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Role of Red Cell Distribution Width and Neutrophil: Lymphocyte Ratio in Adults with Sepsis

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ABSTRACT

Introduction: Sepsis is a significant contributor to morbidity and mortality in admitted patients. A large number of markers have been studied as biomarkers for sepsis. Most of them are either expensive or lack good sensitivity and specificity.

Objective: In this study, we want to evaluate the role of simple blood tests such as Red cell distribution width (RDW) and neutrophil-lymphocyte ratio (NLR) in the evaluation of the severity of sepsis cases.

Methods: 173 sepsis patients were included in this ICU cross-sectional study. Red cell distribution width and neutrophil-lymphocyte ration were measured at admission. Both these parameters were compared with quick sequential organ failure assessment (qSOFA) score. They were also compared with the outcome of patients.

Results: The mean RDW was 14.455 and it showed a significant correlation with qSOFA score and outcome of sepsis patients. An RDW of 15.050 was found to predict the worse outcome with a sensitivity of 82.4% and specificity of 74.7%. The mean NLR was 5.1645 and it also correlated with qSOFA score in sepsis patients. An NLR of 3.22 predicted worse outcome but only with the sensitivity of 66.2% and specificity of 65.7%.

Conclusion: RDW and NLR both showed good correlation with sepsis outcome. However, RDW had a better sensitivity and specificity in predicting worse outcomes in sepsis.

Key Words: Neutrophil lymphocyte ratio, Outcome, Red cell distribution width, Sepsis, Severity, Intensive care unit

INTRODUCTION

Sepsis continues to be a major cause of morbidity and mortality in Intensive Care Units (ICU) despite the better understanding of its pathophysiology in recent years. Bloodstream infections are an important cause of serious morbidity and mortality and the incidence of sepsis is reported up to 30% in patients admitted in the intensive care units.[1,2] Since sepsis is a heterogenous process with various manifestations, severity levels and cellular processes involved, a definitive biomarker that could aid in the diagnosis, staging, prognosis, and response to intervention has been difficult to determine. Scores such as APACHE II score on admission are associated with high mortality.[3] Researchers have proposed more than a hundred different molecules as useful biomarkers of sepsis. C-reactive protein (CRP) and Procalcitonin (PCT) have been frequently used in the evaluation of the severity of sepsis and deciding the duration of therapy in ICU patients.

Nevertheless, they are expensive and have insufficient predictive value for an individual.[4] Since the definition of the new criteria was published, qSOFA score and SOFA score have been used to predict severity of sepsis and related in-hospital mortality for patients in the emergency department or the ICU.[5] Red cell distribution width (RDW) is routinely done as a part of the routine blood count. Various studies have shown that it may be used as a prognostic marker in hypertension, coronary artery disease, stroke, and acute kidney injury. It has also been shown to correlate with all-cause mortality and nutritional status. [6] Total White blood cell (WBC) count is recognised as an important systemic inflammation marker. Leucocytosis has also been shown to independently predict all-cause mortality. Previous studies have also shown relative lymphocytopenia and neutrophilia in patients with sepsis. In critically ill patients the "neutrophil-lymphocyte ratio" (NLR) is a simple, rapid and inexpensive novel marker of inflammation and stress. It has also been found to have

predictive value in patients with suspected bacteraemia in medical emergencies; and also found to be associated with short-term and long-term clinical outcomes in critically ill patients.[7] With this background, the current study aims to study the relationship between RDW and neutrophil: lymphocyte ratio with the severity of illness in patients admitted to medical ICUs with sepsis has been undertaken.

MATERIALS AND METHODS

The study design was a cross-sectional study. The study type was an analytical study. It was done in an ICU in a tertiary care centre in South India. Permission from the local ethics committee was obtained. Informed consent was obtained from all participants.

Inclusion criteria: All participants who were more than 18 years and diagnosed to have sepsis in ICU and in whom blood sampling was done within 24hrs of admission were included in the study.

Exclusion criteria: Immunosuppressed patients such as HIV infection, cancer or patients receiving immunosuppressive therapy, patients with haematological disorders and pregnancy.

Sample size was estimated using the formula n= $2(Z_\alpha + Z_\beta)^2$ x σ^2 / d^2 where Z_α =1.96 at 95% confidence interval, Z_β = 1.28 at 90% power, σ = SD and d=mean difference. With 95% confidence level and 90% power the sample size came to 180. Sampling strategy followed was convenient sampling. Adult patients presenting to ICU diagnosed as sepsis as per 2016 Sepsis – 3 guidelines[2], were considered for the present study. Basic demographic data, comorbidities, source of a new infection, presenting vital signs were recorded as per the proforma. Patients were stratified according to Q-SOFA scoring. q-SOFA score and SOFA score were calculated on the fifth day of admission to ICU, to assess the progress of the patient.

Blood samples were collected at the time of admission for the following tests: Complete blood counts with RBC indices. Blood urea, serum creatinine and serum electrolytes. Liver function test (LFT), coagulation studies (INR, aPTT), Serum glucose, Blood culture and other cultures (e.g., of sputum, stool, urine, wounds, catheters, prosthetic implants, epidural sites, pleural or peritoneal fluid). Arterial blood gas (ABG). Chest x-ray, ECG was performed as per protocol. Other investigations as appropriate were carried out such as lumbar puncture, echocardiogram (trans-thoracic or trans-oesophageal), ultrasound scan, CT chest or abdomen. RDW was measured at admission to ICU. The RDW is a measure of variability or red blood cells in size. It may be elevated due to ineffective production or increased destruction of red blood cells. This happens usually in inflammation and in-

fections. Neutrophil to lymphocyte ratio (NLR) was determined by dividing the absolute neutrophil count by the absolute lymphocyte count. The patients were followed to check their condition whether SOFA score improved or worsened. The patient outcome on Day 5, including mortality, was recorded.

