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Original Research Article

Red cell distribution width as a diagnostic marker in neonatal sepsis

Anupama Deka, Aravind P.*

Department of Pediatrics, Silchar Medical College and Hospital, Assam, India

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***Correspondence:**
Dr. Aravind P.,
E-mail: aravindpalraj@yahoo.co.in

ABSTRACT

Background: The early diagnosis of neonatal sepsis, a significant cause of neonatal morbidity and mortality still remains a challenge. Red-cell Distribution Width (RDW) vary significantly in conditions associated with inflammation and infection like sepsis. The study aims to find the normal range of RDW in healthy newborns and investigate the role of RDW in the early diagnosis of neonatal sepsis.
Methods: This is a prospective observational study, 50 normal and 50 sepsis neonates were considered for the study. The neonatal sepsis group consisted of neonates with (i) Positive sepsis screen with/without clinical features of neonatal sepsis and/or (ii) Blood, urine or CSF culture positive or signs of pneumonia on chest x-ray. The mean RDW and the relationship between RDW and neonatal sepsis were analysed using appropriate statistical methods in SPSS-25 software.
Results: Mean RDW (%) was significantly higher in sepsis neonates (18.59±1.28) than in normal newborns (16.21±1.35). RDW had statistical significance with CRP (C-Reactive Protein) in the sepsis group. RDW had significant relationship with the diagnosis of neonatal sepsis with a p value of 0.000. An RDW cut-off level of 17.25% had 86% sensitivity, 87% specificity, and 93.5% accuracy in diagnosing neonatal sepsis.
Conclusions: RDW helps as a diagnostic test in the early diagnosis of neonatal sepsis.

Keywords: C-Reactive Protein, Neonatal sepsis, Pneumonia, Red-cell distribution width, Sepsis screen

INTRODUCTION

Neonatal sepsis refers to the systemic infections affecting infants within 28 days of life and includes bloodstream infections (BSIs) or septicaemia, pneumonia, meningitis, urinary tract and bone/joint infections. Neonatal sepsis is classified into confirmed or culture positive sepsis and clinical or culture negative sepsis based on culture positivity. Sepsis occurring at or before 72 hours of age is called Early Onset Sepsis (EOS) and that occurring beyond 72 hours of age is called Late Onset Sepsis (LOS).[1] Neonatal sepsis is defined as a systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection.[2]

Blood culture, though a gold standard test in the diagnosis of neonatal sepsis requires a long turnaround time and comes out positive in less than a third of suspected neonates. C-Reactive Protein in the sepsis screen begins to rise only after 6 to 8 hours of onset of infection and could come negative if tested earlier. Therefore, in suspected infants, a repeat sepsis screen is needed 12-24 hours later if the initial sepsis screen is negative to rule out sepsis.[1]

Red Cell Distribution Width (RDW) is the quantitative assessment of the variation in red cell volume and it corresponds to the microscopic analysis of the degree of anisocytosis. RDW can be expressed either as standard deviation (SD) in fl or as the coefficient of variation (CV)

of the measurements of the red cell volume in percentage.[3] It is the subjective confirmation of the objective anisocytosis seen under the microscope and comes automatically in the counter report print out.[4] RDW indicates whether the size of red cell volume is uniform or not. The more the RDW is, the more is the unevenness in the red blood cell size and the higher is the volume heterogeneity.[5] Higher RDW and normal RDW indicate anisocytosis and absence of anisocytosis respectively.[4]

Some studies have observed that red cell distribution width (RDW) varies significantly in pathological conditions associated with inflammation and infection.[6] RDW is increased in sepsis because of the effect of the proinflammatory cytokines on red cell production.[7] The markers of inflammation like RDW-associated interleukin-6 (IL-6), tumour necrosis factor-alfa (TNF-α) and proinflammatory cytokines suppress the maturation process of RBCs, which increases their half-lives with a resultant rise in the RDW.[8,9]

Neonatal sepsis is one of the leading causes of morbidity and mortality in neonates and thus an early diagnosis of neonatal sepsis is very important for better outcomes. There is a paucity of studies on RDW in the newborns and its association with neonatal sepsis. Therefore, this study is done to find the normal range of RDW in healthy newborns and the role of RDW in the diagnosis of neonatal sepsis.

