

Clinical Significance of Red Cell Distribution Width as an Early Prognostic Marker in Early Onset Neonatal Sepsis

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ABSTRACT

Objective: To assess the diagnostic and prognostic value of red cell distribution width (RDW), an easily available parameter from complete blood count, in neonates with suspected early-onset neonatal sepsis (EONS).

Methodology: A prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of the Pediatrics Department, Capital Hospital, CDA Islamabad from June to December 2024. A total of 127 term neonates presenting within 72 hours of life with suspicion of EONS were included. RDW was measured within 12 hours of admission and blood cultures were obtained. According to the outcome of the cultures, the neonates were categorized into septic and non-septic. Prognostic evaluation was carried out by comparing RDW values between groups and comparing them to ventilatory support, mortality and length of NICU stay. The analysis of data was performed using SPSS and the p value of 0.05 was regarded as statistically significant.

Results: A total of 127 neonates with a mean gestational age of 38.2±0.8 weeks were included. Of these, 20.5% (n=26) had culture-proven EONS. Mean RDW was higher in septic neonates compared to non-septic neonates (16.9 ± 3.8% vs 11.6 ± 4.2%, p-value=0.183), this difference was not statistically significant. A raised RDW was correlated with prolonged NICU stay (p=0.033) and increased ventilatory support (p=0.24).

Conclusion: RDW itself does not appear to be a reliable marker for diagnosing neonatal sepsis however, high RDW was associated with poor clinical outcomes, indicating that it may serve as a useful prognostic marker than a diagnostic one in case of suspected EONS.

Keywords: Neonatal sepsis, Early-Onset Neonatal Sepsis, Red Cell Distribution Width, Prognostic markers, Inflammatory Biomarkers.

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Introduction

Neonatal sepsis remains one of the leading causes of morbidity and mortality among newborns worldwide, particularly in low and middle-income countries. It is a systemic bacterial infection that affects newborns under 28 days of age and is divided into early-onset neonatal sepsis (EONS), primarily acquired through vertical transmission and presenting within the first 72 hours of life; and late-onset neonatal sepsis which occurs after 72 hours and usually results from environmental exposure.^{1,2} Clinical manifestations of EONS are usually non-specific

which may include fever or hypothermia, tachypnea, lethargy, altered mental status, hypotonia, and poor oral intake. Without treatment, it can rapidly develop into multi-organ failure over a period of hours.¹

Despite advances in neonatal care, EONS continues to contribute substantially to neonatal intensive care admissions and early neonatal deaths. Every year, about three million newborns are affected by neonatal sepsis, around the world.^{3,4} A meta-analysis reported a global rise from 2204 to 2824 cases per 100,000 live births between 2018 and 2021.⁴⁻⁶ It remains as a critical public health challenge in resource-limited countries where it

accounts for a disproportionate burden of neonatal mortality with 35-50 times higher incidence than high-income countries (28.2 to 39.3 vs 0.3 to 0.8 per 1000 live births).^{5,7,8} In South Asian population, a meta-analysis revealed EONS incidence of 15.8 per 1,000 live births with a case fatality proportion of 34.4% from 2000 to 2018.⁹

Blood culture remains as a gold standard test but has a turnaround time of 24 to 48 hours which often lead to treatment delays or overuse of broad-spectrum empiric antibiotics in setting of rising antibiotics resistance.^{2,6,10} In order to reduce it, several biomarkers such as hematological indices, acute-phase reactants, interleukins, and cell adhesion molecules, have been used in investigations for timely diagnosis of the disease^(2,10). Red cell distribution width (RDW), a measure of anisocytosis, is readily available parameter from complete blood count and has shown independent association with mortality and disease severity in neonatal sepsis despite requiring no additional cost, blood sampling or specialized laboratory infrastructure.¹¹⁻¹³

