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Case Study

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THE VALUE OF RED CELL DISTRIBUTION WIDTH AS A PROGNOSTIC FACTOR OF EARLY ONSET NEONATAL SEPSIS: A CASE-CONTROL STUDY

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ABSTRACT

Context: Neonatal sepsis is an inflammatory systemic. Early-onset neonatal sepsis is a significant health challenge associated with high rates of both morbidity and mortality. **Objectives:** This study aimed to compare red cell distribution width (RDW) values in neonates with early-onset sepsis (EONS) and healthy newborns; and to determine the role of RDW as a diagnostic factor in the occurrence of early-onset neonatal sepsis. **Methods and Material:** A case-control study was conducted in the neonatal intensive care unit (NICU) of Lattakia Hospital, Syria. This study included all neonates admitted to the hospital between March 2024 and March 2025. Neonates at the age of one day, who completed 37 weeks of gestation were included in this study. After obtaining parental consent, all cases were subjected to history taking, thorough clinical examination and Investigations. All analyses were performed using R v 4.5.0. **Results:** RDW width was statistically significantly increased in the EONS group (18.9 ± 2.0%) compared to controls (13.3 ± 0.9%; $p < 0.001$). Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of RDW as a potential biomarker for EOS. The AUC for RDW (%) was 0.999 (95% CI: 0.997– 1.000). At the optimal threshold of 15.2, RDW showed a sensitivity of 98.1%, specificity of 100.0%. **Conclusion:** Our findings suggest that RDW, which can be practically assessed in complete blood count as part of the routine sepsis evaluation, may be helpful as a diagnostic marker in neonatal sepsis.

KEYWORDS: Early Onset Neonatal Sepsis, Red Cell Distribution Width, Prognostic Marker.

INTRODUCTION

Neonatal sepsis is an inflammatory systemic syndrome caused by the transmission of pathogenic agents such as bacteria, viruses or their toxins and associated antigens into the bloodstream, resulting in changes accompanied by nonspecific clinical signs and symptoms.[1] Neonatal sepsis is classified into relatively distinct syndromes; Early-onset (EONS) and late-onset Neonatal sepsis (LOS) depending on the timing of symptom onset. EOS typically occurs within the first 72 hours of life, whereas LOS manifests after this period.[2]

EONS is a significant health challenge associated with high rates of both morbidity and mortality, especially in developing countries, with an incidence of 3-4 cases per 1,000 live births.[3] The clinical signs and symptoms of EONS are nonspecific and may include respiratory distress, tachycardia, hypotension and thermal instability, so the differential diagnosis is broad; however, a high index of suspicion must be maintained during clinical evaluation.[1]

The early diagnosis of neonatal sepsis continues to pose a substantial clinical challenge. Blood culture remains the most widely used conventional method; however, it typically requires a minimum of 2-5 days to yield results. Its sensitivity is significantly decreased when maternal intrapartum antibiotic therapy is administered. Additional key laboratory diagnostic markers include total leukocyte count, absolute and relative neutrophil counts, thrombocytopenia, C-reactive protein (CRP), and procalcitonin levels. No single laboratory marker is sufficient for diagnosis.[4,5]

Red Cell Distribution Width (RDW) reflects the variability in volume of erythrocyte within circulation and is commonly included in the complete Blood Count (CBC) without incurring additional costs. RDW is calculated by dividing the standard deviation of red blood cell (RBC) volume by the mean corpuscular volume (MCV) and multiplying the result by 100. Elevated RDW values indicate an increased variability in erythrocyte volume.[6,7]

Although the exact mechanism underlying RDW elevation in sepsis remains unclear, recent studies have indicated that inflammatory cytokines, impair erythropoiesis by inhibiting erythropoietin-induced maturation of red blood cells, downregulating erythropoietin receptor expression, and prolonging the red blood cell lifespan, which subsequently increases RDW.[8]

RDW has been extensively studied as a diagnostic marker in the differential diagnosis of anemia and in the assessment of various conditions, including sepsis, cardiovascular diseases, pulmonary edema and pneumonia.[7]

Several studies have demonstrated the role of RDW as a diagnostic factor of sepsis and sepsis-related mortality in adults, however, few studies have addressed its role in neonatal sepsis.

