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RESEARCH ARTICLE

CLINICAL SIGNIFICANCE OF RED CELL DISTRIBUTION WIDTH (RDW) AND CIRCULATING NEUTROPHIL - LYMPHOCYTE COUNT RATIO (NLCR) AS PROGNOSTIC MARKERS IN SEPSIS

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ABSTRACT

A study on establishing the role of RDW and NLCR as biomarkers for the early detection of sepsis, severe sepsis and septic shock and in prediction of outcome was conducted. A total of 85 subjects meeting the inclusion and exclusion criteria and diagnosed with mild sepsis, severe sepsis and septic shock were selected. After a thorough clinical examination, blood sampling was done for all the subjects, within 3 hours of presenting the illness. The values of RDW and NLCR were studied on the day of admission, after 72 hours and after 7 days. Statistical studies were done by SPSS software and analyzed by unpaired t test, chi-square test and Pearson's correlation coefficient. After analysis, we found that in patients of severe sepsis and septic shock class, in survivor and non-survivor group, significant elevation of RDW and NLCR was found. The cut off values of RDW and NLCR in predicting the mortality in 95% confidential interval were calculated. There was a good correlation of SOFA score with NLCR and RDW in predicting the 28 days outcome. The study revealed that RDW and NLR can be used as potential markers for early detection of severe sepsis and septic shock and in predicting the outcome

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INTRODUCTION

Sepsis and septic shock are one of the leading causes of death worldwide. Rapid and precise diagnosis and appropriate antibiotic therapy is necessary to reduce mortality and morbidity in patients with sepsis. Though several biomarkers and scoring systems have been evaluated, prognostic markers to quickly and precisely establish the diagnosis or prognosis of patients with sepsis and septic shock are yet to be evaluated. Hence this study is being done to assess the efficiency of the haemogram parameters RDW and NLCR as biomarkers in predicting the clinical outcome of patients with sepsis, severe sepsis and septic shock and to study the correlation of RDW and NLCR with SOFA score. Despite advances in intensive care and antimicrobial therapy, the incidence of sepsis and related mortality rate has increased over the last thirty years (Cho, 2015).The mortality rate is estimated at 30% in sepsis and 80% in septic shock in the USA (Martin, 2012) and at 12.8% in sepsis and 45.7% in septic shock in Europe (Esteban et al., 2007). A delay in the diagnosis and treatment of sepsis will result in the rapid progression of circulatory failure, multiple organ dysfunction and eventually death (Kim et al., 2014). There are many biochemical markers, clinical parameters and scoring systems used to assess the severity and in predicting the mortality in patients with sepsis. Some of which include- estimating serum procalcitonin levels, clinical scoring system like Sequential Organ Failure Assessment (SOFA), quick SOFA (qSOFA), acute physiology and chronic health evaluation (APACHE II) scoring systems. However, calculating SOFA score is cumbersome. Moreover, assessment of the septic patient outcome during treatment needs to be focused on, as currently used clinical and biological criteria are undefined and inadequate for this purpose. The need for simple, cost effective and easily available, yet reliable markers has pushed researchers in identifying such markers for assessing the severity and predicting the prognosis of sepsis. The Red Cell Distribution width (RDW) is one of the various biomarkers which have been shown to predict the mortality and morbidity of sepsis. The Red Cell Distribution Width (RDW) is the coefficient of variation of Red Blood Cell (RBC) volume and is a representation of the RBC size heterogeneity of an individual patient (Martin, 2003). Recent studies have reported that Red Cell Distribution Width (RDW) is associated with prognosis in Critical Illness, Heart Failure, Acute Myocardial Infarction, Pulmonary Embolism, Pneumonia and Cardiac Arrest (Felker et al., 2007). Research has shown that Neutrophil-lymphocyte count ratio (NLCR) may be considered a novel marker of subclinical inflammation (Okyay Vet al., 2013). It represents a combination of two markers; neutrophils, which represent the active nonspecific mediator initiating the first line of defense and lymphocytes, representing the regulatory or protective component of inflammation.