The pathophysiological basis for elevated RDW in sepsis involves multiple interconnected mechanisms including impaired erythropoiesis due to elevated inflammatory cytokines, iron dysregulation due to IL-6 induced hepcidin production and oxidative stress directly leading to elevated RDW by decreasing erythrocyte volume and inducing eryptosis.¹⁴⁻¹⁶ Abdullah et al. in a study reported higher RDW in 45.7% of EONS survivors and 92.9% of non-survivors.¹⁷ Similarly, another study found raised RDW in 30.2% of admitted neonates with sepsis⁽¹¹⁾. On the contrary, a Sudanese cohort of 111 culture-confirmed septic neonates observed the RDW increase in only 1.8% participants, which, in turn, highlights the heterogeneity of current data.¹⁸

Despite the biological plausibility and emerging evidence showing the clinical significance of RDW as a diagnostic and prognostic marker in neonatal sepsis as stated above, significant literature gap exists. Most of the studies combine early onset and late onset sepsis together without separate analysis, and no prospective study has specially evaluated RDW's prognostic value in EONS.¹¹ Thus, we planned this study to evaluate the diagnostic and prognostic value of red cell distribution width (RDW) in neonates with suspected early-onset neonatal sepsis (EONS) in our setting of limited access to resources.

Methodology

A prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of the Pediatrics Department, Capital Hospital, CDA Islamabad, Pakistan from June to December 2024 after obtaining ethical approval from institutional ethical review committee (Ref no. IRB-31-3-10-23). The WHO calculator was used to estimate a sample size of 127, applying a 95% confidence level, an 8% margin of error, and an expected RDW elevation rate of 30.2% in neonates with sepsis⁽¹¹⁾. An informed consent was taken from parents prior to inclusion of neonates in the study.

A total of 127 term babies between gestational age 36⁺ and 42⁺ weeks delivered in the hospital and admitted to the NICU with clinical signs suggestive of EONS within 72 hours of birth were included, irrespective of the gender or mode of delivery. The presence of symptoms like temperature instability (an axillary temperature >38.5°C or <36°C), lethargy, respiratory distress, feeding intolerance, hypotonia, or poor perfusion, and laboratory parameters including C-reactive protein levels ≥10 mg/L and a Tollner score ≥10 were included for clinical diagnosis of EONS. Neonates with congenital heart disease, other congenital anomalies, prior blood transfusion, hypoxic-ischemic encephalopathy, home birth, and those who already received antibiotic treatment were excluded.

Demographic and clinical data including gestational age, birth weight, gender, and mode of delivery were collected using a structured form mentioned in Annexure 1. CBC and peripheral blood cultures were taken within 12 hours of admission before initiation of antibiotic therapy. Complete blood count (CBC) analysis was performed using an automated hematology analyzer (Sysmex KX-21N). Red cell distribution width (RDW) values obtained from the CBC were recorded for all neonates. An RDW value greater than 13% was considered elevated based on the institutional laboratory reference range. Neonates were later divided into two groups; septic group which included neonates with positive blood cultures and recognized source of infection, and non-septic group which consists of neonates with clinical suspicion of EONS but negative blood cultures.

The main purpose of the research was to measure the diagnostic utility of RDW through the comparison of the change in the RDW levels in all suspected septic babies. To determine the predictive value of RDW in the EONS prognosis, clinical outcomes which included need of

ventilatory support, duration of NICU stay and inpatient mortality at day 7 in the septic group was studied. The Statistical Package of Social Sciences (SPSS) version 25 was used to analyze the data through the application of descriptive statistics. The Mann Whitney U test was used to compare the septic and non-septic groups in terms of the continuous variables, and Chi-square test was used to compare the categories. P value that was below 0.05 was regarded as significant.

Results

A total of 127 neonates who presented to hospital with clinical suspicion of EONS were included in the study. The mean gestational age was 38.2 ± 0.8 weeks with 75 (59.1%) males and 52 (40.9%) females. Around 65.3% of the neonates were born via spontaneous vaginal delivery, and 34.6% were delivered through the caesarean section.