This study aims to compare the RDW values in neonates with early-onset sepsis (EONS) and healthy newborns, and to determine the role of RDW as a diagnostic factor in the occurrence of Early-Onset Neonatal Sepsis.

METHODS AND MATERIAL

Study design: a case-control study.

Study Population and Sampling

This research was conducted within the neonatal intensive care unit (NICU) at lattakia Hospital in Syria. all neonates admitted to the hospital from March 2024 to March 2025 were enrolled in this study.

Inclusion Criteria

Neonates at the age of one day, who completed 37 weeks of gestation.

Exclusion Criteria

1- Neonates diagnosed with lethal congenital anomalies and/or severe encephalopathy.
2- Family history demonstrates hematologic diseases such as thalassemia.
3- Neonates born to mothers with severe anaemia (haemoglobin<8mg/dl).
4- Neonates with a 5 minutes Apgar score of < 7 after delivery.
5- Neonates from multiple gestation pregnancies.

After obtaining parental consent, all cases were subjected to the following

1. History Taking

A comprehensive history was obtained for each neonate, including:

- Clinical signs suggestive of neonatal sepsis, such as poor feeding, lethargy, fever, respiratory distress, cyanosis, and jaundice.
- Maternal history, including the presence of diabetes mellitus, maternal fever exceeding 38 °C, use of intrapartum antibiotics, urinary tract infections (UTIs), premature rupture of membranes (PROM), and prolonged second stage of labor.
- Postnatal history, including low Apgar scores at 1 and 5 minutes, the need for aggressive resuscitation at birth, signs of respiratory distress, cyanosis, fever, and jaundice.

2. Thorough Clinical Examination

A detailed clinical examination was performed for each neonate, including:

1- Assessment of gestational age using the New Ballard Score.
2- Measurement of birth weight.
3- Identification of clinical signs indicative of sepsis.

3. Investigations

- Complete blood picture with differential count (CBC)
- Red cell distribution width (RDW) was automatically calculated from CBC.
- C-reactive protein (CRP)
- Blood culture for cases with neonatal sepsis.

Statistical Analysis

All analyses were performed using R v 4.5.0. Shapiro-Wilk tests and Q-Q plot were used to test for normal distribution. continuous variables showed as Mean ± SD and number (percentage) for categorial variables.

To test for differences between study groups (EOS and control group) Welch Two Sample t-test were performed and Pearson's Chi-squared test or Fisher's exact test for categorical variables, as appropriate. Pearson correlation plot was used to show correlation between continuous variables.

Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of RDW as a potential biomarker for early- onset neonatal sepsis. The performance metrics include the area under the curve (AUC), sensitivity, specificity, and optimal cutoff value. The optimal threshold was obtained by using Youden's J statistic.

RESULTS

This study included 100 neonates, who met the inclusion criteria during the study period. Accordingly, the study sample was divided into two groups; those with EONS and control group. Maternal and neonatal characteristics are summarized in **Table 1**. The mean maternal age was significantly higher in the EONS group compared to the control group (30.7 ± 5.1 years vs. 24.5 ± 2.6 years; $p < 0.001$). No significant differences were found in gestational age between the two groups (37.3 ± 0.6 vs. 37.4 ± 0.6 weeks; $p = 0.416$). Regarding delivery type, cesarean section was more common in both groups, although the difference was not statistically significant ($p = 0.213$). Among neonates, gender distribution was identical in both groups, with males representing 61% and females 39% ($p = 0.980$). However, birth weight was

significantly lower in the EONS group compared to controls (2.5 ± 0.5 kg vs. 2.8 ± 0.6 kg; $p = 0.004$).