METHODS

This study was a prospective analytical study conducted in the Special Newborn Care Unit (SNCU) and the Neonatal Intensive Care Unit (NICU) of a tertiary care hospital in the northeastern region of India in Assam from September to November 2019.

Inclusion criteria

A total of 50 normal newborns born by normal vaginal delivery or caesarean section and 50 neonates with the diagnosis of neonatal sepsis were taken for the study. The normal newborns group consisted of healthy term neonates without any associated health problems and without any symptoms of clinical sepsis and whose sepsis screens are negative. The neonatal sepsis group consisted of neonates with (i) Positive sepsis screen with/without clinical features of neonatal sepsis and/or (ii) Blood, urine or CSF culture positive or signs of pneumonia on chest x-ray.

Exclusion criteria

Neonates with severe birth asphyxia, meconium aspiration syndrome, congenital malformations, metabolic disease and ABO/Rh isoimmunization are excluded from the study.

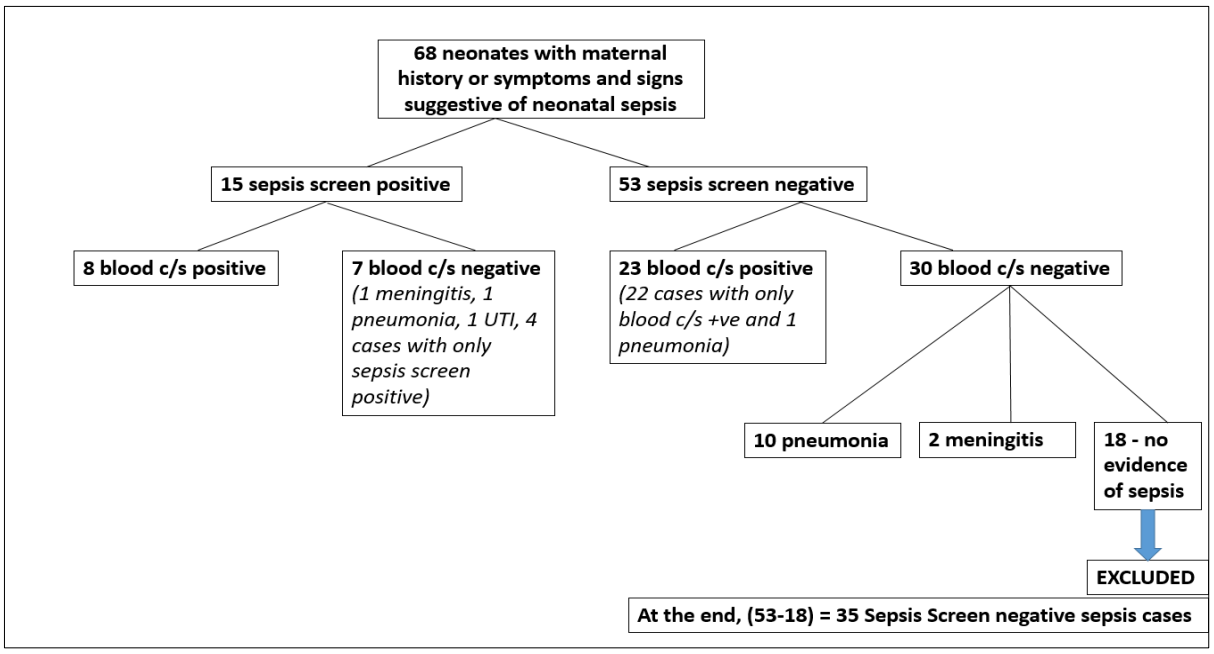

Figure 1: Study design.