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Neutrophil-lymphocyte ratio (NLR) is calculated by dividing the number of neutrophil count by number of lymphocyte count, usually from peripheral blood sample. In this work, the haemogram parameters RDW and NLCR which are part of a complete blood count, easy to evaluate and which do not incur additional costs to routine analysis are studied. Aim of the study is to assess the efficiency of these parameters as prognostic markers in sepsis and in predicting the clinical outcome after 28 days as assessed by SOFA score in patients with sepsis, severe sepsis and septic shock and to investigate whether changes in RDW and NLCR during the first week correlates with the severity of sepsis and related complications.

MATERIALS AND METHODS

The study was performed at the Government Stanley Medical College Hospital Chennai from April 2017- September 2017, after obtaining the approval of the Internal Ethical Committee of Government Stanley Medical College & Hospital, Chennai. Informed written consent from all the patients considered for the study was procured before conducting the study. It is a prospective observational study. 85 adult patients of both sex with a diagnosis of sepsis and admitted in the emergency wards and Intensive medical Care unit in the Stanley Medical college hospital under the Department of Medicine were included in the study.

Inclusion criteria

- Patients admitted to the emergency ward and intensive medical care unit who meet the criteria of sepsis, severe sepsis and septic shock.
- Patients of Age > 18 years

Exclusion criteria

- Patients of Age < 18 years
- Patients diagnosed with anemia or with hematological disorders
- Patients with diseases causing trauma, intoxication
- Patients with immuno-suppressive disease, receiving immuno-suppressive therapy or using drugs that can change the morphology of red blood cells
- Patients with bleeding > 10% volume
- Patients who had received recent transfusion of blood products
- Patients with malignancies and on chemotherapy (within the last 6 months)
- Pregnant individuals.

Patients were assessed for sepsis, severe sepsis, and septic shock. Blood samples were collected and analyzed within 3 hrs from the time of presentation. Clinical and laboratory data were obtained and blood culture was studied before administration of broad spectrum antibiotics. Red blood cell distribution width (RDW), circulating Neutrophil to lymphocyte counts ratio (NLCR) was obtained from the values measured at the time of presentation. The value considered to be normal for leukocyte was5.2-12.4 x103µL for neutrophil and 0.9-5.2 x103µL for lymphocyte. The principles of initial resuscitation (fluid therapy, vasopressors, inotropic support) and infection issues (source identification and control, appropriate antibiotic therapy) were followed regularly and the outcome studied. SOFA score was recorded at admission in the emergency ward or ICU for studying the in- hospital outcome.RDW, Neutrophil count, Lymphocyte count and calculation of NLCR were done at the time of admission, after 72 hours and after 7 days of treatment. Major adverse cardiovascular events in the form of cardiogenic shock requiring inotropic support, pulmonary edema and death were recorded. The correlation studies of RDW, NLCR, and SOFA score is done.

RESULTS AND ANALYSIS

85 subjects of both sex, male and female had been chosen in our study. Out of the 85 subjects studied, 69 were survivors. This accounts to 81.18% of the sample population. The Non-survivors were 16 (18.82%) including 5 patients who died on the day of presenting the illness. The mean age was 52.61 years in survivors group and 64 years in non-survivors. Group. It shows that increase in age in sepsis patient is associated with increase in mortality. The male-female survival ratio was 59.42:40.58. Among the non-survivors, Females showed a high rate of mortality (62.5%). Co-morbidities like Diabetes Mellitus and hyper tension and chronic kidney diseases pose a higher risk of death outcome. Among the survivors group, respiratory tract infection, urinary tract, blood stream, soft tissue and abdominal infection were found to be the common source of infection, (26.09%, 21.74%, 15.94%, 15.94% and 14.49%). Respiratory/urinary tract infection was observed in non-survivors group (n=5, 31.25%). The causative agents in majority of the study subjects were gram –ve agents in survivors group (n=30, 43.48%) and gram +ve/gram –ve agent in non-survivors group (n=4, 25%). When compared statistically using chi squared test, based on the causative agent, percentage differences between study groups was found to be insignificant ($p>0.05$). Majority of the study subjects in survivors group had mild sepsis (n=44, 63.77%) and in

Non-survivors group majority had septic shock (n=13, 81.25%). The chi squared test analysis ($p>0.05$) and Cohen's effect size value ($d=0.71$) suggested a moderate practical significance showing that septic shock is associated with the significant increase in death outcome. In our study, the mean SBP was 96.23mm Hg in the survivors group and 53.75 mm Hg in the non-survivors group. When compared statistically using unpaired t- test, the difference in mean between study groups was found to be significant ($p<0.05$). SBP was inversely associated with decreasing mean difference of 42.48 mm Hg in non-survivors group compared to survivors group (44% decrease). Cohen's effect size value ($d = 2.45$) suggested a high practical significance (96% study subjects with SBP below 54mm Hg suffering from sepsis will have death as outcome.

