At least 2 ml of blood was collected from a peripheral vein into an EDTA tube, and within 60 min, all samples were analyzed by an automated hematologic analyzer (RUBY®). Complete blood cell parameters, including total white cell count, absolute lymphocyte count, absolute neutrophil count, hemoglobin, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean platelet volume (MPV), neutrophil percentage, PDW, and RDW. In addition, all participants had C-reactive protein and blood culture and sensitivity. Finally, RPR and PPR were calculated from the results of the complete blood count on separate Excel sheets, and the results of all these tests were compared between the case and control groups. Informed consent in accordance with the Declaration of Helsinki was obtained from all adult guardians of neonates included in the study. The Ethical Committee approved the study with IRB number 30/2024 dated September 11, 2024.

The sample size was calculated based on the case–control study sampling formula.[19]

$$Sample\ size = \frac{r+1}{r} \times \frac{\left(P^*\right)\left(1-P^*\right)\left(Z_\beta + Z_{\alpha/2}\right)^2}{\left(P_1 - P_0\right)^2}$$

r = ratio of cases to control, P_1 = exposure proportion in cases and P_2 = exposure proportion in controls.

$$P^* = \frac{P_1 + rP_0}{r+1}$$

taking an odds ratio = 1.8 based on previous studies.[14] $\alpha = 0.05$, $Z_{\alpha/2} = 1.96$. Power = 90%, $Z_\beta = 1.28$, while assuming exposure (high RPR) among controls $P_0 = 0.2$. Hence, n = 165 per group and total sample size required N = 330. After incorporating a 5% of nonresponse rate based on a previous study,[20] we did manage to enroll 352 neonates in the current study.

Statistics

The inferential analysis was performed using version 26.0 of the Statistical Package for the Social Sciences software SPSS version 26 (IBM, Armonk, New York, USA). The *t*-test was used for analyzing continuous variables presented as mean and standard deviation. A Chi-square test was used to assess categorical variables, presented as numbers and percentages. The predictive value of PPR and RPR for sepsis was assessed using the receiver operating characteristic (ROC) curve. The optimal cutoff threshold for EONS prediction was identified by the Youden index (sensitivity + specificity − 100%). A P value under 0.05 denoted a statistically meaningful difference.

Results

A total of 352 neonates (176 cases and 176 controls) were included in the study. Males outnumbered females, and the mode of delivery was cesarean section in the majority. There was no statistically significant difference in demographical characteristics between the groups [Table 1].

On univariate analysis of hematological indices, from leukocyte indices, only the absolute lymphocyte count and lymphocyte percentages were significantly higher than the control ($P = 0.03$ and 0.01) consecutively. From erythrocyte indices, PCV, MCV, and RDW were significantly higher than the controls, $P = 0.007$, 0.019, 0.017 consecutively. The mean platelet count was significantly lower in sepsis cases than controls, $P = 0.005$ [Table 2].

The associations of red cell distribution width-to-platelet ratio and platelet distribution width-to-platelet ratio with early-onset neonatal sepsis

The RPR in cases diagnosed with EONS showed higher mean and standard deviation (0.13 ± 0.11) than the control group (0.07 ± 0.03), $P = 0.02$. On the other hand, the mean of PPR failed to show a statistically validated distinction between cases (0.06 ± 0.04) and controls (0.05 ± 0.03), $P = 0.77$ [Figure 1].

Predictive value of platelet distribution width-to-platelet ratio and red cell distribution width-to-platelet ratio

A ROC curve was constructed to evaluate the predictive value of RPR and PPR for EONS. For RPR, the area under the curve was 0.725, 95% confidence interval = 0.614–0.837, $P = 0.001$. At a cutoff value = 0.0565, the RPR had a sensitivity of 88.4% and a specificity of 36.4% for predicting sepsis. For PPR, the area under the curve is 0.539, 95% confidence interval 0.415–0.664, $P = 0.570$. At a cutoff value = 0.0335, the PPR had a sensitivity of 77.9% and specificity of 27.3% for predicting sepsis [Figure 2].