RDW and Sepsis Screening was performed in all the 50 normal newborns on day 1 of life. RDW, Sepsis Screening, Culture and Sensitivity of blood, urine and CSF and a chest x-ray was performed in the babies with

(i) Maternal history of fever, prolonged rupture of membranes and clinical chorioamnionitis and (ii) In babies with clinical features suggestive of neonatal sepsis (Early onset or Late onset neonatal sepsis) like hypothermia or fever, poor cry, refusal to suck, poor perfusion, lethargy, CRT prolongation, hypotonia, absent neonatal reflexes, respiratory distress, apnea and gasping respiration, brady/tachycardia and hypo/hyperglycemia. 18 neonates who did not have any evidence of sepsis after all the investigations were excluded from the study. A total of 50 babies with neonatal sepsis (with positive sepsis screen or blood/urine/CSF culture or pneumonia on chest x-ray).

A positive sepsis screen requires 2 out of the 5 parameters of sepsis screen to be positive (Total Leukocyte Count <5000/cmm, Absolute Neutrophil Count <1800/cmm, Immature to Total Neutrophil ratio ≥0.2, Micro-ESR of 3+ age in days in the 1st week of life and C-reactive Protein >10mg/L).

The neonatal sepsis group was subdivided into Early Onset and Late Onset Neonatal Sepsis groups (EONS/LONS) based on the time of presentation of sepsis (EONS- <72 hours and LONS- >72 hours). The study design is described in Figure 1.

Sample collection was done under strict aseptic conditions, 2ml of blood is collected by venipuncture with a needle in an EDTA vial for CBC and RDW. 1 ml of blood was collected in a clot activated vial for CRP analysis. Both the samples were sent to the Hospital Laboratory immediately for analysis. Blood, Urine or CSF cultures were collected under strict aseptic precautions and sent to the Department of Microbiology for analysis.

Informed consent was obtained from the parents after the delivery of the baby for the study. Ethical clearance was obtained from the institutional research board of Silchar Medical College and Hospital.

Statistical analysis

The collected data were analysed with IBM.SPSS statistics software 25.0 Version. To describe about the data, descriptive statistics, frequency analysis, percentage analysis were used for categorical variables and the mean and S.D were used for continuous variables. The Receiver Operator Characteristic (ROC) curve analysis was used to find the Sensitivity, Specificity, PPV and NPV to identify the efficacy of the tool. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value of less than 0.05 is considered as significant level.

RESULTS

The baseline characteristics of 50 normal newborns and 50 neonatal sepsis cases are compared in Table 1.

Table 1: Baseline characteristics of the study groups.

Parameter	Normal newborns group (n=50)	Neonatal sepsis group (n=50)
Age in days	1.94±0.81	2.34±1.43
Mode of delivery	NVD=30 CS=20	NVD=31 CS=19
Gender	Females = 25 Males = 25	Females = 20 Males = 30
Gestational age in weeks	38.9±0.88	37.88±2.46
Birth weight in kg	3.05±0.33	2.50±0.58
Platelet count	$196x10^3$/µL± $87x10^3$/µL	$159x10^3$/µL± $109x10^3$/µL

NVD- Normal Vaginal Delivery; CS- Caesarean Section

Mean RDW level was higher in neonatal sepsis cases (18.40±1.18%) than in the normal newborns (16.18±1.23%). The RDW levels were significantly higher in the neonatal sepsis group than in the normal newborns group with a p value of 0.000 (Table 2).

Table 2: Mean RDW% in normal and sepsis neonates.

Parameter		Normal newborns group (n=50)	Neonatal sepsis group (n=50)	p value
RDW%	Mean	16.18±1.23	18.40±1.18	0.000
	Median	16.45	18.20	
	Minimum	12.80	16.70	
	Maximum	18.30	21.90	

The relationship between RDW and various parameters in the normal and the sepsis neonates are shown in Table 3 and 4.