The mean Diastolic blood pressure was 60.29 mm Hg in the survivor group and 36.25mm Hg in the non-survivors group. Using the unpaired t- test, the difference in mean between study groups was found to be significant ($p<0.05$). DBP was inversely associated with decreasing mean difference of 24.04 mm Hg in non-survivors group compared to survivors group (40% decrease). Further, Cohen's effect size value ($d = 2.65$) suggested a high practical significance (100% study subjects with DBP below 36 mm Hg suffering from sepsis will have death as outcome). SOFA score analysis showed that the SOFA score was ≤ 5 for 73.91% of the survivors, the mean SOFA score being 3.36. The SOFA score for non-survivors was found to be high (between 11 and 15) and the mean was 11.06.

Table 1 Age of survivors and non-survivors

Age groups	Survivors	%	Non-survivors	%
≤ 20 years	1	1.45	1	6.25
21-40 years	14	20.29	0	0.00
41-60 years	36	52.17	2	12.50
61-80 years	18	26.09	12	75.00
> 80 years	0	0.00	1	6.25
Total	69	100.00	16	100.00

Table 2. Table showing sofa score

Organ system	SOFA score				
	0	1	2	3	4
Respiration PaO_2/FiO_2 mm Hg	≥400	< 400	< 300	<200 with respiratory support	<100 with respiratory support
Coagulation platelets $x10^3/\mu L$	≥ 150	>150	>100	>50	>20
Hepatic Bilurubin mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
CNS Glascow Coma Scale	15	13-14	10-12	6-9	<6
Cardiovascular	MAP ≥70mm Hg	MAP <70mm Hg	Dopamine<5 or dobutamine (any dose)*	Dopamine 5.1-15 or epinephrine≤0.1 or norpinephrine≤0.1*	Dopamine >15 or epinephrine>0.1 or norpinephrine>0.1*
Renal Serum Creatnine mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0 or dialysis
Or urine output				Or < 500mL/24 h	Or < 200mL/24 h

*Catecholamine doses are given as µg/kg/min for at least 1 hour
PaO_2 - Partial pressure of Oxygen; FiO_2 –Fraction of inspired Oxygen
PaO_2/FiO_2 ratio is calculated without reference to the use or mode of mechanical ventilation and without reference to the use or level of PEEP.
Glascow Coma Score- For the patient receiving sedation or muscle relaxants, normal function is assumed unless there is evidence of intrinsically altered mentation.

Table 3. Mean RDW in survivors and non-survivors.

RDW		At Admission	After 72 Hours	After 7 Days
Survivors	Mean	16.22	15.94	15.79
	SD	0.89	0.84	0.76
Non-survivors	Mean	19.08	18.93	18.87
	SD	1.04	0.63	0.76
P value Unpaired t-Test		<0.0001	<0.0001	<0.0001

Table 4. Mean NLCR in survivors and non-survivors

NLCR		At Admission	After 72 Hours	After 7 Days
Survivors	Mean	8.95	7.41	5.34
	SD	1.54	1.78	1.61
Non-survivors	Mean	13.24	11.95	10.67
	SD	1.37	1.36	0.58
P value Unpaired t-Test		<0.0001	<0.0001	<0.0001

