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RED CELL DISTRIBUTION WIDTH (RDW) – A USEFUL TOOL IN PREDICTING 5 DAYS MORTALITY IN PATIENTS HOSPITALIZED WITH SEPSIS

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Abstract

Background: Sepsis is a frequent illness with a high mortality, and many patients who recover from it experience long-term, irreversible morbidity. The pathophysiology of sepsis is now well understood, but this information hasn't led to any practical interventions that can alter the course of the disease. The lack of economically feasible and easily available prognostic markers is a major issue in current day sepsis management, especially in resource limited settings. Red cell Distribution Width is the measurement of variability in size of erythrocytes and it has association with the prognosis of many major diseases. It is a comparatively low-cost and easily available investigation. The main objective of this study was to evaluate Red cell Distribution Width (RDW) as a prognostic marker for predicting 5 day mortality in patients admitted with sepsis. **Materials and Methods:** A single centre, prospective, observational study was conducted. A total sample of 100 patients meeting the diagnostic criteria of sepsis, severe sepsis or septic shock were included in the study from October 2015 to April 2017. Complete Blood Count including Red cell Distribution Width was measured by flow cytometry using automated analyser. **Result:** Of the total 100 patients studied, 64 were males and 36 were females. Out of these, 30 males (57.6%) and 22 females (42.4%) survived less than or equal to 5 days, whereas 33 males (68.8%) and 15 females (31.3%) survived more than 5 days. Relation of sepsis with outcome, 48 patients survived more than 5 days, 28 had elevated RDW > 14.8 % (58.3 %) and the remaining 20 (41.7 %) had normal RDW. The mean RDW among the first group was 16.32 ± 1.52 and in the second group was 14.95 ± 0.99. The p value was 0.001 which was statistically significant. **Conclusion:** Sepsis and septic shock are major causes of in-hospital mortality. Red cell Distribution Width (RDW) is a routine blood test and is in-expensive. Red cell Distribution Width (RDW) is a significant prognostic marker in predicting outcome in patients admitted with sepsis, severe sepsis or septic shock.

INTRODUCTION

Early identification and treatment of sepsis and its complications has been made a priority in global health by World Health Organisation in the year 2017.[1] Sepsis is a frequent issue that critically sick patients deal with. Hippocrates claimed sepsis as a process of rotting flesh, swamps generating foul airs, and festering wounds. The definition of septic shock has recently been changed to life-threatening organ failure brought on by an infection. Despite best efforts and established procedural paths, septic shock mortality is still high, hovering around 35% to 40%.[2] On the contrary, Galen considered sepsis as an event which is necessary for wound healing. Sepsis was described by Pasteur and others as a blood poisoning condition brought on by the invasion of the host by pathogenic organisms that spread through the bloodstream. The development of modern antibiotics has made this germ hypothesis less acceptable, because many sepsis patients have perished despite the effective elimination of the bacteria that caused it.[3]

Sepsis may be caused by almost any infectious agent. As a result, there are many different ways that the syndrome might manifest itself, and these

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variations greatly depend on a particular geographical region. Sepsis is a condition where an infection manifest with its signs as well as signs of severe organ failure, and both are manifestations of the host's reaction to the infection. This may result in mortality, acidosis, and failure of many organs.[4] In cases of severe sepsis, the brain and kidneys are frequently harmed. Obtundation or delirium are signs of CNS dysfunction, without any major abnormalities in the EEG or MRI. Renal failure shows up as reduced urine output and elevated serum creatinine. Patients who spend a significant amount of time in the ICU frequently develop polyneuropathy and myopathy. Patients with severe sepsis may also encounter paralytic ileus, increased transaminases, poor glycaemic control, thrombocytopenia, disseminated intravascular coagulation, and adrenal insufficiency.[3]

It is now commonly acknowledged that treating infections with appropriate antibiotics early on lowers morbidity and death in sepsis patients.[5] Since systemic inflammatory response syndrome (SIRS) affects a large percentage of critically sick patients, it is crucial to reliably distinguish SIRS from sepsis (a patient with SIRS is considered to have sepsis if infection is suspected or diagnosed).[6] Procalcitonin (PCT) and CRP have been suggested as sepsis biomarkers in various centres across the globe, and recently they have been included into standard clinical practise also.[6] PCT, a precursor of the hormone calcitonin, is naturally produced by the thyroid C cells. CRP, on the other hand, is an acute phase protein that is mostly produced by hepatocytes but is also made by alveolar macrophages in response to a number of cytokines, most notably IL-6.[7] CRP has pro- and anti-inflammatory actions and participates in immune regulation. Procalcitonin has been found to be an effective sepsis prognostic and diagnostic marker in a number of recent studies.[8] CRP has been demonstrated to control bacterial opsonization and phagocytosis during the host infection phase and to alter the complement cascade.[9] The most often utilised biomarkers for sepsis are PCT and CRP, however they are not particularly economical. Therefore, it is important to have a test that doctors can access quickly.