Table 3: Relationship between RDW and MOD, gender and APGAR score.

Relationship between		p value	
		Normal newborns group (n=50)	Neonatal Sepsis group (n=50)
RDW	mode of delivery	0.291	0.239
RDW	gender	0.471	0.085
RDW	APGAR score at 5 minutes	0.684	0.338
RDW	Platelet count	0.166	0.170

Out of the 100 newborns in the study, 50 neonates had neonatal sepsis and 50 neonates did not have neonatal sepsis. Statistical significance was seen between RDW and the diagnosis of neonatal sepsis with a p value of 0.000. None of the 7 neonates with RDW between 12%

and 15% developed sepsis. Out of 63 neonates with RDW between 15% and 18%, 22 neonates had sepsis and out of 24 neonates with RDW between 18% and 20%, 22 neonates had sepsis. All 6 neonates with RDW more than 20% had sepsis (Figure 2). In the neonatal sepsis group, 42 neonates had Early Onset Neonatal Sepsis (EONS) and 8 neonates had Late Onset Neonatal Sepsis (LONS).

Table 4: Relationship between RDW and various parameters in the sepsis group.

Relationship between		p value
RDW	Gestational age	0.677
RDW	CRP	0.037
RDW	Sepsis screen	0.023
RDW	Blood culture positive sepsis	0.923
RDW	EOS/LOS	0.372

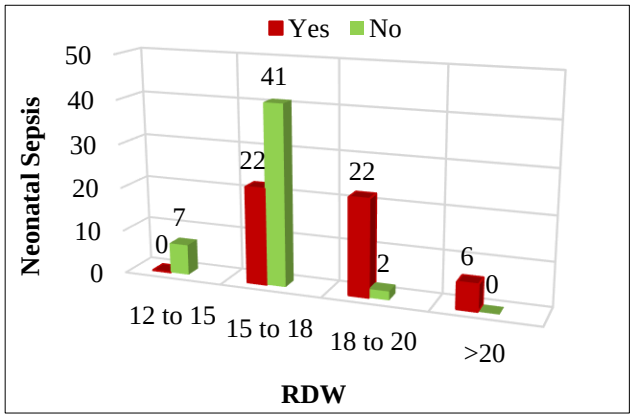

Figure 2: Relationship between RDW and the diagnosis of neonatal sepsis.

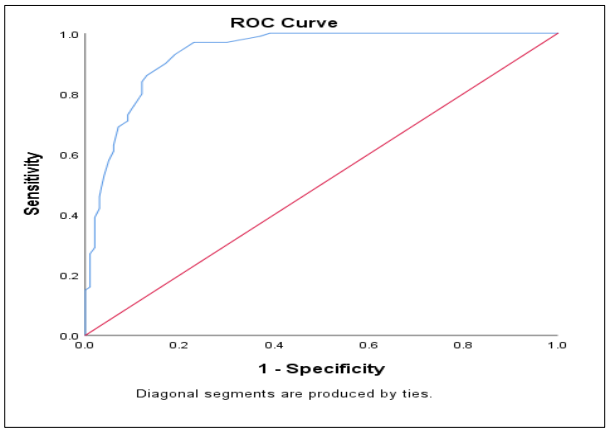

Figure 3: ROC curve for the diagnosis of neonatal sepsis by RDW.

The ROC curve analysis of RDW in the diagnosis of neonatal sepsis is shown in Figure 3. The Area Under Curve was found out to be high (0.938) which proves that RDW is a very useful test in the diagnosis of neonatal sepsis. An RDW cut off of 16.95% has a sensitivity of 96%, specificity of 80%, PPV of 82.75%, NPV of 95.23% and an accuracy of 93.8% in the diagnosis of neonatal sepsis.

ROC analysis of CRP for the prediction of neonatal sepsis revealed an AUC for CRP of 0.643, which indicates the poor utility of CRP as a sole diagnostic marker in neonatal sepsis in this study.