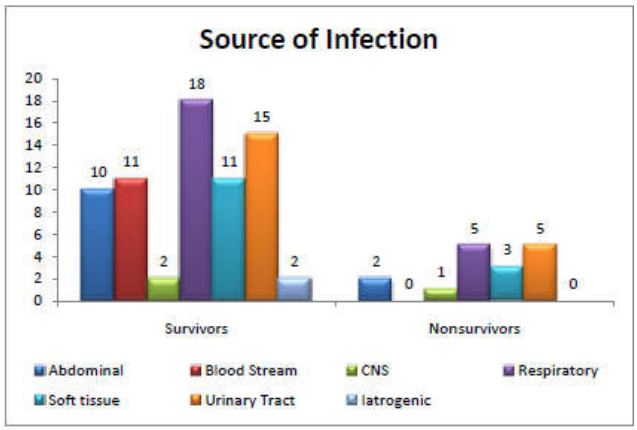
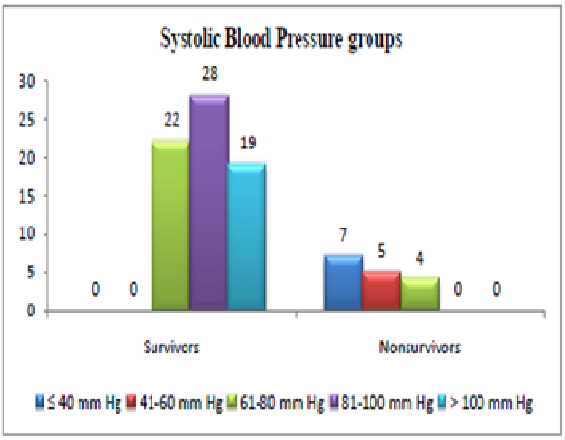


Figure 1. Major source of infection in survivors and non-survivors

The unpaired t test ($p<0.05$) and Cohen's effect size value (d = 3.59) showed high significance of SOFA score in predicting the outcome of patients during the in-hospital stay, higher the SOFA score, higher would be the mortality rate.



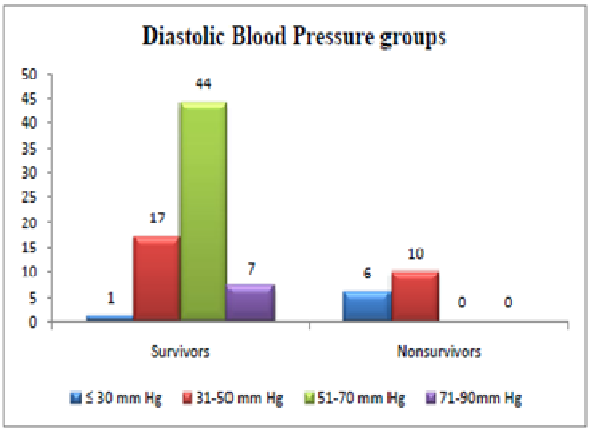


Figure 2. Systolic pressure and diastolic pressure groups

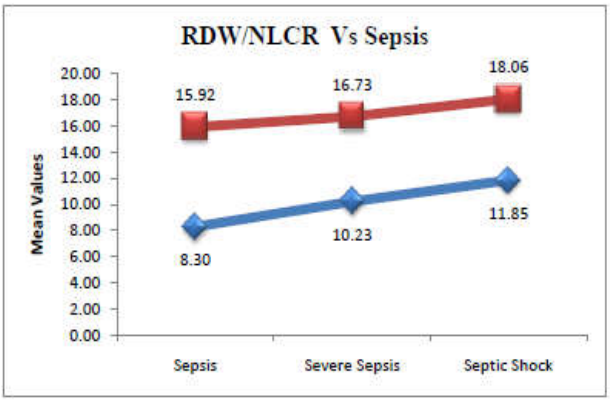


Figure 3. Mean values of RDW and NLCR.

Mean duration of in-hospital stay was 10.48 in the group of survivors and majority of them belonged to 6-10 days class interval. In the non-survivors group, all were treated in the ICU including 5 patients who died on the day of presenting the illness. Inotropic support was given to all the 16 non-survivors (100%). Among the survivors group, only a few (20.29%) needed inotropic support**.** When compared statistically using chi squared test, a percentage difference of 79.71% was found to be insignificant ($p>0.05$). Further, Cohen's effect size value (d = .80) suggested a moderate practical significance (79%) of the study subjects leading to a conclusion that increase in the need for inotropic support in sepsis patients is associated with a significant increase in death outcome. Majority of the subjects in both the survivors and the non-survivors were presenting with multiple complications, like Acute Kidney Injuries(20.29%; 56.25%), thrombocytopenia (30.43%; 6.25%), coagulopathy (8.7%; 31.25%), metabolic acidosis (18.84%; 62.5%), encephalopathy (8.7%; 87.5%), jaundice