Statistical Methods

Data was entered and analyzed by using statistical software- Statistical Package for Social Sciences (SPSS) Version 17.0. Descriptive statistics like proportions, mean (standard deviation) and median (IQR) was used for expressing the results. For qualitative data Chi-square test and ANOVA was applied and P < 0.05 was considered as a statistically significant association.

RESULTS

A total of 173 patients were included in the study. Males formed 62.4% of the subjects. Majority of the patients with sepsis were over 50 years of age. Pulmonary infections (38.2%) were the most common source of infection in the majority of sepsis cases, followed by tropical infections (27.2%). Table 1 shows the organisms responsible for sepsis. Gram-negative sepsis was the most common cause of sepsis in the study population. Dengue fever, detected by dengue IgM positivity, was the most common individual cause of sepsis in the study population. No organisms could be isolated in around 23.7% of the cases. Hypertension (41.6%) and Diabetes (41%) were the most common co-morbidities present in this study. Outcomes on day 5: 43% of the patients improved, 39% of the patients worsened and 18% of the patients died. RDW was found to be between 14.2 and 15.2 in the majority (59%) of patients with sepsis in the study group. Most of the patients belonged to qSOFA score of 3 (41%). 36% of the patients had a qSOFA score of 2 and 23% of the patients belonged to qSOFA score of 1. As the RDW increased the qSOFA score also increased as shown in Table 2. It was statistically significant. As seen in Table 3 patients with high RDW had poorer outcome and it was statistically significant. ROC was plotted for RDW vs outcome: The area under the curve was found to be 0.834, which implied RDW was a good test to predict the outcome. An RDW of 15.050 was found to predict the worse outcome with a sensitivity of 82.4% and specificity of 74.7%. It was found in the study that as the q SOFA score increases, median NLR increases as seen in Table 4. ROC was plotted for NLR vs Outcome. The area under the curve was found to be 0.663, which showed that NLR was only a fair test to predict the outcome. An NLR of 3.22 predicted worse outcome with the sensitivity of 66.2% and specificity of 65.7%.

DISCUSSION

In this study, 173 patients who were admitted to the ICU, diagnosed as sepsis as per the 2016 Sepsis – 3 guidelines, were studied. Respiratory infections were the most common source of sepsis, and this was by previous studies.[8] However, tropical/non localised diseases such as dengue fever, leptospirosis and malaria had a much higher incidence in our study population, this might be explained by the endemicity of these diseases to this region. Hypertension and diabetes mellitus were the most common comorbidities seen in this study. In another study of sepsis in India, 28% of those patients had diabetes and 16.5% of the patients had hypertension.[9] In our study mortality rate was 18%. In another study by Pandya et al. they found a mortality rate of 28% in sepsis patients.[10] In our study there was a good correlation between RDW and qSOFA score. RDW correlated well with the APACHE II score in sepsis patients.[11] In our study RDW correlated well with the outcomes and as the RDW increased the outcome of the patients worsened. In another study, RDW not only predicted short term mortality but also had a good correlation with the 4-year mortality rate.[12] In our study an RDW greater than 15.050 predicted a worse outcome. In the study by Jandial A, they found that an RDW greater than 17.3 showed significant correlation with mortality in sepsis patients.[11] In our study the median NLR showed a reasonable correlation with the qSOFA score. As the median NLR increased the clinical outcome of the patient worsened. De Jager et al. observed NLR as a better predictor of severity and outcome in bacteremia than conventional markers.[13] In our study NLR of 3.22 predicted worse outcome in sepsis patients however it was not as strong a predictor as the RDW. Martins EC in their study showed that the cutoff point of 5.0 for the NLR was associated with a high risk for sepsis.[14]

CONCLUSION

We found that RDW correlated well with qSOFA score in sepsis patients and offered a clinically reliable cut off for prognostication of sepsis. We determined such a cut off to be 15.050 above which the outcome was bad. But we found Neutrophil lymphocyte ratio to be of limited clinical value as it lacked a discernible cut off and had a weak association with clinical outcome.

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Table 1: Group-wise organisms isolated

Group of organisms	Number of patients	Percentage
None isolated	41	23.7%
Gram negative Bacteria	64	36.9%
Gram positive Bacteria	17	9.8%
Rickettsia	1	0.005%
Mycobacteria (Tuberculosis)	7	4%
Protozoa	9	5.2%
Viruses	30	17.3%
Fungi	4	2.3%

Table 2: RDW at admission vsqSOFA

Q-Sofa	N	Mean	Standard deviation	95% CI for Mean		Anova (p value)
				Lower Bound	Upper Bound	
1	39	14.744	.5098	14.578	14.909	0.0001
2	63	14.783	.6637	14.615	14.950	
3	71	15.224	.7769	15.040	15.408	
Total	173	14.955	.7160	14.847	15.062	

Table 3: RDW at admission vs outcome

Outcome	N	Mean	Standard deviation	95%CI for Mean		Anova (p-value)
				Lower Bound	Upper Bound	
Improved	74	14.522	.6968	14.360	14.683	0.001
Worsened	68	15.194	.2764	15.127	15.261	
Dead	31	15.465	.8523	15.152	15.777	
	173	14.955	.7160	14.847	15.062	

Table 4: Neutrophil: Lymphocyte ratio vsqSOFA

Q SOFA	N	Mean	Std. Deviation	Median	Kruskall-Wallis test (p value)
1	39	3.8763	3.04724	2.9545	0.006
2	63	5.1069	3.96250	3.5733	
3	71	5.1645	5.62915	3.1818	