Red cell Distribution Width (RDW), a less expensive option to these biomarkers, can be used in some cases. RDW, which is computed by dividing the standard deviation of erythrocyte volume by the MCV and multiplying the result by 100 to express the result as a percentage, is an indicator of the heterogeneity of the erythrocytes (anisocytosis).[10] RDW is a component of typical CBC outcomes. It is easy, non-intrusive, and imposes no additional costs on patients. The doctor can start an antibiotic as soon as the findings are ready, which takes only a few minutes. There is, however, a dearth of research that demonstrates a direct link between elevated RDW and death in sepsis patients. To determine if Red cell Distribution Width (RDW) may be a significant predictive factor in determining 5-day mortality in patients hospitalised with sepsis, severe sepsis, or septic shock, we thus designed this study.

MATERIALS AND METHODS

The study was designed as a single centre prospective, observational study. The study was conducted at Holy cross hospital, Kottiyam, which is a 550 bedded multi-speciality hospital, in a suburban area of Kollam district, Kerala. The population included in the study were from low and middle socioeconomic status, from both rural and urban areas.

The patients involved in the study were from intensive care units of various departments of Holy Cross hospital, Kottiyam and who satisfied the inclusion criteria were included in the study. An ethical clearance had been taken from the institutional ethical committee of Holy cross hospital, Kottiyam. Further, all the participants included in the study consented to participate and a written consent was obtained from them. All patients were enrolled using simple random method. Sample size was calculated using 80% power and a minimum sample of 82 was achieved. However, to avoid attrition the final sample size included in the study was 100. The time frame to achieve the sample was set from October 2015 to April 2017

Inclusion Criteria
1. Male and female patients who fulfil the diagnostic criteria for septic shock, severe sepsis or sepsis.
2. above the age of 18 years and willing to participate in the study were included.

Exclusion Criteria
1. Patients with haematological malignancy
2. Patients with HIV
3. Patients with anaemia
4. Patients with coronary artery disease
5. Patients with chronic kidney disease
6. Patients with chronic liver disease
7. Patients with heart failure
8. Patients with bone marrow failure syndrome

Data from the baseline survey was gathered using a pre-structured proforma. All patients had thorough clinical examinations and biochemical testing.

Methodology
Complete blood count including Red cell Distribution Width was measured by flow cytometry using automated analyser. Several other laboratory parameters were also collected like glycaemic status, Renal function test, Liver Function test, Arterial Blood Gas, Serum Lactate, Peripheral blood smear and blood as well as urine culture and sensitivity.

Statistical Analysis

Data was input and analysed in Microsoft Excel spreadsheet. Standard SPSS software was used for the analysis of significant values. Mean and standard deviation were used to express quantitative variables. Proportions were used to express qualitative factors. The independent sample t test was used to compare quantitative data between the two groups. The chi-square test was used to compare qualitative factors between two groups. Odds ratio with 95% CI was used to evaluate the degree of correlation between qualitative variables. Multivariate analysis was used to variables that were substantially related to the outcome. Statistics were judged significant at p value < 0.05. In order to assess the effectiveness of RDW in predicting mortality, a receiver operator characteristic curve was created. In order to analyse the data, SPSS version 22.0 was used.

RESULTS

The study included 100 individuals who had sepsis, severe sepsis, or septic shock. The patients were divided into two groups, those who survived less than or equal to 5 days and those who survived more than 5 days. [Table 1] shows the frequency distribution in accordance to Gender.

[Table 2] Of the total 100 patients studied, 64 were males and 36 were females. Out of these, 31 males (57.6%) and 21 females (42.4%) survived less than or equal to 5 days, whereas 33 males (68.8%) and 15 females (31.3%) survived more than 5 days. There was no significant difference observed with respect to the gender among patients who survived or died following sepsis, severe sepsis or septic shock. Odds ratio and 95% confidence interval were not calculated as this observation was not statistically significant.
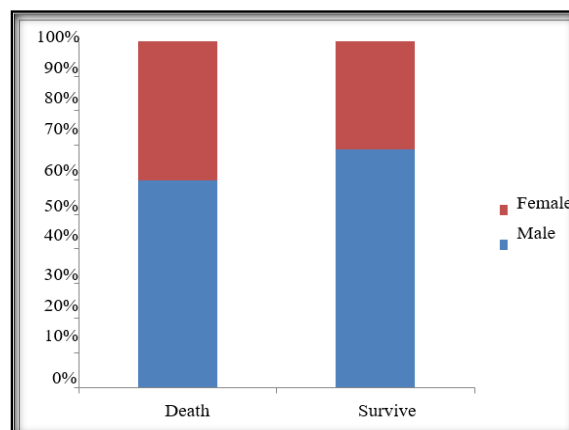