Table 1: General Characteristics of the Study Participants.

Characteristics	Total (N = 100) *	Study Groups		p-value †
		EONS (N = 54) *	Control (N = 46) *	
Mother characteristics				
Mother age (years)	27.9 ± 5.1	30.7 ± 5.1	24.5 ± 2.6	<0.001
Gestational age (weeks)	37.4 ± 0.6	37.3 ± 0.6	37.4 ± 0.6	0.416
Delivery type				0.213
C-section	89 (89%)	50 (93%)	39 (85%)	
Normal	11 (11%)	4 (7.4%)	7 (15%)	
Neonatal characteristics				
Gender				0.980
Female	39 (39%)	21 (39%)	18 (39%)	
Male	61 (61%)	33 (61%)	28 (61%)	
Weight (kg)	2.6 ± 0.6	2.5 ± 0.5	2.8 ± 0.6	0.004

* Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.
† p-values are based on Welch's two-sample t-test for continuous variables, and Fisher's exact test or Pearson's Chi-squared test for categorical variables, as appropriate.
Abbreviations: EONS: Early-onset sepsis; C-section: Cesarean section.

Table 2 presents the comparisons of hematological and inflammatory markers between neonates with sepsis and the control group. Although white blood cell (WBC) counts were higher in the EONS group (17.1 ± 6.5 $\times 10^9$/L) than in controls (15.1 ± 3.3 $\times 10^9$/L), this difference did not reach statistical significance ($p = 0.054$). Lymphocyte and neutrophil didn't differ significantly between the groups ($p = 0.446$ and $p = 0.506$, respectively). Hemoglobin levels were also comparable ($p = 0.290$). C-reactive protein (CRP) levels were significantly elevated in the EONS group (11.0 ± 5.8 mg/L) compared to the control group (1.9 ± 1.0 mg/L; $p < 0.001$). Similarly, platelet counts were significantly lower in the EOS group (175.0 ± 90.3 $\times 10^9$/L) than in controls (268.2 ± 61.8 $\times 10^9$/L; $p < 0.001$). Red blood cell (RBC) counts were slightly but significantly higher in the EONS group (4.7 ± 0.2 $\times 10^{12}$/L) versus controls (4.5 ± 0.1 $\times 10^{12}$/L; $p < 0.001$). Mean corpuscular volume (MCV) was significantly greater in the EONS group (90.7 ± 5.7 fL) compared to the control group (88.0 ± 3.8 fL; $p = 0.005$).

Table 2: Comparisons of Laboratory Markers Between Early- Onset Neonatal Sepsis and Control Group.

Characteristics	Total (N = 100) *	Study Groups		p-value†
		EONS (N = 54) *	Control (N = 46) *	
WBC (10^9/L)	16.2 ± 5.3	17.1 ± 6.5	15.1 ± 3.3	*0.054*
Lymph (10^9/L)	37.7 ± 13.8	38.6 ± 15.5	36.5 ± 11.4	*0.446*
Neut. %	52.7 ± 14.1	51.8 ± 15.7	53.7 ± 12.1	*0.506*
HGB (g/dL)	16.1 ± 1.8	16.3 ± 1.9	15.9 ± 1.6	*0.290*
CRP (mg/L)	6.8 ± 6.3	11.0 ± 5.8	1.9 ± 1.0	<0.001
Plt (10^9/L)	217.9 ± 91.0	175.0 ± 90.3	268.2 ± 61.8	<0.001
RBC (10^{12}/L)	4.6 ± 0.2	4.7 ± 0.2	4.5 ± 0.1	<0.001
MCV (fL)	89.5 ± 5.0	90.7 ± 5.7	88.0 ± 3.8	0.005
RDW (%)	16.3 ± 3.2	18.9 ± 2.0	13.3 ± 0.9	<0.001

***** Data are presented as mean ± standard deviation (SD) for continuous variables and as number (percentage) for categorical variables.
† *p*-values are based on Welch's two-sample *t*-test for continuous variables, and Fisher's exact test or Pearson's Chi-squared test for categorical variables, as appropriate.
Abbreviations: EONS – Early-onset sepsis; WBC – White blood cell count; Lymph – Lymphocyte count; Neut. % – Neutrophil percentage; HGB – Hemoglobin; CRP – C-reactive protein; Plt – Platelet count; RBC – Red blood cell count; MCV – Mean corpuscular volume; RDW – Red cell distribution width; C-section – Cesarean section.