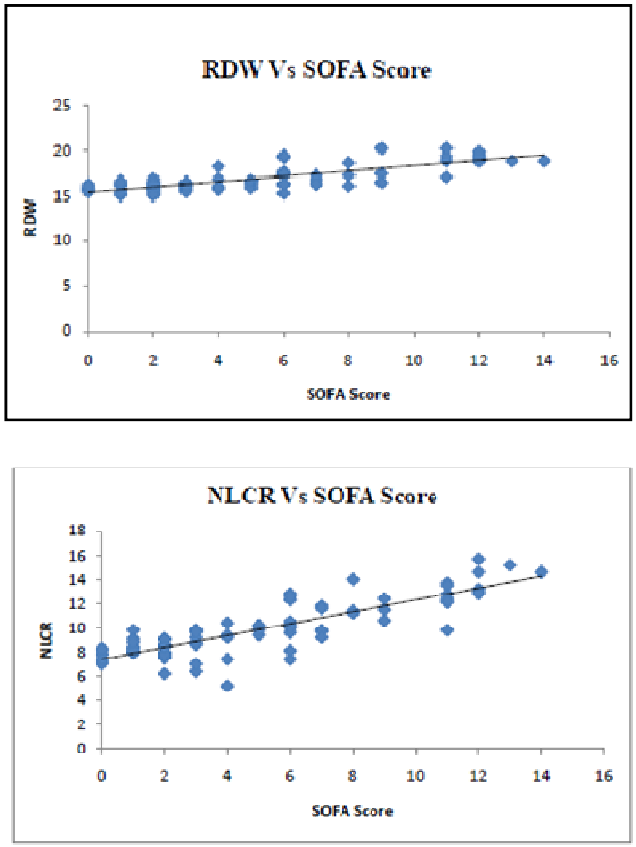


Figure 4. Correlation between RDW, NLCR and SOFA

(5.8%; 18.75%) and ARDS (1.45%; 31.25%).This was associated mostly with patients with a history of diabetes and hypertension. Presence of complications was associated with increased incidence of death outcome in non-survivors group compared to survivors group (48% increase). Further, Cohen's effect size value (*d* = 1) suggested a moderate practical significance (84% study subjects suffering from sepsis presenting with complications will have death as outcome). RDW and NLCR values were studied on Day 1(within 3 hours), after 72 hours and after 7 days. From the RDW Vs Sepsis table, it was evident that the study subjects with sepsis had a mean RDW of 15.92, with severe sepsis had a mean RDW of 16.73 and with septic shock had a mean RDW of 18.06.

When compared statistically using single factor ANOVA test, the difference in mean RDW between various stages of sepsis was found to be significant ($p<0.05$). RDW in sepsis patients was progressively associated with increased sepsis status exhibiting a increasing mean difference of 0.80 between sepsis stage and severe sepsis stage (5% increase) followed by a increasing mean difference of 1.33 between severe sepsis stage and septic shock stage (7% increase). Also, Cohen's effect size value (*d* = 1.88) suggested a high practical significance (97%) study subjects with RDW at admission above 18.06 will have septic shock as outcome). With respect to NLCR Vs Sepsis, it was evident that the study subjects with sepsis had a mean NLCR of 8.30, with severe sepsis had a mean NLCR of 10.23 and with septic shock had a mean NLCR of 11.85. When compared statistically using single factor ANOVA test, the difference in mean NLCR between various stages of sepsis was found to be significant ($p<0.05$). NLCR in sepsis patients was progressively associated with increased sepsis status exhibiting a increasing mean difference of 1.93 between sepsis stage and severe sepsis stage (19% increase) followed by an increasing mean difference of 1.62 between severe sepsis stage and septic shock stage (14% increase). Further, Cohen's effect size value (*d* = 2.43) suggested a high practical significance (99% study subjects with NLCR at admission above 11.85 will have septic shock as outcome). We might conclude that the increasing trend of RDW and NLCR in patients treated for sepsis is associated with a significant up-scaling of sepsis status from sepsis to septic shock. To study the effectiveness of RDW and NLCR in the prediction of mortality, and the outcome after 28 days, the cut off value, odds ratio and probability value were calculated. The cut off value suggested that sepsis patients with NLCR> 14 had 50 times more risk of death after 28 days compared to sepsis patents with NLCR ≤ 14 .Sepsis patients with RDW> 18 had 162 times more risk of death at 28 days compared to sepsis patents with RDW ≤ 18. Correlation studies of (a) RDW with SOFA score and (b) NLCR with SOFA score were made. In sepsis patients, when RDW was cross matched against SOFA score, a positive correlation with Pearson's correlation coefficient of r=0.81 was found. In sepsis patients, the increase in levels of RDW correlates with the increase in SOFA score 81% of times. The statistical significance was found to be p value is < 0.0001. When NLCR was cross matched against SOFA score, the increase in levels of NLCR correlates positively and strongly with the increase in SOFA score 85% of times. This correlation is statistically significant as the p value is < 0.0001 with a Pearson's coefficient of 0.85. It may be concluded from the highly significant and positive correlation of RDW with SOFA score and that of NLCR with SOFA score indicate that RDW and NLCR can be used as the prognostic markers in patients with sepsis, severe sepsis and septic shock.