After stratification on the basis of confirmed diagnosis of EONS, 26 (20.5%) were included in the culture proven septic group and 101 (79.5%) were stratified in non-septic group. The septic group had higher rate of cesarean deliveries (69.2% vs 35.6%) and low birth weight neonates (57.7% vs 37.6%). Further baseline characteristics of the two groups are mentioned in Table I.

Mean RDW levels at presentation were higher in the septic group as compared to non-septic group ($16.9 \pm 3.8\%$ vs $11.6 \pm 4.2\%$, mean difference 5.3%, p-value 0.183). Among 81 patients with Tollner score of ≥ 10 indicating high suspicion of EONS, there was no difference in RDW levels among septic and non-septic neonates (16.0 vs 10.9%, p-value 0.790). Thus, our study

reveals a limited diagnostic value of RDW in EONS.

In order to further evaluate the clinical significance of RDW in EONS, we studied clinical outcomes of neonates in the septic group and associated it with RDW at presentation. Among 26 patients with confirmed sepsis, 19 (73.1%) recovered, 5 (19.2%) required ventilatory support and 2 (7.6%) died. When compared with septic neonates who recovered, higher RDW values was observed in neonates who required ventilatory support ($18.9 \pm 7.2\%$ vs $15.3 \pm 3.6\%$, p-value = 0.24) and who died ($19.0 \pm 5.4\%$ vs $15.3 \pm 3.6\%$, p-value = 0.39) (Table II).

Among all neonates who were included, those who had a NICU stay of >5 days had raised RDW levels as compared to neonates who stayed in NICU for 5 days or less ($17.2 \pm 4.3\%$ vs $12.8 \pm 3.5\%$, p = 0.033). Thus, elevated RDW values is associated with worse clinical outcomes in patients with neonatal sepsis.

Discussion

Neonatal sepsis is a significant challenge for healthcare professionals in neonatal care as it remains a diagnostic challenge leading to delayed diagnosis, inappropriate antibiotics use and is linked with a high mortality rate in resource-limited settings.⁴⁻⁶ As RDW is rapidly and automatically calculated as a part of CBC in all modern hematological analyzers, it could serve as a readily available marker for detecting EONS in our setting, however our study revealed limited diagnostic value of RDW in EONS in 127 neonates with clinical suspicion of EONS. RDW levels showed probable prognostic value as elevated levels were associated with prolonged NICU

Baseline Characteristics	Septic (n = 26)	Non-Septic (n = 101)	Total (n = 127)
Mean gestational age (weeks)	37.9 ± 0.5	38.6 ± 1.2	38.2 ± 0.8
Gender			
Male	16	59	75
Female	10	42	52
Mode of delivery			
Spontaneous vaginal	18	65	83
Cesarean section	08	36	44
Birth Weight			
Low-birth weight (≤ 2.5 kgs)	15	38	53
Normal birth weight (>2.5 kgs)	11	63	74
Tollner Score			
≥ 10	19	62	81
< 10	07	39	46
Mean RDW at presentation	$16.9 \pm 3.8\%$	$11.6 \pm 4.2\%$	14.25 ± 2.3

Clinical Outcomes.	Frequency (%)	Mean RDW	p- value
Recovery with clinical improvement	19 (73.1%)	$15.3 \pm 3.6\%$	-
Inpatient mortality	05 (19.2%)	$19.0 \pm 5.4\%$	0.24
Requirement for ventilatory support	02 (7.7%)	$18.9 \pm 7.2\%$	0.39

stay, increased need for ventilatory support, and mortality in confirmed sepsis cases.