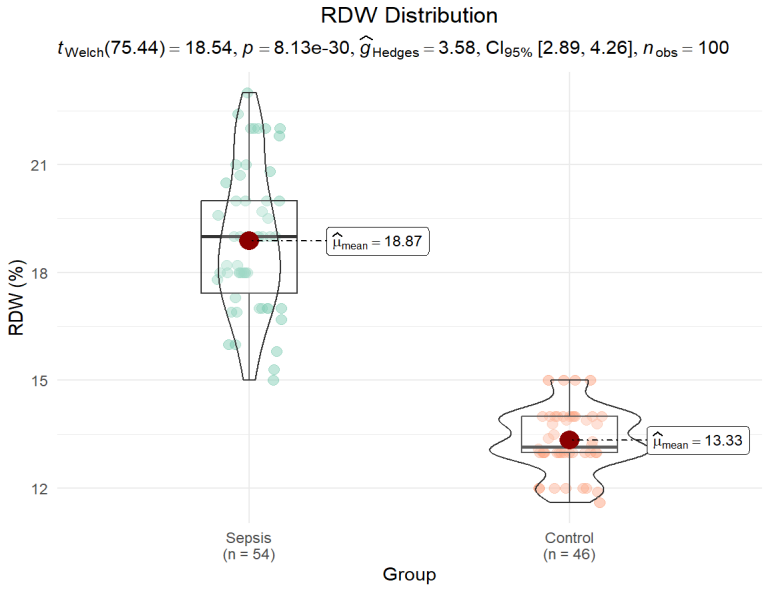

Figure 1: Distribution Of RDW Between EOS and Control Group. Red cell distribution width (RDW) was markedly increased in the EONS group (18.9 ± 2.0%) compared to controls (13.3 ± 0.9%; $p < 0.001$)**. Abbreviations***:* RDW – Red cell distribution width