Table 1: Demographics of studied neonates

Variables	Cases (*n*=176)	Control (*n*=176)	*P*
Gestational age#	36.48±2.89	36.09±1.48	0.89
Birth weight#	2.32±0.74	2.41±0.599	0.12
Sex*			
Male	100 (56.8)	136 (77.3)	0.72
Female	76 (43.2)	40 (22.7)	
Mode of delivery*			
Vaginal	66 (37.5)	56 (31.8)	0.78
Cesarean	110 (62.6)	120 (68.2)	

**n* (%), #Mean±SD. SD=Standard deviation

Table 2: Hematological indices obtained from complete blood count

Variables	Cases (*n*=176)*	Control (*n*=176)*	*P*
Hct (%)	47.95±6.18	43.78±7.17	0.007
Hb (g/dL)	16.46±3.86	15.72±2.14	0.39
RBC count (million/μL)	4.67±0.63	4.42±0.72	0.11
MCV (fL)	101.66±10.64	94.34±9.32	0.019
MCH (pg)	34.61±2.52	35.81±2.48	0.05
MCHC (g/dL)	34.44±3.25	36.02±1.56	0.37
RDW	18.09±1.72	17.69±1.91	0.017
WBC (cells/μL)	11.57±6.92	10.65±3.50	0.549
ALC (cells/μL)	3.74±1.75	2.89±1.05	0.03
Lymphocyte (%)	38.93±17.83	28.82±10.9	0.01
ANC (cells/μL)	9.78±4.3	6.30±3.52	0.26
Neutrophil (%)	49.63±20.57	55.80±15.87	0.195
Platelet count (platelets/μL)	197.98±86.3	255.09±68.39	0.005
PDW (fL)	12.86±2.21	12.25±2.63	0.28
MPV (fL)	10.18±0.86	10.56±1.55	0.14

*Mean±SD. Hct=Hematocrit, Hb=Hemoglobin, RBC=Red blood cell, MCV=Mean corpuscular volume, MCH=Mean corpuscular Hb, MCHC=Mean corpuscular Hb concentration, RDW=Red cell distribution width, ALC=Absolute lymphocyte count, ANC=Absolute neutrophil count, PDW=Platelet distribution width, MPV=Mean platelet volume, SD=Standard deviation, WBC=White blood cell

Discussion

This study analyzed the predictive value of RPR and PPR for EONS. On univariate analysis, RPR had a significant association with EONS that was not mirrored by PPR. By ROC analysis, both RPR and PPR had high sensitivity in identifying neonates with EONS. Concurrently, their low specificity limits their clinical utility in diagnoses of EONS.

Despite significant advances in clinical laboratory medicine, accurate diagnosis of EONS still represents a considerable health challenge.[21] Since EONS carry high mortality rates even in developed countries, timely diagnosis is vital to improve outcomes. New inflammatory markers are being continually investigated for early detection of EONS including CRP, procalcitonin, immature to total neutrophil ratio (I/T ratio), MPV, and distribution widths such as RDW and PDW.[22,18] Despite that, no single inflammatory biomarker can be considered ideal for early diagnosis of EONS with high sensitivity, specificity, PPV, and NPV.[11,23]

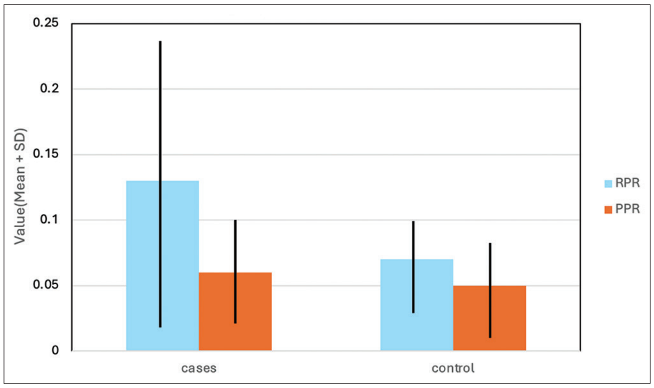

Figure 1: The associations of red cell distribution width-to-platelet ratio and platelet distribution width-to-platelet ratio with early-onset neonatal sepsis. RPR = Red cell distribution width-to-platelet ratio, PPR = Platelet distribution width-to-platelet ratio, SD = Standard deviation

