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Red Cell Distribution width as a Diagnostic Marker in Neonatal Sepsis

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ABSTRACT

Objectives: To determine the diagnostic accuracy of red cell distribution width in the detection of presence of sepsis in neonates.

Study Design: Cross-sectional validation study.

Place and Duration of Study: Department of Pediatrics, Pak-Emirates Military Hospital, Rawalpindi Pakistan, from Jul 2021 to Feb 2022.

Methodology: A total of 77 neonates suffering from acute febrile illness were included for study. Neonates born premature, low birth-weight, with meconium aspiration, or suffered from iron deficiency or haemoglobinopathies were excluded. The diagnosis of sepsis was established clinically using the 2005 International Pediatric Sepsis Consensus Conference guidelines. All patients were tested for red cell distribution width index via a phlebotomy on admission.

Results: The mean age of patients in our study was 16.38±6.71 days, of whom 44(57.1%) were male. A total of 27(35.1%) of patients had a family history of febrile seizures. The mean red cell distribution width of the patients was 17.71±2.89% and of these, 37(48.1%) patients had a value above the 18.0% cut-off level. Sepsis was present in 41(53.2%) cases. Red cell distribution width with a cut-off of value of greater than 18.0% as an indicator of the presence of neonatal sepsis had a sensitivity of 58.4%, specificity of 63.9% and a diagnostic accuracy of 61.0%.

Conclusion: Red cell distribution width is a useful marker in the detection of the presence of sepsis, but lacks the appropriate diagnostic accuracy, precluding its use in isolation as a single marker for sepsis.

Keywords: Neonates, Neonatal Sepsis, Phlebotomy Red Cell Distribution Width.

How to Cite This Article: *Abbasi AN, Ikram F, Rehman A, Nawaz SH, Hussain S, Mumtaz S. Red Cell Distribution width as a Diagnostic Marker in Neonatal Sepsis. Pak Armed Forces Med J 2025; 75(6): 1051-1054. DOI: https://doi.org/10.51253/pafmj.v75i6.8461*

INTRODUCTION

Sepsis occurring within the first twenty-eight days of life is a common causes of neonatal mortality, with an estimated incidence of 2824 per 100,000 live births, of whom approximately 17.6% die.[1] This mortality rate is expected to increase, especially with the emergence of multi-drug resistant bacteria.[2] Establishing early diagnoses are helpful in instituting timely and appropriate management, which result in a significant reductions in morbidity and mortality.[3] A number of biomarkers and testing modalities have been proffered as being useful indicators for the presence of neonatal sepsis, some novel, with variable degrees of utility,[4] which includes testing modalities such as blood cultures, complete blood counts, inflammatory markers/acute phase reactants and novel compounds.[5]

Red cell distribution width index is a measure of the variation in size of red blood cells, an increase in variation in size results in an increase in the index, thus it serves as a reliable marker for anisocytosis.[6] Sepsis has been purported to be associated with the development of anisocytosis, the reasons for which are multifactorial but largely occur due to the increased number of precursor cells in peripheral blood, increased red blood cell destruction, alterations in membrane permeability and cell membrane content.[7,8] However, the research on the subject currently available is hardly definitive with the regards to establishing a concrete relationship between the presence of sepsis and its role in causing derangements in red cell distribution width, with studies reporting completely conflicting results.[9,10]

With burgeoning populations and limited healthcare resources, developing countries like Pakistan are obliged to pay special attention to problems associated with the neonatal period, neonatal sepsis in particular. Early detection of sepsis at this fragile age in imperative, as even the appropriate treatment given too late while result in poor outcomes, and with sepsis the first one hour after presentation is where the patient is saved or lost. Red cell distribution width index may serve as a marker

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Received: 29 Mar 2022; revision received: 27 Jun 2022; accepted: 29 Jun 2022

for the presence of sepsis in neonates, which is cheap and readily available, however, the studies conducted on the subject are contradictory to each other, perhaps due to the differences in the populations/ ethnicities in which the studies took place. This study was conducted to determine the utility of red cell distribution width index with regards to detecting the presence of sepsis in neonates with objective of determining the role, if any, this test had in the rapid diagnosis of neonatal sepsis.

