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Role of Red Cell Distribution Width as a Prognostic Marker in Neonatal Sepsis

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Funding Source: None
Conflict of Interest: None

Received: Aug 05, 2022
Accepted: Dec 28, 2022

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ABSTRACT

Objective: To determine the prognostic value of red cell distribution width (RDW-CV%) in predicting the outcome in neonatal sepsis.

Methodology: It was an observational study conducted at the Pakistan Institute of Medical Sciences, Islamabad, from December 2018 to April 2020. A total of 136 neonates at term with clinical suspicion of neonatal sepsis were equally divided based on RDW into two groups as normal and raised RDW. A complete blood count and C-reactive protein were done on the day of admission and repeated on Day 3. Outcomes were observed in terms of discharges, expiries and length of hospital stay.

Results: The mean RDW of Group 1 (normal RDW) was 14.71±0.65 on Day 1 and 17.14±0.14 on Day 3 with a significant p-value of <0.001. In group 2 (Raised RDW) on Day 1 it was 17.14±1.46 and at day-3 was 17.8±1.90 with a p<0.001. Discharged neonates in group 1 were 57 (83.8%) and in group 2 were 46 (67.6%). (p=0.458). Expired neonates in Group-1 were 11(16.2%) and in group-2 were 22(32.4%) with significant p-value of 0.028. Neonates shifted to ventilator in group-1 were 10 (14.7%) and in group-2 were 24(35.3%) with p-value (0.006). Length of hospital stay in terms of days in group1 with mean 5.85± 4.03 and group-2 it was 7.63± 4.82 with a significant p-value of <0.001.

Conclusion: Raised RDW in clinically septic neonates was associated with poor outcomes in terms of length of hospital stay, mechanical ventilation and deaths compared to neonates with normal RDW.

Keywords: Red cell distribution width, Sepsis, Neonatal

Cite this article as: Asghar R, Tariq J, Ali S, Saeed M, Naseem L, Tariq M. Role of Red Cell Distribution Width as a Prognostic Marker in Neonatal Sepsis. Ann Pak Inst Med Sci. 2022; 18(4):279-285. doi. 10.48036/apims.v18i4.677

Introduction

Neonatal sepsis is an important cause of morbidity and death in underdeveloped countries.[1] Clinically, neonates may present with a history of fever, lassitude, unwilling to feed, tachypnea, fits and an increase in heart rate. Sepsis in neonates is classified into two categories, early and late-onset sepsis depending upon the time of beginning and means of transmission of infection. Early-onset sepsis (EOS) is defined as neonatal sepsis during first seven days of life, or few studies defined EOS to infections occurring in the first 72 hours. Late-onset sepsis is usually defined as an infection occurring after 1 week and is acquired in postnatal period. Both maternal and neonatal factors are related to the risk of infection in the neonatal period. The most common causative organism involved in early-onset neonatal sepsis are Group B streptococcus and Escherichia coli, whereas staphylococci are involved in the majority of cases of late-onset sepsis. Early diagnosis of neonatal sepsis is challenging because the clinical manifestations are uncertain and are problematic to differentiate from those of non-infectious etiologies. [2]

Sepsis causes a broad effect on the red blood cells as well. Some of which include altering the metabolism, decreased[2,3] bisphosphoglycerate, decreased erythrocyte deformability and redistribution of membrane phospholipids. [3]

Red blood cells have a life span of 120 days. Macrophages are accountable for the detection and red cells phagocytosis that are about to complete their life in human body and this process of removal of erythrocytes is called erythrophagocytosis.[4] There can be reduced red blood cell life due to inflammation and oxidative stress in sepsis. This results in suppression of red blood cells maturation leading to the release of large number of immature RBCs into circulation, resulting in different sized red blood cells which refers to as red blood cells distribution width CV(RDW-CV) and red cell distribution width-SD (RDW-SD).[5]

