# A STUDY OF THE PROGNOSTIC VALUE OF RED CELL DISTRIBUTION WIDTH AND NEUTROPHIL: LYMPHOCYTE RATIO IN ADULTS WITH SEPSIS

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| ARTICLE INFO | ABSTRACT | ORIGINAL RESEARCH ARTICLE |
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**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. This may manifest as organ dysfunction such as hypotension, altered mental status, abnormal coagulation, increase in bilirubin levels, deranged renal function and increase in oxygen requirements. With this background, the current study of the relationship between RDW and neutrophil: lymphocyte ratio with severity of illness in patients admitted to medical ICUs with sepsis, has been undertaken.

**Objectives:** To study the prognostic value of red cell distribution width and neutrophil: lymphocyte ratio in sepsis.

**Materials and Methods:** This study was conducted on adult patients, who were admitted in ICUs of Tertiary care hospitals attached to Dr. VVP RMC, Loni, Maharashtra and whose haematological investigations were done within 24 hours of ICU admission. Patients with haematological disorders, immunocompromised patients, patients whose haematological investigations were not done within 24 hours of admission and who were not admitted in ICU were excluded from the study. The study was conducted for a two-year timespan, from September 2020 to September 2022. On admission, patients were stratified according to q-SOFA scoring[10] and SOFA score were calculated. Haematological investigations were done within 24 hours of admission. q-SOFA score and SOFA score were calculated at the fifth day of admission to ICU, to assess progress of the patient.

**Results:** Majority of the patients with sepsis were over 50 years of age. Hypertension, diabetes and obstructive airway diseases were the most common comorbidities present in the patients that were present in the study. Pulmonary infections were the most common source of infection

|  | in majority of sepsis cases, followed by tropical/ non- localised infections. RDW was found to be between 14.2 and 15.2 in majority of patients with sepsis in the study group. It was found that higher the RDW, higher the q-SOFA score and worse is the outcome at the end of 5 days. RDW at admission vs Outcomes assessed using ANOVA obtained a p value of p<0.0001 (highly significant). Patients with worse outcomes had a high RDW at admission. NLR vs q-SOFA assessed using Kruskal Wallis and then checked using Mann Whitney U test showed a significant p value of 0.006. It was found in the study that as the q-SOFA score increases, median NLR increases. |
|---|---|
|  | **Conclusion:** The study implies that patients with sepsis having an RDW more than 15.050 may benefit from early interventions and more aggressive management. In low resource settings, the RDW, in the emergency department could afford the earliest opportunity to identify patients at risk of bacteremia and the administration of antimicrobials at the appropriate time. |
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## 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. The incidence of sepsis is reported up to 30% in patients admitted in the intensive care units[1].

Sepsis, often fatal, is a clinical syndrome that involves systemic inflammatory response to an infection with bacteria, fungus, virus, or parasites. This may manifest as organ dysfunction such as hypotension, altered mental status, abnormal coagulation, increase in bilirubin levels, deranged renal function and increase in oxygen requirements. This may be objectively measured as an increase in "Sequential Organ Failure Assessment" score of $\geq 2$[2].

Factors involved may include generation of pro-inflammatory cytokines, continued activation of neutrophils and macrophages/monocytes, delayed apoptosis of neutrophils, decline in lymphocytes due to apoptosis and dysfunction of coagulation and inappropriate deposition of intravascular fibrin[3].

Since the definition of the new criteria was published, q-SOFA score and SOFA score have been used to predict severity of sepsis.

Red cell distribution width is routinely done as a part of the routine blood count. It has also been shown to correlate with all-cause mortality and nutritional status. RDW has also shown correlation with APACHE II scores in sepsis[4].

In critically ill patients the "neutrophil-lymphocyte count ratio" (NLCR) is a simple, rapid and inexpensive novel marker of inflammation and stress[5]. It has also been found to have predictive value in patients with suspected bacteremia in medical emergencies; and also found to be associated with short-term and long-term clinical outcomes in critically-ill patients[6,7,8].

With this background, the current study of the relationship between RDW and neutrophil: lymphocyte ratio with severity of illness in patients admitted to medical ICUs with sepsis, has been undertaken; as per 2016 definitions of sepsis and clinical predictors such as SOFA score and q-SOFA score.