Our findings showed that while RDW levels were higher in culture proven septic vs non-septic neonates (16.9% vs 11.6%), this difference did not meet statistical significance for diagnostic purpose ($p = 0.138$). This contrasts with several previous studies. A retrospective cohort study of newborns done by Bulut et al. in 2021 showed significantly higher RDW levels in sepsis group as compared to controls ($p = 0.001$) with an odds ratio of 2.21 (95% CI: 2.19 to 3.36).¹⁹ Similarly, Martin et al. in his prospective observational study showed higher RDW levels in septic neonates as compared to controls (19.9% vs 18.9%, $p < 0.001$).¹² Khadka et al. also found a median RDW of 18% (IQR 16.9-20) in culture-proven sepsis cases.¹³ The differences between our studies and these previous studies could be linked to several factors. These studies did not clearly mention whether EONS, LONS or both were included; however, our study included neonates with clinical suspicion of EONS only. The small sample size of confirmed sepsis cases in our study may have limited the statistical power to detect the difference. Lastly, the variations in the timing of RDW measurement, gestational age distribution, mode of delivery, and severity of sepsis among the study populations could have led to the heterogeneity in the results.

The limited diagnostic value observed in our study aligns with the existing evidence suggesting that RDW has modest value for predicting the positive blood culture in suspected sepsis. Hu et al in their narrative review on adults and neonatal populations with sepsis also concluded that RDW has limited diagnostic value.²⁰ A study by Samson et al. on 513 neonates showed sensitivity of 61.54% and specificity of 54.60% of increased RDW in EONS detection.²¹ Similarly, Bulut et al. Reported a sensitivity of 60% for elevated RDW in diagnosis sepsis indicating that around 40% of the cases would be missed if we rely solely on it.¹⁹ This is consistent with the observation that there is no single biomarker available that has a sufficient diagnostic value to preclude the need for antibiotics when sepsis is suspected.²² Previous meta-analysis had identified interleukin-6 and procalcitonin in umbilical blood, presepsin and serum amyloid A in neonatal serum as reliable markers, but they also have insufficient positive predictive values when used alone.⁷

In our study we found prognostic value of RDW in EONS, as elevated levels were associated with poor

clinical outcomes. Neonates in septic group needing ventilatory support or who died had high RDW values (18.9% and 19.0% respectively) as compared to those who recovered (15.3%). However, the differences were statistically insignificant, due to small sample size of septic group. These findings were in line with the previous studies highlighting the prognostic role of RDW. Ellahony et al. reported higher RDW in non-survivors compared to survivors ($p = 0.0001$) with an AUROC of 0.75 for predicting 30-day mortality, and a positive association with mortality (OR 1.31, 95% CI 1.241-1.399).¹¹ Similarly, Martin et al. also noted that septic neonates with $RDW \geq 20\%$ had high mortality ($p=0.02$).¹² Another study mentioned a strong predictive value of RDW noted on day 3 of admission for 28-day mortality in very low birth weight neonates (AUROC = 0.89).²³

We observed that higher RDW levels were linked to longer NICU stay (17.2% vs 12.8%, $p = 0.033$), favoring RDW use as a prognostic marker. This aligns with recent studies showing changes in RDW during the first week of illness are associated with disease severity and clinical outcomes.^{23,24}

Although our research has given insight about the importance of RDW in EONS at a tertiary care setup, being a single-center study with a small sample size due to less patient inflow and a shorter duration, the number of patients included was limited. This explains why despite higher RDW values observed in septic group, result did not reach statistical significance. Further research with larger multicenter cohort studies would help improve generalizability of these findings. Observing RDW with other inflammatory markers such as CRP, IL-6 and procalcitonin will increase diagnostic ability overall. Making standardized cut-off values of RDW for initial risk screening of neonatal sepsis and observing changes in RDW over time for further disease progression and prognosis will make it more useful.

Conclusion

Our findings suggested that alone RDW has a limited role as a diagnostic marker for EONS. However, higher RDW values were observed in patients with poor clinical outcomes, including need for ventilatory support, prolonged NICU stay and mortality. Thus, RDW is better suited as a prognostic rather than a diagnostic marker.

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