Out of the 35 neonates with negative sepsis screen in the sepsis group, all the neonates had an RDW more than 16.18% (normal RDW in the normal neonates group in our study).

DISCUSSION

According to a study by Alparsian Tonbul et al, mean normal range of RDW in neonates ≤34 weeks was 17.8±2.1 and that of neonates ≥35 weeks was 16.7±1.6.[10] According to a study by Kook et al, the normal range of RDW in newborns is 17.1±1.7, independent of gestational age.[11]

The range of RDW in normal neonates in this study is more or less similar to the values obtained by the authors Kook et al, Dr. Monu Singh et al, and Cosar H et al, (Table 5).[11-13]

Table 5: Comparison of mean RDW in normal newborns with other studies.

Study	Mean RDW (%)
Dr. Monu Singh et al[12]	16.23±1.16
Cosar H et al[13]	15.33±1.87
Martin SL et al[14]	18.90
Our study	16.18±1.23

The mean RDW in the sepsis newborns in this study is less compared to that in studies by other authors in Table 6. This could be explained by the fact that Dr. Monu Singh et al, and Cosar H et al, conducted studies on term and near term neonates and in this study both term and preterm neonates were included.[12,13]

Table 6: Comparison of mean RDW in sepsis newborns with other studies.

Study	Mean RDW (%)
Dr. Monu Singh et al[12]	21.31±3.08
Cosar H et al[13]	22.35±5.27
Martin SL et al[14]	19.90
Our study	18.40±1.18

In a study by Cosar H et al, a significant and positive correlation was found between CRP levels and RDW (p=0.01) in the total population of 88 newborns including normal and EONS groups.[13] This study found a significant and a positive correlation between CRP levels and RDW in the neonatal sepsis group with a p value of 0.037. However, this study did not find a significant

relationship between CRP level and RDW in the total population of 100 newborns (p value=0.429). This could be due to the lower mean CRP in the sepsis group in the study (7.51±6.18 vs 21.2±19.06).

The initial sepsis screen done at the time of suspicion of neonatal sepsis was negative in 35 sepsis cases. One of the reasons for this is the fact that CRP begins to rise only after 6-8 hours of onset of infection and could come negative, if tested earlier.[1]

Compared to the studies by other authors mentioned in the Table 7, the RDW in our study had a better sensitivity of 96% and a better negative predictive value of 95.23% and a more or less equal diagnostic accuracy of 93.8%, while the specificity and the positive predictive value of RDW in the diagnosis of neonatal sepsis are a little less (80% and 82.75% respectively).

Table 7: Comparison of ROC analysis of RDW in the diagnosis of neonatal sepsis in other studies.

RDW	Abdullah et al[15]	Dr. Monu Singh et al[12]	Our study
Cut off	>14.3	≥18.55	≥16.95
Area Under Curve	0.924	0.988	0.938
p value	<0.001	<0.001	0.000
Sensitivity	85%	94.55%	96%
Specificity	100%	96.36%	80%
PPV	-	96.3%	82.75%
NPV	-	94.64%	95.23%
Diagnostic accuracy	-	95.45%	93.8%

Limitations of the study are as follows, RDW is also elevated in other conditions like iron, vitamin B12 and folate deficiencies and after blood transfusions. Serial RDW measurements to look for rise or fall in levels after the initiation of antibiotics is not done in our study. Follow up after the discharge of septic infants to study the morbidity is not done in our study.

CONCLUSION

RDW is an easily available and a cost effective simple test that can be performed in any laboratory with an automated haematology analyser and is readily available in the print out of CBC report without the need for manual calculation. In this country, where neonatal sepsis is one of the leading causes of morbidity and mortality in neonates, early diagnosis of neonatal sepsis is very important and RDW is a very promising test in serving this purpose. This study proved the efficacy of RDW in the diagnosis of neonatal sepsis. Further large trials are needed to prove the usefulness of this simple test which can have a large impact in reducing the morbidity and mortality of neonatal sepsis.

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