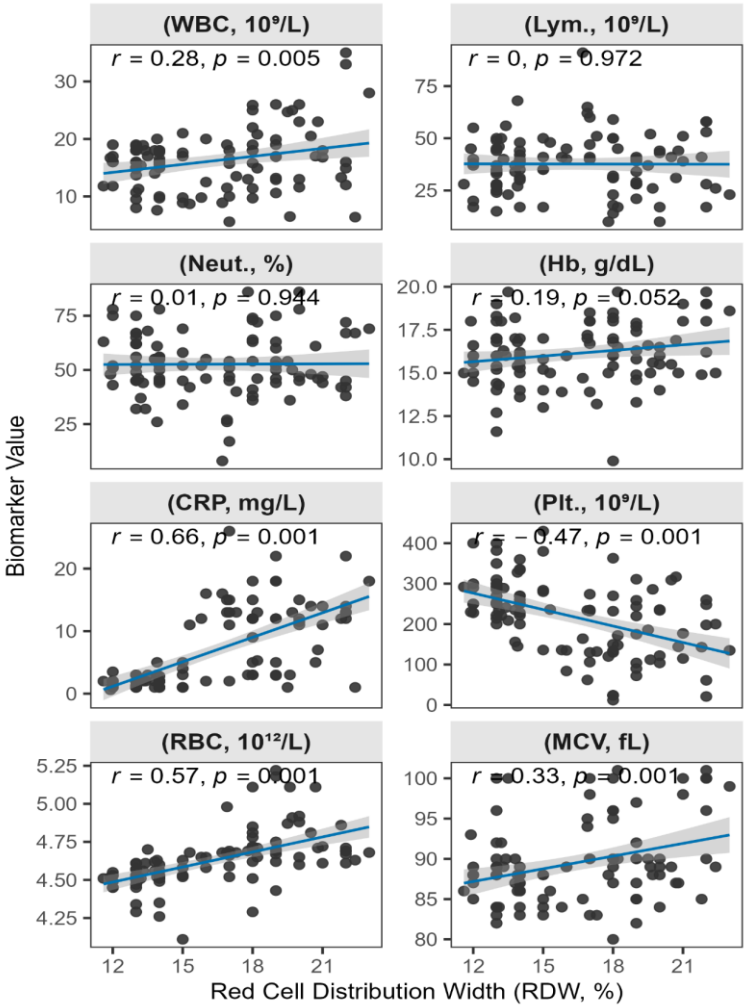

Figure 2. Correlation Between RDW and Selected Biomarkers. RDW exhibited statistically significant positive correlations with WBC (r = 0.28, p < 0.05), CRP (r = 0.66, p < 0.05), RBC (r = 0.57, p < 0.05) and MCV (r = 0.33, p < 0.05), while there was statistically significant negative correlation between RDW and platelet (r = - 0.47, p < 0.05).

Abbreviations*:* RDW – Red cell distribution width; WBC – White blood cell count; Lym.– Lymphocyte count; Neut. % – Neutrophil percentage; Hb – Hemoglobin; CRP – C-reactive protein; Plt – Platelet count; RBC – Red blood cell count; MCV – Mean corpuscular volume.

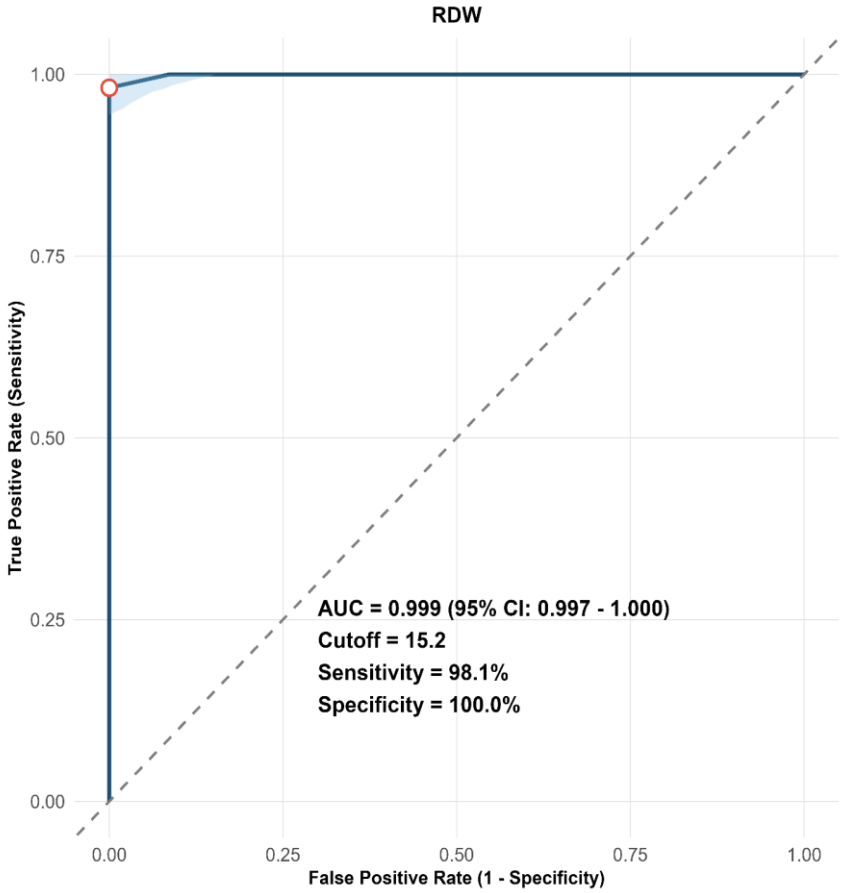

Figure 3. Receiver Operating Characteristic (ROC) Curve for RDW (%). The AUC for RDW (%) was 0.999 (95% CI: 0.997– 1.000), indicating excellent discriminatory ability. At the optimal threshold of 15.2, RDW showed a sensitivity of 98.1%, specificity of 100.0%.