DISCUSSION

Most of the subjects were in the 42-65 years age group, of which 47 were males and 38 being females. This may point out to the high incidence of sepsis in elderly group's individuals. Angus et al[7]., observed that the incidence of severe sepsis was higher in older population. The mean age of patients with severe sepsis was 63.8 years. In another study conducted by Martin et al. (2003) there was an increased incidence of sepsis by about 20 % more in the elderly population compared to younger individuals. The reason for this high incidence among elderly population may be due to the fact that, in recent years life expectancy has increased in general and that with increasing age, individuals develop various co-morbidities like diabetes and malignancy which increase the risk of developing sepsis. In our study the mortality rate in patients above 60 years of age was found to be the highest (75%) among all age groups. This is in correlation with many studies that have been conducted worldwide that have observed that there was an increased mortality rate among elderly patients diagnosed with sepsis. The incidence of sepsis was slightly higher among male patients compared to females. Studies have shown that women appear to be at a lower risk of developing sepsis than men. The reason for this is unclear though in a study Angele et al. (2013) explored and published the possible role of estrogens and androgens that lead to gender differences in the incidence of sepsis. We could not come to a conclusion based on gender incidence as our study group was small and as there was not much significant difference in male and female incidence. The most common presenting symptom was fever followed by cough and altered sensorium.

The most common source of infection was respiratory tract followed by urinary tract infections. Community-acquired

Pneumonia was the other most common cause of infection. This was partly in correlation with the study conducted by Mayr et al. (2010) respiratory tract infection accounted to the highest etiology of sepsis followed by bloodstream and site unspecified infections. The highest mortality was observed in patients with respiratory tract infections (31.25%) and urinary tract infections (31.25%). Gram Negative organisms were found to be the most common causative organisms (41.18%) followed by Gram Positive organism (24.71%). Diabetes and hypertension were the most common associated co-morbidities observed. The mortality rate was highest among diabetes patients. The duration of hospital stay was also increased among diabetic patients. Interestingly, this was in contrary to a nationwide population based study of Taiwan patients with the severe sepsis conducted by Chang et al[11] who observed that diabetes status does not influence the subsequent outcome with respect to hospital mortality or length of hospital stay.

Though patients categorized as sepsis were higher in number as compared to those with severe sepsis and septic shock, there was an expected high mortality among patients with severe sepsis (12. 5%) and septic shock. (81.5%). Among the subjects studied, there was relatively increased number of patients who were dependent on inotropic support during admission. And those patients who were dependent on inotropic support showed a very high mortality rate. The survivors also had an increased duration of hospital stay. Vance Beck et al[12] observed that delayed initiation of vasopressor or inotropic medications in patients with septic shock is associated with increased organ failure risk and decreased survival outcome. From our study we could not come to a conclusion on the basis of the timing of initiation of vasopressor, inotropic agents and the outcome because of the major limitation being that, we could not risk delaying the initiation of inotropic agents in patients with the refractory septic shock who did not improve in spite of adequate fluid resuscitation. Yet it would be wise to understand that administration of vasopressors/ inotropic agents should not be delayed in patients with septic shock. The SOFA score was calculated with the available laboratory parameters during admission. The SOFA scores during admission correlated well with the outcome of the patients. Those patients with scores less than 5 had a better survival rate and short duration of hospital stay. Those patients with the SOFA scores above 10 had a high rate. In the survivors group, SOFA scores more than 10 during admission had a prolonged duration of hospital stay and also developed complications. These patients needed vigorous intervention compared to those with a SOFA score of less than 10 during admission.