RDW-CV is calculated directly from impedance and the flow cytometric method. It may provide various significant clues that help in diagnosing different types of red cell disorders.[6] An increase in red cell distribution width shows dysregulation in red cells homeostasis in the form of impaired production of red cells and its survival, which might lead to oxidative stress, inflammation, poor state of nutrition.[7] Previous studies on RDW values were headed to discover relation of RDW-CV with severity of disease and prognosis in neonates having sepsis.[8] Many studies had found that red cell distribution width-CV (RDW) and morphology of platelets vary significantly in pathological conditions that are linked with infection and inflammation. A number of studies have reported that RDW-CV shows prognostic value of all-cause mortality in terminally ill ICU patients.[9] Recently, RDW-CV is acknowledged as an independent prognostic indicator in various forms of malignancies like lung carcinoma, gastric and colorectal carcinoma, breast carcinoma, prostatic carcinoma, as well as several forms of blood cancers. Raised levels of RDW-CV might link the relationship between inflammation and tumor formation, which correlates to the poor prognosis of cancer patients.[10] Few studies have shown the red cell volume distribution width-CV (RDW-CV) value increased significantly in the patients who suffered from severe COVID-19, showing that the role of red cell parameters as risk indicators. RDW-CV can be used as a predictor for the prognosis of severe patients.[11]

An extensive literature review has shown that very scanty work has been done to establish an association between a raised value of RDW-CV and the prognosis of neonates suffering from sepsis. The purpose of this study was to highlight the role of RDW-CV in the prognosis of neonatal sepsis. This study can explore to what extent the value of RDW is used as prognostic indicator in diagnosing neonatal sepsis, and correlate its severity with alternative markers.

Methodology

After taking approval from the hospital's ethical committee (No. F. 1-1/2015/ERB/SZABMU/294, dated August 30, 2018) and getting informed consent from the patients' parents. A comparative observational study by non-probability convenient sampling was done in the neonatal Intensive Care Unit, Children Hospital Pakistan Institute of Medical Sciences Islamabad, from December 2018 to April 2020. A total of 136 neonates at term (38-39 weeks of gestation) having post-natal age ranging from 0-29 days in both groups with suspicion of sepsis were recruited in the study. The sample size was calculated using WHO calculator taking the level of significance as 5% and power of test as 90%, anticipated population proportion (rate of survival with raised RDW group=62.10% and with normal RDW group=94.0%).[11] The newborns with clinical features of sepsis were equally distributed into two groups on the basis of RDW from a blood sample taken on the day of admission.

Group 1 (normal RDW) had neonates with a normal value of RDW (RDW-CV%). Group 2 (Raised RDW) had neonates with raised value of RDW (RDW-CV%). Complete blood picture and C-reactive protein were done on the day of admission (Day 1) and then repeated at Day 3 (72 hour) of admission. All neonates born at full term (1-28 days) presenting with symptoms and signs of sepsis (like decreased feeding, lethargy, increase in respiratory rate, hypothermia, fits)

Neonates with predisposing factors (i.e., history of fever in pregnancy, history of PV leaking and UTI, in pregnancy, etc) were included in the study. Hyperbilirubinemia in neonates due to causes other than sepsis, including physiological jaundice, Rh incompatibility and ABO incompatibility, severe asphyxia at the time of birth, congenital anomalies, birth trauma, parents not giving consent, pre-term infants were excluded from the study. The demographic data and hematological laboratory profile of all patients at the time of admission in to the hospital were recorded on a proforma. The investigations included: Complete blood counts done on an automated hematology analyzer (Mindray BC-6200) and C-reactive protein by qualitative and semi quantitative latex agglutination method. About 3ml of blood were collected in gel tube to analyze CRP. The assays were performed by suspending latex particles CRP antibodies (anti human antibodies) against unknown

serum. Agglutination in serum of patient indicated raised levels of CRP. For the qualitative technique one drop of patient serum was mixed with one drop of latex reagent and checked for agglutination along with positive and negative controls. Agglutination indicated value of CRP ≥ 6mg/L was proceeded further. When Semi-quantitative technique was used to evaluate the quantity of CRP. Serial dilution were made as1:2, 1:4, 1:8, 1:16, 1:32 by using normal saline and then mixing with one drop of latex reagent and results were reported in numerical value in mg/dl.