Abbreviations*:* AUC – Area Under the Curve

DISCUSSION

The diagnosis of neonatal sepsis remains challenging due to its nonspecific clinical manifestations, especially in neonates admitted to the NICU. Consequently, reliable biomarkers are essential for accurate diagnosis, which can ultimately reduce morbidity and mortality rates. While numerous studies have evaluated the prognostic and predictive value of red cell distribution width (RDW) in adult sepsis, limited data are available regarding its role in newborns. The primary objective of the study was to evaluate the role of RDW as a prognostic marker in Early neonatal sepsis compared to healthy neonates.

In this study, a statistically significant differences in maternal age between study groups was observed, which was lower in control group compared to EONS group. Similarly, birth weight was lower in EONS group compared to control group. These findings may be explained by the fact that higher maternal age and low birth weight are recognized risk factors of the development of EONS.

This study also demonstrated a statistically significant elevation in CRP and a significant reduction in mean PLT among EONS group. These findings similar to[9] and consistent with the pathophysiology of sepsis, wherein CRP, as an acute-phase reactant, increases in response to systemic inflammation, while PLT consumption during the inflammatory cascade contributes to thrombocytopenia.

In present study, the mean RDW level was significantly higher in neonatal sepsis cases (18.9 ± 2.0) as compared of controls (13.3± 0.9). Previous research by[10],[11] and [9] also found that the mean RDW level was significantly higher in sepsis group. A study by[11] found that mean RDW level in cases was (16.4±3.8) as compared to controls (13.7±1.6).

This observation can be attributed to the fact that inflammation induces an increase in neurohormonal and endocrine factors, including noradrenaline, angiotensin

1, and other components of the renin-angiotensin system, as well as renal ischemia. These neurohormonal changes stimulate erythropoiesis by enhancing erythropoietin (EPO) secretion, leading to an elevated red cell distribution width (RDW). Moreover, inflammatory mediators can impair bone marrow hematopoietic function and disrupt iron metabolism, further contributing to increased RDW levels.

The AUC for RDW (%) was 0.999 (95% CI: 0.997–1.000), indicating excellent discriminatory ability. At the optimal threshold of 15.2, RDW showed a sensitivity of 98.1%, specificity of 100.0%. in a study on 110 newborns, found that at cut-off RDW 18.55 had sensitivity and specificity of 94.50% and 96.36% respectively, through this, we could consider that the RDW value could be both a predictive and diagnostic marker for sepsis.[12]

Previous research by[9], and[13] reported that there was a significant positive correlation between RDW and serum CRP levels, and a significant negative correlation between RDW and PLT, which was similar to our study, indicating that inflammation results in elevated RDW. The underlying mechanism of increased red cell distribution width in sepsis is not yet elucidated; however, elevated RDW levels have been increasingly recognized as a marker of systemic inflammation. Proinflammatory mediators such as interleukin-6 (IL-6), Tumor Necrosis Factor-Alpha (TNF-a), and other cytokines may disrupt normal erythropoiesis and extend red blood cell survival, thereby contributing to the observed rise in RDW during septic states.[7,14]

CONCLUSION

Our findings suggest that RDW, which can be practically assessed in complete blood count as part of the routine sepsis evaluation, may be helpful as a diagnostic marker in neonatal sepsis.

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Conflicts of Interest: None
Authorship Criteria Confirmation: All authors meet the criteria for authorship, have read and approved the final manuscript, and believe the work is honest and accurate.

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