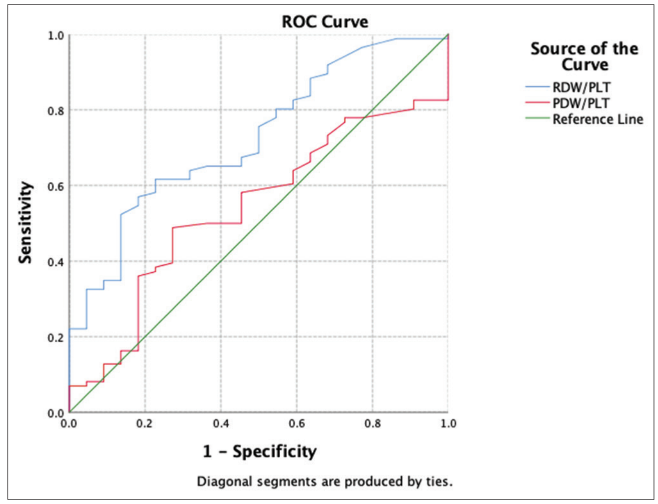

Figure 2: A receiver operating characteristic curve for red cell distribution width-to-platelet ratio and platelet distribution width-to-platelet ratio in the diagnosis of early-onset neonatal sepsis. ROC = Receiver operating characteristic, RDW = Red cell distribution width, PDW = Platelet distribution width, PLT = platelete

In the current study, six parameters from complete blood count showed statistically significant differences between EONS patients and healthy controls including PCV, MCV, RDW, ALC, L%, and platelet counts with $P = 0.007, 0.019, 0.017, 0.03, 0.01$, and 0.005 consecutively. However, previous studies demonstrate low sensitivity and specificity for these parameters in the diagnosis of EONS.[24-26]

In an attempt to find a superior predictor for EONS, two hematologic ratios associated with inflammation derived from complete blood counts: PDW/PL ratio and RDW/PL ratio were tested for an association with EONS. Based on analysis using the Independent Sample's *t*-test, only the RPR demonstrated a statistically significant elevation in mean and standard deviation relative to the control group ($P = 0.02$), a finding not mirrored by PPR. Moreover, at the diagnostic threshold of 0.0565, the RPR had high sensitivity approaching 88.4%, indicating its effectiveness in identifying true positive cases of EONS. However, the specificity of the test is 36.4% reflecting a substantial propensity of false positive results. Collectively, the result of the current study supports the use of RPR as a screening test for EONS but not as a diagnostic test.

The result of this study is in partial agreement with a study by Karabulut and Arcagok[11] that demonstrated an elevated level of RPR in EONS in comparison to healthy neonates. However, in their study, RPR showed a sensitivity of 79% and specificity of 93.7% for the detection of EONS. This high specificity of RPR disagrees with the result in the current study which could be attributed to differences in sample size and characteristics as Karabulut and Arcagok recruited only term neonates while gestational age was not an exclusion criterion in the current study.

In addition to the diagnostic value, RPR has emerged as a significant predictor for neonatal mortality. Studies indicated that RPR correlates with the severity of various neonatal diseases with sepsis at the top of the list.[13,27-29] This all suggests that RPR holds potential as a predictor for neonatal morbidity and mortality.[28,30]

This study has several limitations, including the inclusion of neonates irrespective of gestational age, which may have influenced the results. Additionally, the single-center design and relatively small sample size limit the generalizability of the findings. However, in this study, all neonates were evaluated on the first day of life, unlike previous studies in which a major limitation was the variability in the timing of RDW and platelet measurements relative to the onset of sepsis.

Conclusion

The RPR demonstrated potential utility as a reliable screening biomarker for EONS, although its low specificity limits its standalone diagnostic power. PPR lacks clinical utility based on current data and should not be relied upon for sepsis prediction. Further research with larger cohorts and integrative diagnostic models is warranted.

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Conflicts of interest

There are no conflicts of interest.

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