## AIM

To study the prognostic value of red cell distribution width and neutrophil: lymphocyte ratio in sepsis.

**OBJECTIVES**

1. To evaluate the ability of red blood cell distribution width (RDW) and neutrophil-lymphocyte ratio for the prediction of outcome of sepsis patients.
2. To evaluate the association of RDW and neutrophil-lymphocyte ratio with risk stratification according to q-SOFA score.
3. To evaluate the association of RDW and neutrophil-lymphocyte ratio with SOFA score at admission to ICU.

**MATERIAL AND METHODOLOGY**

**Study Setting:** ICUs of Tertiary care hospitals attached to Pravara Institute of Medical Sciences, Loni, Maharashtra.

**Study design:** Cross-sectional study.

**Study Type**: Analytical study.

**Study population:** Adult patients with sepsis admitted to the ICU in the hospital of Dr. VVP RMC, Loni, Maharashtra.

**Inclusion Criteria:**

1. Age >/= 18 years.
2. Patients with sepsis admitted in ICU.
3. Blood sampling within 24 hours from admission.

**Exclusion Criteria:**

1. Immunosuppressed patients such as HIV infection, cancer or patients with receiving immunosuppressive therapy.
2. Previously diagnosed hematological disorders.
3. Pregnancy.
4. Patients who did not undergo required investigations on ICU admission[25].

**Study Sample: 173**.

**Sample size calculation:**

With 95% confidence level and 90% power with reference to previous study, the sample size comes to be 180.

The sample size was calculated using the formulae:

$$n= 2(Z\alpha +Z\beta)2 \text{ x } \sigma2 / d2$$

where $Z\alpha$ = 1.96 at 95% confidence interval, $Z\beta$ = 1.28 at 90% power, σ = SD and d=mean difference[9]

**Sampling strategy:** Convenient sampling.

**Study duration**: September 2020 to September 2022.

**METHODS:**

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 new infection, presenting vital signs were recorded as per the proforma. Patients were stratified according to q-SOFA scoring[10] and SOFA score was calculated. q-SOFA score and SOFA score were calculated at the fifth day of admission to ICU, to assess progress of the patient. Blood samples were collected at the time of admission for the following tests: FBC with differential, RBC indices, Blood urea, serum creatinine and serum electrolytes, 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 or venous blood gas (VBG), Chest x-ray, ECG were performed as per protocol. Other investigations as appropriate were carried out such as: lumbar puncture echocardiogram (trans-thoracic or trans-oesophageal), ultrasound scan[11].CT chest or abdomen RDW was measured at admission to ICU 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 at Day 5, including mortality was recorded.

**Data collection methodology:**

The study protocol was submitted for the approval from the Institutional Ethics Committee (IEC) of Dr. V P RMC, Loni, Maharashtra. Patients with sepsis meeting the inclusion and exclusion criteria were approached. The study participants were

briefed about the study objectives. A written informed consent was obtained from those willing to participate. After obtaining consent, relevant data was collected.

**Data Management:**

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 statistically significant association.
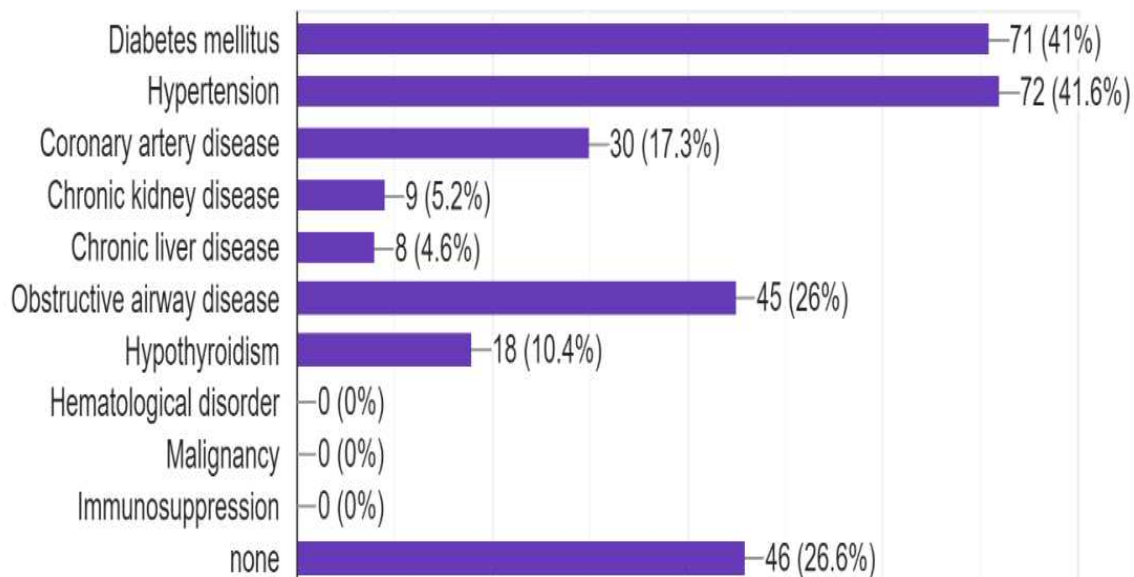
**RESULTS:**