The entry of data and statistical analysis was done using SPSS version 20. Qualitative variables were expressed as a percentage, whereas quantitative variables were measured as means and standard deviation and presented in tables. The chi-square test and independent sample t-test were applied to calculate p-value, <0.05 was considered significant.

Results

A total of 136 neonates were recruited and divided into two groups on the basis of RDW –CV value. 68 neonates were included in Group 1 (Normal RDW-CV) and 68 neonates were included in Group 2 (Raised RDW-CV). Comprised of 45 (66.2%) males and 23 (33.8%) females with male to female ratio of 1.9:1. Group 2 included 39 (57.4%) males and 29 (42.8%) females with male to female ratio of 1.34:1. The mean age of the patients in Group-1 was 5.36± 3.10 days, and in Group 2, it was 3.36 ± 2.51 days. (p<0.001) The changes observed in the hematological parameters of Group-1 and Group 2 neonates on Day 1 and Day 3 are shown in Table I and II.

Table I: Comparison of Hematological parameters in both groups at Day 1.

Parameters	Group 1 (Normal RDW) (Mean ±SD)	Group 2 (Raised RDW) (Mean ±SD)	P-Value
RBC Count	4.52 ±0.37	4.90 ±0.77	0.011
TLC	11.31 ±5.91	12.9 ±5.15	0.399
Hemoglobin	15.82 ±1.62	17.2 ±2.58	0.05
Hct	46.4 ±4.94	52.9 ±9.24	0.759
MCV	103 ±6.51	104 ±5.57	0.641
MCH	35.17 ±2.10	34.5 ±1.54	0.153
MCHC	33.97 ±0.73	32.8 ±1.43	<0.01
RDW	14.71 ±0.65	17.14 ±1.46	<0.001
Platelet Count	245 ±115	243 ±103	0.112

The mean CRP observed at day 1 in Group 1 was 7.52±7.47 mg/dl and in Group 2 it was 8.54±13.00 with p-value of 0.60. The mean CRP observed at day-3 in Group-1 was 18±25.4 mg/dl and in Group 2 it was14.7±13.7 with p-value of 0.41.

Table -II Comparison of Hematological parameters in both groups at Day-3

Parameters	Group 1 (Normal RDW) (Mean ±SD)	Group 2 (Raised RDW) (Mean ±SD)	P-Value
RBC Count	4.07 ±0.63	5.04 ±0.63	0.005
TLC	11.8 ±5.98	16.25 ±7.65	0.190
Hemoglobin	13.7 ±1.65	16.9 ±2.25	0.031
Hct	40.2 ±5.06	51.5 ±8.93	0.009
MCV	101 ±5.85	100.8 ±6.42	0.505
MCH	34.5 ±2.20	33.7 ±2.14	0.230
MCHC	34.2 ±1.11	33.1 ±1.82	0.014
RDW	15.3 ±0.91	17.8 ±1.90	<0.001
Platelet Count	157 ±128	168 ±107	0.515

Table III Gender stratification according to RDW-CV Groups. (n=136)

RDW Groups	Gender Groups		
	Males	**Females**	**Total**
Normal RDW	45 (66%)	23 (33.8%)	68 (100%)
Raised RDW	39 (57.4%)	29 (42.8%)	68 (100%)

Gender stratification into the RDW-CV groups and according to outcome have been shown in Table III and Table IV, respectively. Outcome was observed in both groups which included discharged and expired neonates, as depicted in Table V.