METHODOLOGY

This was a cross-sectional validation study which was conducted from July 2021 to Febrayry 2022 in the Department of Paediatrics, Pak-Emirates Military Hospital, Rawalpindi Pakistan, on 77 neonates suffering from a febrile illness. Informed consent was obtained from guardians/parents. The WHO sample size calculator was used to calculate the sample size keeping an expected sensitivity of 44.40%, expected specificity of 57.97%, expected prevalence of 42.42%, a desired precision of 2 and a confidence level of 95%.[11] All participants were chosen via non-probability consecutive sampling.

Inclusion Criteria: Patients under the age of 1 month of both genders were included.

Exclusion Criteria: Neonates who were born before 37 weeks of gestation, had low birth-weight, or suffered from meconium aspiration syndrome, blood group incompatibility, iron deficiency anaemia, blood transfusions, haemoglobinopathies or were born with congenital anomalies were excluded from the study.

All patients were thoroughly evaluated by history and clinical examination on enrollment in the study, along with the collection of demographic data, to determine whether they fulfilled the requirements of the sample selection criteria. The presence of sepsis was defined according to the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) guidelines.[12] All patients underwent blood sampling which was conducted by a trained phlebotomist with a minimum of two years' experience in paediatric phlebotomy. The samples were tested by a control-tested and calibrated Sysmex XP-300 Haematology Analyzer, which measured complete blood indices including red cell distribution width index, and a value greater than 18 was considered abnormal.

Data was analyzed using Statistical Package for the Social Sciences version 26.0. Mean and SD was calculated for quantitative variables specifically age, gestational age at birth, birth-weight, leucocyte count, thrombocyte count and red cell distribution width index. Qualitative variables like gender, presence/ absence of sepsis and presence/absence of red cell distribution width abnormality were recorded in terms of frequency and percentage. A 2 x 2 table was constructed to calculate the sensitivity (True Negative/True Negative + False Positive x 100), specificity (True Positive/True Positive + False Negative x 100), positive predictive value (True Positive/True Positive + False Positive x 100), negative predictive value (True Negative/True Negative + False Negative x 100) and diagnostic accuracy (Sensitivity × Prevalence + Specificity × (1 − Prevalence)) of red cell distribution width in predicting the presence of neonatal sepsis.

RESULTS

We studied a total of 77 patients with a mean age of 16.38±6.71 days, of these 44(57.1%) were male. The mean gestational age at birth of the sample was 39.03±1.20 weeks, with a mean birth-weight of 3240.75±427.59 g. A total of 27(35.1%) of patients had a family history of febrile seizures. The mean total leucocyte count at the time of enrollment was 12.50±7.09 x 109/µL while the mean total platelet count was 222.18±102.52 x 109/µL. The mean red cell distribution width of the sample was 17.71±2.89%, and 37(48.1%) patients had an abnormally high red cell distribution width. Sepsis was seen in 41(53.2%) of neonates. The results of the study are displayed in Table-I, where the variables are divided according to gender.

Table-I: Study Results according to Gender Distribution (n=77)

Variables	Male Patients (n=44)	Female Patients (n=33)	*p*-value
Age (days) (Mean±SD)	17.34±6.83	15.09±6.42	0.146
Gestational Age (weeks) (Mean±SD)	38.95±1.18	39.12±1.24	0.551
Birth-Weight (g) (Mean±SD)	3242.05±468.04	3239.03±373.99	0.976
Family History of Febrile Seizures	17(38.6%)	10(30.3%)	0.448
Total Leucocyte Count (109/µL) (Mean±SD)	11.97±7.22	13.19±6.96	0.459
Total Platelet Count (109/µL) (Mean±SD)	223.16±107.30	220.88±97.41	0.924
Red Cell Distribution Width (%)(Mean±SD)	17.97±2.86	17.37±2.93	0.371
High Red Cell Distribution Width	22(50.0%)	15(45.5%)	0.693
Neonatal Sepsis Present	24(54.5%)	17(51.5%)	0.792

Table-II shows the two by two contingency table construction to calculate the various test parameters

such as sensitivity and specificity of red cell distribution width in predicting the neonatal sepsis.