**Table 1:** Age distribution

| Age of the patient | Number of patients | Percentage |
|---|---|---|
| 18 – 30 | 21 | 12.1% |
| 31 – 40 | 15 | 8.7% |
| 41 – 50 | 28 | 16.2% |
| 51 - 60 | 34 | 19.7% |
| 61 - 70 | 40 | 23.1% |
| Above 70 | 35 | 20.2% |
| Total | 173 | 100.0% |

Majority of the patients with sepsis were over 50 years of age.

**Comorbidities**



Hypertension, diabetes and obstructive airway diseases were the most common comorbidities present in the patients that were present in the study.

**Source of new infection**
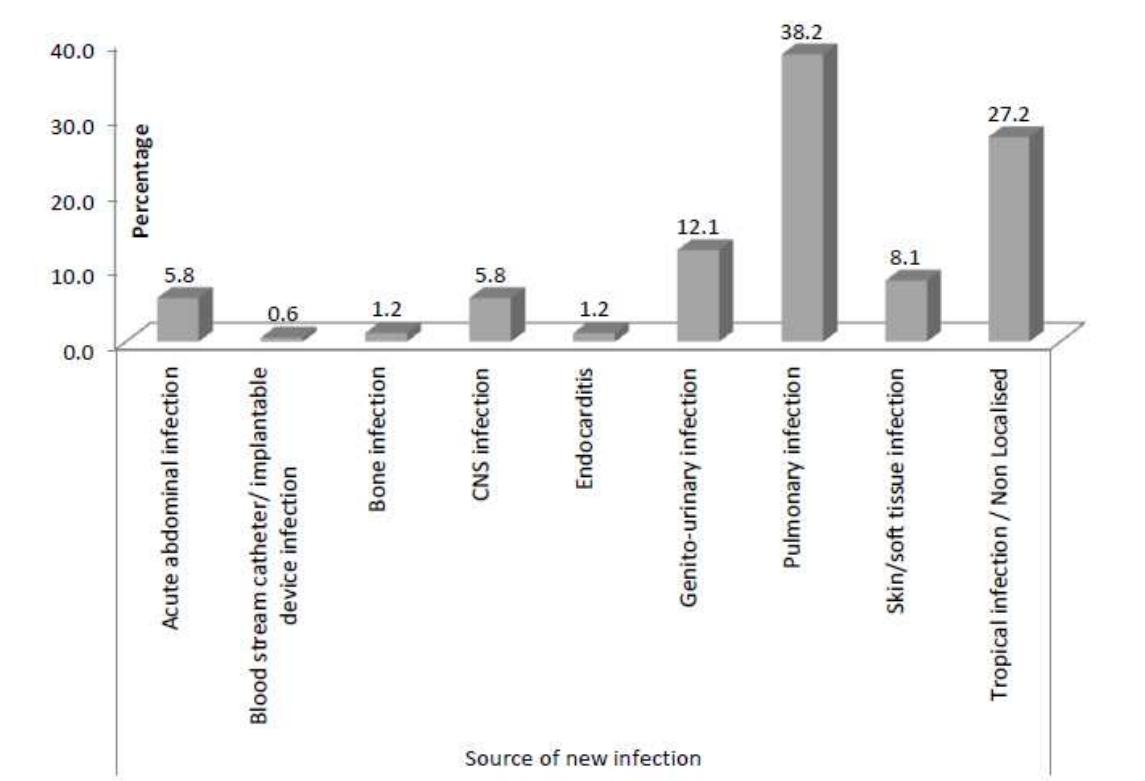
Pulmonary infections were the most common source of infection in majority of sepsis cases, followed by tropical/ non- localized infections.