Table IV: Outcome of patients according to Gender stratification. (n=136)

Outcome	Gender Groups		
	Males	**Females**	**Total**
Discharged	62 (45.6%)	41 (30.1%)	103 (75.7%)
Expired	22 (16.2%)	11 (8.1%)	33 (24.3%)

Table-V Outcome of patients in both RDW Groups. (n=136)

Outcome	RDW Groups			
	Normal RDW Group	**Raised RDW Group**	**Total**	**p-value**
Discharged	57 (83.8%)	46 (67.6%)	103 (75.7%)	0.45 *
Expired	11 (16.2%)	22 (32.4%)	33 (24.3%)	0.028 *

* chi-square test used to calculate p values

Out of a total of 136 patients, 34 had mechanical ventilation. In Group-1, 10(14.7%) while in Group-2, 24 (35.3%) were shifted to ventilator which showed a significant p-value of 0.006. The length of hospital stay in term of days in Group 1 was 5.85± 4.03 and in Group

2, it was 7.63± 4.82 days with significant p-value of <0.001. Maternal risk factors observed in both groups were Urinary Tract Infection (UTI) and Premature Rupture of Membranes (PROM). Out of 136 patients, 19 mothers had history of UTI out of whom 10(14.7%) were in Group 1 and 9 (13.2%) in group-2 (p=0.805). A total of 16 mothers had history of PROM, 8 mothers in each group (p=0.59)

Discussion

Neonatal sepsis is a common condition, but its difficult diagnosis has always been a challenge for neonatologists. The gold standard technique for the diagnosis of sepsis is blood culture. [13]

C-reactive protein is considered an acute phase reactant and is used as a sensitive marker in patients with sepsis. In various conditions where patients presented with acute infection or inflammation, the value of CRP in serum can be detected within two hours of infection, reaching the highest values within 48 hours.[14] A study performed by hisamuddin et al explained that qualitative analysis of CRP on two occasions, first at Day-1 then at 72 hours of admission, is very important to check the validity of the test.[15]

RDW is a representation of the difference in size of the red blood cells. It is amplified when excessive reticulocytes are released into circulation. Above all, it has a role in the assessment of anemia. RDW has been found to be a significant prognostic marker in patients suffering from pulmonary embolism, cardiovascular disorders, pneumonitis, and life-threatening illnesses. Inflammation and oxidant stress have been proposed to decrease red blood cell life span and inhibit their maturation leading to release of large number of premature red blood cells into circulation, resulting in elevated RDW. Inflammation and oxidative stress are important parts of sepsis cascade. A complete blood count (CBC) is routinely performed in the majority of sepsis cases by automated analyzers. RDW is a component of the CBC.[16]

Leonardo et al showed the value of RDW-CV was raised in patients with sepsis who expired during first seven day of ICU admission as compared to those patients who survived. It also showed that during first week of admission, RDW was linked with severity of sepsis and death. The results of this study was comparable with our study, as in newborns with raised RDW-CV who were admitted during first week of life few expired, some had prolonged hospital stay with mechanical ventilation and then expired.[17]

In terms of severity, RDW was significantly linked with septicemia with a p-value of < 0.001 in Group-2 (Raised RDW) on both day-1 and day-3. It is higher in severe cases as compared to mild cases (19.4 ± 1.8 & 17.2± 0.58 respectively) as observed in a study done by Saleh et al., Who also stated that mean value of RDW in less severe patients were 16.04 ± 0.7 and mean value of RDW in more severe patients were 19.75± 1.9. [18]

RDW in both of the groups was significant with p-value of <0.001 both at Day 1 and at Day 3, and number of deaths was more in Group 2 in this present study that was comparable to the study that was performed Ellahony et al which stated that RDW was significantly elevated in neonates who died as compared to the survivors that suffered from neonatal sepsis and mortality was elevated among infants with increased RDW as compared with those with normal RDW.[19]

A study performed by Jandial et al.,indicated that RDW at admission is higher in dead patients with a mean value of 17.84 ± 3.38% as compared to survivors with mean value of 16.84 ± 2.90%. [7]

Suspected cases of neonatal sepsis in Group-2 (Raised RDW) in current study showed M:F of 1.34:1 that is comparable to the study done by Akindolire et al, that also showed M:F of 1.3:1. [20]

The outcome of the neonates was assessed in term of expiries, mechanical ventilations, and hospital stay in term of days and number of discharges. Regarding outcomes in terms of expired and survived in Group1 with normal RDW, 10 neonates (40%) died and 15 (60%) survived. In group 2 with raised RDW, 17 (68%) died and 8(32%) survived.