Table-II: Two by Two-Contingency Table for Red Cell Distribution Width (n=77)

		Presence of Sepsis according to the International Pediatric Sepsis Consensus Conference Guidelines	
		Yes	No
Neonatal Sepsis according to Red Cell Distribution Width	Yes	True Positive: 24(31.2%)	False Positive: 13(16.9%)
	No	False Negative: 17(22.1%)	True Negative: 23(29.8%)

Red cell distribution width at cut-off levels of 18% as a marker for the presence of neonatal sepsis had a sensitivity of 58.4%, a specificity of 63.9% and a diagnostic accuracy of 61.0% in our study. The results for the various characteristics of the tests are shown in Table-III.

Table-III: Diagnostic Parameters (n=77)

Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy
Red Cell Distribution Width	58.4%	63.9%	64.9%	57.5%	61.0%

DISCUSSION

We conducted this study to determine whether a cut-off level of greater than 18% red cell distribution width was useful in predicting whether sepsis was present in neonates or not, if found to be an accurate marker, the test could be a useful surrogate to the use of cumbersome scoring systems, or tests that take time to establish a diagnosis, such as blood cultures. The 2005 International Pediatric Sepsis Consensus Conference guidelines were used to establish the diagnosis of neonatal sepsis, which have been previously reviewed and validated in the paediatric population.[13]

In our study, 44(57.1%) of the patients were male, which was similar to Golhar *et al.*, who reported on a population which was 60% male, and the male population was similarly in majority in Singh *et al.*, i.e., 67.3%.[11,14] The reason for increased sepsis in male neonates has been demonstrated in a recent meta-analysis by Murthy *et al.*, and, while the mechanism has not been clearly established, it is attributed to the "male disadvantage hypothesis", which proposes that males have a weaker immune system and longevity in exchange for physiological fitness and reproductive energy expense.[15,16]

A total of 37(48.1%) had a high red cell distribution width index in our study. Golhar *et al.*, reported a similar incidence i.e., 42.4% in their study.[11] Conversely, Martin *et al.*, reported a frequency of only 19.9% in cases of sepsis in their study. The difference may have occurred in the manner in which this study defined sepsis.[17] Our study showed that red cell distribution width index at a cut-off of 18% was associated with sensitivity of 58.4%, a specificity of 63.9% and a diagnostic accuracy of 61.0%. Golhar et al reported a sensitivity of 46.15%, a specificity of 67.75% and a diagnostic accuracy was 56.36% in their study which was similar to ours.[11] Deka *et al.*, reported that with a cut-off level of 17.25%, red cell distribution width had a sensitivity of 86.0%, a specificity of 87.0% and a diagnostic accuracy of 93.5%.[18] Singh *et al.*, reported a sensitivity of 94.6%, a specificity of 96.4%, and a diagnostic accuracy of 95.5% at a higher cut-off of 18.5%.[14] We attribute the difference in results to the sample selection criteria in the latter studies wherein they did not exclude patients with nutrient deficiency, blood transfusion and suspected haemoglobin disorders.

Previous studies conducted on the subject of are a mixed bag, with a wide range of sensitivities and specificities reported, we believe that standardization of selection criteria will demonstrate that red cell distribution width has a low diagnostic accuracy in the diagnosis of neonatal sepsis.

LIMITATION OF STUDY

The purpose of this was to determine if the red cell distribution width could serve as a cheap and rapid test to predict the presence of neonatal sepsis, however, this study was limited by lack of testing for haemoglobinopathies, only patients with a family history of haemoglobin disease who were suspected of having a disorder were excluded, patients did not undergo a haemoglobin electrophoresis. Moreover, the index is known to show variability between different populations and ethnicities which was not accounted for in our study.

CONCLUSION

Red cell distribution width is a rapidly performed test, which is easily available and cheap. However, it did not have the diagnostic accuracy required to make it a reliable marker for neonatal sepsis in our study. Disorders in red cell size are all too common, due to a wide variety of causes which produce a confounding effect on the results, and we recommend that the test not be employed as a sole diagnostic test for the disorder, but may be incorporated along with other investigation in devising a diagnostic protocol.

Conflict of Interest: None.
Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ANA & FI: Data acquisition, data analysis, critical review, approval of the final version to be published.

AR & SHN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SH & SM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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