### Red cell Distribution Width
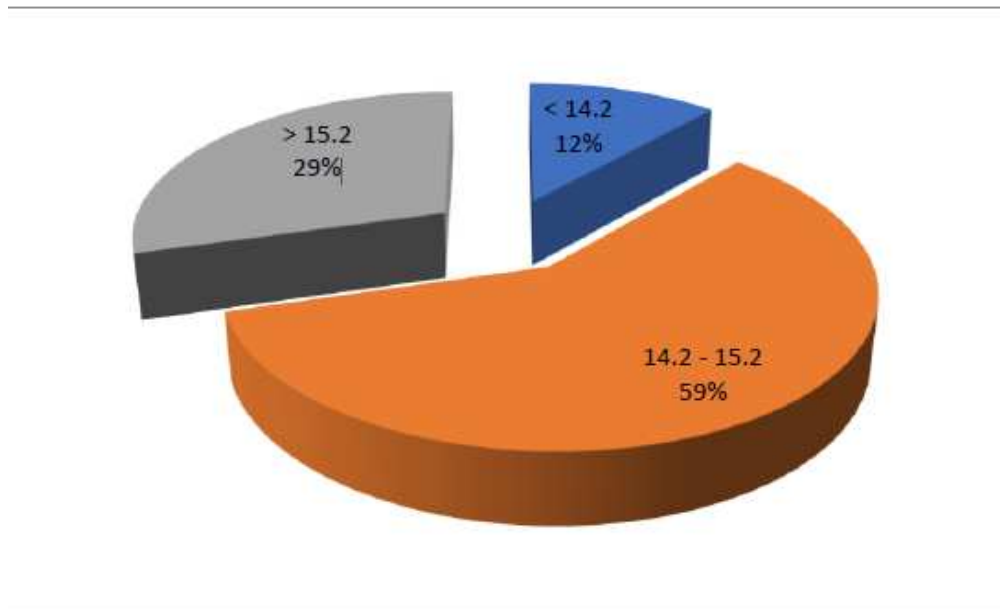


RDW was found to be between 14.2 and 15.2 in majority of patients with sepsis in the study group.

**Table 2:** RDW vs q-SOFA score & Outcome

| | | RDW at admission | | | | | |
| | | < 14.2 | | 14.2 - 15.2 | | > 15.2 | |
| | | Number of patients | Percentage | Number of patients | Percentage | Number of patients | Percentage |
|---|---|---|---|---|---|---|---|
| Q SOFA SCORE | 1 | 4 | 20.0% | 33 | 32.4% | 2 | |
| | 2 | 11 | 55.0% | 37 | 36.3% | 15 | 29.4% |
| | 3 | 5 | 25.0% | 32 | 31.4% | 34 | 66.7% |
| | Total | 20 | 100.0% | 102 | 100.0% | 51 | 100.0% |
| Outcome at 5 days | Improved | 19 | 95.0% | 42 | 41.2% | 13 | 25.5% |
| | Worsened | 0 | .0% | 49 | 48.0% | 19 | 37.3% |
| | Dead | 1 | 5.0% | 11 | 10.8% | 19 | 37.3% |
| | Total | 20 | 100.0% | 102 | 100.0% | 51 | 100.0% |

| Table 3: q-SOFA score and outcome | | |
|---|---|---|
| Fishers exact test p value | | |
| q-SOFA SCORE | 0.0001 | Highly Significant |
| Outcome at 5 days | 0.0001 | Highly Significant |

It was found that higher the RDW, higher the q-SOFA score and worse is the outcome at the end of 5 days.