High value of RDW was linked with poor outcome (68% mortality) compared with normal RDW (40% mortality) that was similar to our study in which 22(32.4%) expired in raised group and 11(16.2%) expired in normal group. Significant difference was seen among two groups as regards to outcome. [21]

Association amongst neonatal death and RDW was also seen, as raised RDW is related with high newborns death in the study done by Saleh et al.[18] Similar result was seen in our study 16.2% expired in group-1 and 32.4% newborns expired in group 2. A total number of 32 neonates were expired in both groups, males were predominant. This also showed that neonates with raised

value of RDW were at great risk of complication and mortality as compared to group with normal RDW.

In current study newborns with raised RDW in Group-2 were 24 (35.3%) that needed ventilator support as compared to Group 1 with normal RDW that were 10 (14.7%) that was comparable to study performed by Otero et al, that also showed that elevated value of RDW lead to mechanical ventilation in medical and also in surgical intensive care units.[11] In our study length of stay in hospital with raised RDW (Group 2) was 7.6 ±4.8 and with normal RDW (Group-1) was 5.8 ±4.03 that was comparable with the study performed by Megahed et al., that showed raised value of RDW was related with prolonged length of stay in ICU with value of 20.0±4.43 days as compared with normal RDW group that was 14.20±3.34 day.[22]

El-Nahhal et al. reported that value of hemoglobin did not change significantly in septic patients during their stay in hospital, as compared to control group. This signifies that hemoglobin is not responsible for complications that occur due to sepsis. [23]

TLC on day 1 showed P value of 0.399 and on day 3 showed p-value of 0.190 which was related to the study done by Saleh et al that also showed non-significant relation of WBC to the severity of disease with p-value of 0.299 and 0.129 respectively. [18]

In our study, there was non-significant difference observed in platelet counts in both of groups which was not comparable to the study performed by Park et al, which showed thrombocytopenia in neonates with sepsis similar to the study performed by Park et al. [24]

In present study, risk factors that include urinary tract infection with p- value of 0.805 and premature rupture of membranes with p-value of 0.587 were not significant in both of groups as compared to the study done by Gebremedhin et al, that showed maternal factors (PROM and urinary tract infections) contributed to risk of neonatal sepsis. [25]

Karabulut et al showed that the mean value of CRP in group having suspicion of neonatal sepsis was 27.5 ± 6.3 mg/L, whereas in group with proven sepsis was 56.9 ± 21.7 mg/L ($p < 0.001$).[26] This was in contrast to the results of present study which showed that the mean value of CRP at Day 1 of Group 1 with normal RDW was 7.59 ± 7.4mg/L and Group 2 with raised RDW was 8.5± 13 mg/L with non-significant p-value of 0.60. On Day 3, Group 1 with normal RDW had a mean value of CRP was 18± 25mg/L and in Group with raised RDW was 14± 13mg/L with a non-significant p-value of 0.41.[26]

Conclusion

RDW-CV is not that expensive and is easily available with a routine complete blood picture, so it should be considered along with other investigations during the laboratory workup of neonatal sepsis. RDW-CV may reflect inflammation, oxidant stress, and arterial hypoperfusion in severely ill newborns, so it should be considered as a prognostic marker in suspected cases of neonatal sepsis. Based upon the results of this study, we recommend that physicians should remain vigilant about the value of RDW-CV in newborns with suspected sepsis. An increase in RDW-CV may be seen as a marker for the deteriorating condition of newborns. This study will support further investigations in view of the change in RDW-CV and its association with seriously ill newborns who are at risk for mortality. Aggressive treatment means switching to broad spectrum antimicrobial agents / selecting antimicrobials depending upon the culture report. Further research work is necessary to decide the exact underlying mechanism that is associated with RDW-CV, bloodstream infection and death. Carrying out such an observational comparative study will also be helpful in decreasing the financial burden on the patients who are from low socioeconomic background and are unable to afford the cost of different laboratory tests for diagnosing neonatal sepsis.

Acknowledgments: Dr. Almas Hashim (MBBS, FCPS Paediatrics) Assistant professor paediatrics department, Fauji foundation hospital, Rawalpindi

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