RDW is a quantitative measure of anisocytosis, the variability in size of the circulating erythrocytes. In the past RDW usually had been used for the differential diagnosis of iron-deficiency anemia and acute appendicitis (Karagoz et al., 2013; Miyamoto et al., 2015). In recent years, RDW has been demonstrated to predict mortality and other outcome in septic and septic shock in aged adults. In our study, the mean red cell distribution width on the day of presenting the illness was significantly higher in non survivors than survivors. Those patients who had a high red cell distribution width during admission were associated with poor survival. These patients also developed associated complications like acute kidney injury, coagulopathy, and encephalopathy. Red cell distribution width was highest among patients with septic shock followed by severe sepsis and with sepsis (Mean 18.06; 16.73; 15.92).These parameters showed strong statistically significant correlation of red cell distribution width with the severity of sepsis. Based on the changes in red cell distribution width during admission, after 72 hours and after 7 days it was evident that majority of the study subjects in the survival group had a mean RDW of 16.22 at admission,15.94 after 72 hours and 15.79 after 7 days. In the non survivors group, the red cell distribution width was 19.08 during admission, 18.93 after 72 hours, and 18.87 after 7 days. From this we might conclude that the increase in red cell distribution width at admission in septic patients is associated with a significant increase in death outcome. No statistical significant conclusion could be made among these groups as far as change in red cell distribution width from baseline to 72 hours and after 7 days of hospitalization is concerned. This result correlates with the study of Mahmood et al. (2014) in which RDW greater than 16 was concluded to be associated with increase in severity of illness. Red Cell Distribution Width is an indicator which can vary in sepsis under the influence of TNF-α, IFN-δ, IL-1β, IL-6, the pro inflammatory cytokines which are released during the inflammatory process. These cytokines cause inefficient erythropoiesis resulting in structural and functional changes of erythrocytes with volume variation. This may be accounted for an increased value of RDW. NLCR reflects the systemic inflammatory response that accompanies chronic disease that might also be influenced by systemic infections, atherosclerosis, hypertension, chronic renal disease and diabetics. A more recent study showed that an initial value of NLCR over 10 could be correlated with an unfavorable prognosis as assessed by the number of SIRS criteria, the presence of organ failure or septic metastasis at the time of admission. In our study also the NLCR values were high at admission Our study showed that septic patients with NLCR value greater than 14 had 50 times more risk of death than those with NLCR less than 14 and RDW>18 had 162 times more risk than septic patients with RDW< 18, at 28 days. In sepsis patients when NLCR was cross matched with SOFA score, there was a strong and positive correlation shown in a similar way as RDW correlates with SOFA score at admission. Thus it may be concluded that RDW and NLCR can be used as prognostic markers of sepsis, severe sepsis and septic shock and also to predict the outcome.

Conclusion

In our study, the efficiency of RDW along with NLCR as biomarkers of sepsis, severe sepsis and septic shock has been made and the correlation of the SOFA score with RDW and NLCR in predicting the outcome of patients has been studied. In sepsis patients when SOFA score was cross matched with RDW and NLCR separately the increase in their values strongly and positively correlated with increase in SOFA score, thus elucidating the usefulness of RDW and NLCR as prognostic markers in the study of severity of sepsis and the outcome. However, there are certain limitations of the study.

- Since both RDW and NLCR levels are affected by many conditions, RDW and NLCR levels without other inflammatory indicators such as C-reactive protein, gamma-glutamyl transferase and albumin, may not give exact information about patient's inflammatory status.
- Only the circulating neutrophil and lymphocyte counts were analyzed but the different subpopulations of the lymphocytes had not been explored.
- Patients` underlying diseases could alter the NLCR levels. Age and Co-morbidities are associated with the

severity of sepsis and mortality. Genuine report of Co-morbidity could not be acquired from the patients.

- The study is a prospective observational study in a single institution in a short duration with less sample size of 85. For validation of the results, the sample size should be large.
- The time elapsed between the blood sampling and the measuring of RDW may significantly affect the RDW levels. Intra-day cell count variations also may be considered. All these necessitate future prospective clinical research.

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