**Table 4:** RDW at admission Vs outcome

| | N | Mean | Std. Deviation | 95% Confidence Interval for Mean | | ANOVA p value | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | Lower Bound | Upper Bound | | |
| Improved | 74 | 14.522 | .6968 | 14.360 | 14.683 | .0001 | HS |
| Worsened | 68 | 15.194 | .2764 | 15.127 | 15.261 | | |
| Dead | 31 | 15.465 | .8523 | 15.152 | 15.777 | | |
| Total | 173 | 14.955 | .7160 | 14.847 | 15.062 | | |

RDW at admission vs Outcomes assessed using ANOVA obtained a p value of p<0.0001 (highly significant).
Patients with worse outcomes had a high RDW at admission.

**Table 5:** Neutrophil: Lymphocyte ratio vs q-SOFA & Outcome

| Q SOFA SCORE | N | Mean | Std. Deviation | Median | Kruskall wallis test p value |
| --- | --- | --- | --- | --- | --- |
| 1 | 39 | 3.8763 | 3.04724 | 2.9545 | .006 |
| 2 | 63 | 5.1069 | 3.96250 | 3.5733 | HS |
| 3 | 71 | 5.1645 | 5.62915 | 3.1818 | |

NLR vs q-SOFA assessed using Kruskal Wallis and then checked using Mann Whitney U test showed a significant p value of 0.006.

It was found in the study that as the q-SOFA score increases, median NLR increases.

**DISCUSSION**

In this study, 173 patients who were admitted to the ICU, diagnosed as sepsis as per the 2016 Sepsis – 3 guidelines[2], were studied. Their baseline demographics, source of infection, organisms isolated. red cell distribution width at admission, neutrophil: lymphocyte ratio at admission, q-SOFA score and SOFA score at admission and 5 days were measured and outcomes were analyzed in an attempt to understand the pattern of sepsis in the region as well as to test the applicability of the hypothesis that red cell distribution width and neutrophil: lymphocyte ratio can be used for risk stratification and prognosis along with established risk stratification scores, that is, q-SOFA score and SOFA score.

**DEMOGRAPHIC PARAMETERS:**

Majority of the patients in the study population were above 50 years. This finding was consistent with prior international 12,13 as well as national data[14] and re-emphasizes that elderly age remains a risk factor for sepsis. Elderly patients were found to have worse outcomes including higher mortality during hospitalization than younger patients. Elderly patients also require more skilled nursing and rehabilitative care after hospitalization. The implications of these findings are that resources should be prioritized for elderly patients with sepsis and interventions such as antimicrobials and vasopressors should be started early in this population.

Around 63 percent of the patients in the study were male. This finding too was found to be similar to worldwide[12] as well as national

data[14] on sepsis. Possible hypothesis for these[15] results suggests a hormonal basis, that is, androgens being suppressive on cell-mediated immune responses and female sex hormones having protective effects16.

Multiple epidemiological studies on sepsis have shown that chronic co-morbid conditions were present in over thirty percent of the patients with sepsis[17,18]. The most common co-morbidities encountered in our study population were hypertension and diabetes mellitus. However, diseases which are known to affect the red cell distribution width and neutrophil: lymphocyte ratio such as prior anemia, immunosuppression including HIV, malignancies and pregnancy were excluded from the study. Presence of these co-morbid conditions correlate with poor outcomes.

Respiratory infections were the most common source of sepsis, and this was in accordance with previous international [19,20] as well as national studies[14]. However, tropical/non localized diseases such as dengue fever, leptospirosis and malaria had much higher incidence in our study population, this might be explained by the endemicity of these diseases to this region. Urosepsis was the next highest source of infection and this corresponded with available literature.

The etiological agents found in our study cohort were epidemiologically similar to those reported globally, with respect to gram negative sepsis being the most common aetiology. However, we found that the study cohort had higher incidence of malaria and dengue fever. However, this was in line with the regional trends[21].

Red cell distribution width (RDW) represents the morphologic variation in the red blood cells (RBCs) in an individual patient. It is part of the routine complete blood count and has the advantage of being inexpensive, routinely available and rapidly measurable. It has been observed that RDW increases in sepsis. This can be attributed to two key components of the sepsis cascade-inflammation and increased oxidative stress.

The release of pro-inflammatory cytokines inhibits erythropoietin-induced erythrocyte maturation and proliferation, and downregulates erythropoietin receptor expression, leading to insufficient erythropoiesis and an increased RDW. Also, the release of reactive oxygen species (ROS) by activated leukocytes in sepsis leads to a state of high oxidative stress, which increases the RDW by shortening RBC survival and causing large premature RBCs to be released into the peripheral circulation. Moreover, the systemic inflammatory response also impacts bone marrow function and iron metabolism, which further affects the RDW.

In the current study, it was found that in the study population higher RDW was associated with high q-SOFA score, which in turn was predictive of poorer overall outcome. We plotted and an AUC/ROC curve to determine an appropriate diagnostic cut-off for prediction of poorer outcomes. We found such a cut-off to be an RDW of 15.050. This had a sensitivity of 82.4% and specificity of 74.7%. It has clinical implications in prognostication as well as in stimulating debate about possible amendments in the management protocol for patients with an RDW of more than the said cut off[22].

In low resource settings, the neutrophil: lymphocyte ratio which can be easily calculated, and its use, along with RDW, in the emergency department setting could afford the earliest opportunity to identify patients at risk of bacteremia and the administration of antimicrobials at the appropriate time. As proposed by Zahorec et al[5], the ratio of neutrophil and lymphocyte count (NLCR) as an additional infection marker in clinical practice has been validated in this study. Neutrophils play an important role in natural immune response by direct phagocytosis of pathogens, releasing various cytokines and activating T cells. As sepsis progresses, pro-inflammatory cytokines release in large quantities. However, if there is uncontrolled immune activation, tissue injury may result, followed by organ

failure. Immune suppression is induced by various anti-inflammatory cytokines, in turn induced by lymphocytes. The balance between neutrophils and lymphocytes controls the inflammatory process. Persistently elevated NLR may suggest continued inflammatory process. The rationale behind its use is that during early hyper-dynamic phase of infection, neutrophils, macrophages and monocytes release inflammatory cytokines resulting in a pro-inflammatory state. The suppression of neutrophil apoptosis results in a systemic inflammatory response that is associated with augmented neutrophil-mediated killing. At the same time, thymus and spleen have an increased lymphocytic apoptosis[23].

NLR has also been shown to be a "better predictor of bacteremia than routine parameters such as C-reactive protein (CRP) levels, white blood cell count and neutrophil count"[8]. In our study cohort we found that as the q-SOFA score increases the median neutrophil: lymphocyte ratio also increases. However, to test whether this ratio can be optimally used as a predictive or diagnostic marker, we plotted an AUC/ROC curve. We found the AUC to be 0.663 implying it to be just a 'fair' test of predicting outcome with a mere sensitivity of 66.2% and a specificity of 65.7%, and not being able to find a clinically reliable cut-off value. Thus, we conclude that in our study cohort the neutrophil: lymphocyte ratio while having some correlation with the outcome does not appear to be a strong prognostic marker. Further large sample studies are warranted in the same study population to further investigate the validity of the proposed neutrophil: lymphocyte ratio.

In a similar study, Hwang et al.[24] showed that NLR measured at admission was independently associated with mortality at one month in patients with sepsis and septic shock. Although our findings are in similar lines with existing studies, it did not reach statistical significance. It has also been mentioned in literature that NLR can be influenced by medications, co-morbidities, and

some disease and treatment related changes in the peripheral blood that occurs in sepsis patients.

**LIMITATIONS OF THE STUDY**

It is a single center study, convenient sampling, lack of inclusion of other biomarkers of sepsis such as CRP, procalcitonin and lactate, and exclusion of immunocompromised, anemic and pregnant patients.

**CONCLUSION**

We investigated two non-conventional markers of evaluating and prognosticating sepsis. These were red cell distribution width and neutrophil: lymphocyte ratio. We tested them against the clinical outcome and established prognosticating scores, that are, q-SOFA and SOFA scores. We found that RDW correlated with q-SOFA and SOFA scores and offered a clinically reliable cut off for prognostication of sepsis. We determined such a cut off to be 15.050.

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.

**IMPLICATION**

The study implies that patients with sepsis having an RDW more than 15.050 may benefit from early interventions and more aggressive management. In low resource settings, the RDW, in the emergency department could afford the earliest opportunity to identify patients at risk of bacteremia and the administration of antimicrobials at the appropriate time.

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