Figure 1: Gender distribution

Table 1: Gender distribution

	Survived ≤5 days		Survived > 5 days	
	N	%	N	%
Male	30	57.6	33	68.8
Female	22	42.4	15	31.3
Total	52	100	48	100

Table 2: Relationship between age and outcome

	Survived≤5 days		Survived > 5 days	
	Mean	SD	Mean	SD
Age	65.08	19.35	52.23	21.76

t = 3.125   p = 0.002

Mean age of the study sample was 65.08 ± 19.35 in patients who died within less than or equal to 5 days and 52.23 ± 21.76 in those who survived more than 5 days. The p value is 0.002 and is statistically significant which influences the outcome.

Table 3: Impact of severity of sepsis on outcome

Categories	Survived ≤5 days		Survived ≥ 5 days	
	N	%	N	%
Sepsis	13	25	35	72.9
Severe Sepsis	23	44.2	13	27.1
Septic Shock	16	30.8	0	0
Total	52	100	48	100

Chi -28.747

Table 4: Relationship between RDW and outcome

	Survived≤5 days		Survived > 5 days		t	P
	Mean	SD	Mean	SD		
RDW	16.32	1.52	14.92	0.99	5.324	0.000

Table 5: Relationship between RDW and Outcome

Category	Survived ≤ 5 days		Survived > 5 days		Odds Ratio	95% Confidence Interval	
	N	%	N	%		Lower	Upper
>14.8	46	88.5	28	58.3	5.476	1.963	15.281
<14.8	6	11.5	20	41.7			
Total	52	100	48	100			

Chi=11.77   p=0.001

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[Table 3] Out of the total 100 patients in this study sample, 48 had sepsis, 36 had severe sepsis and the rest 16 had septic shock. Among the 52 patients who had mortality within the initial 5 days, 13 patients had sepsis (25 %), 23 had severe sepsis (44.2 %) and 16 had septic shock (30.8 %). Among the other group, 35 had sepsis (72.9 %), 13 had severe sepsis (27.1 %). The p value was < 0.001 which was statistically significant
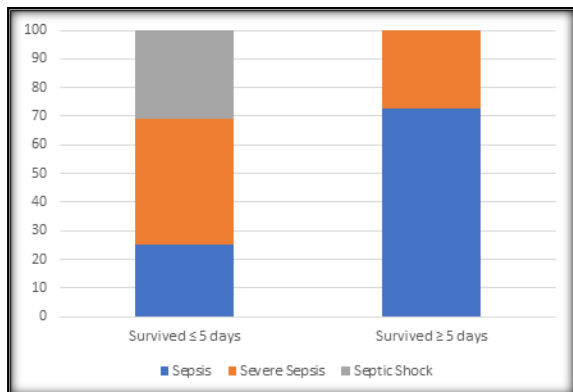

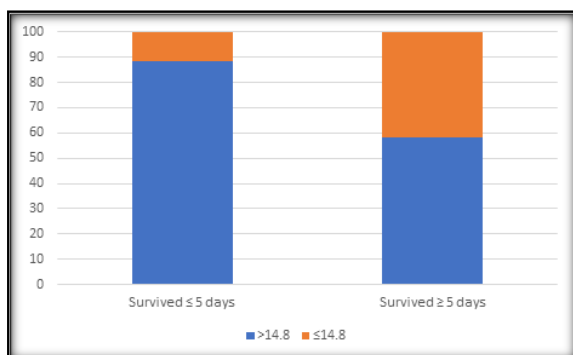**Figure 2: Impact of severity of sepsis on outcome**

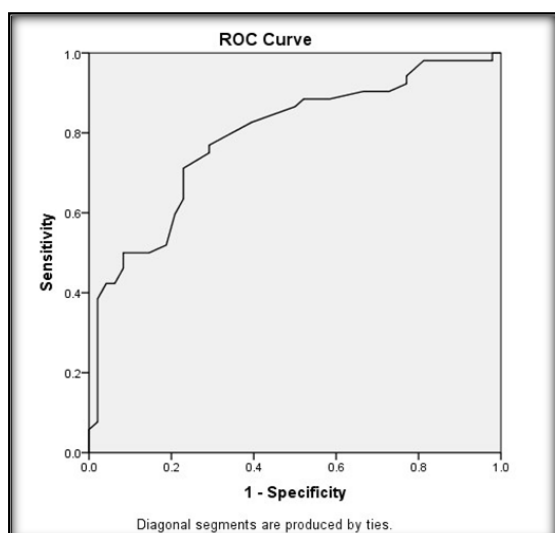**Figure 3: Relationship between RDW and outcome**

Figure 4: Receiver operator characteristic (ROC) curve for determining cut off point for RDW score to predict mortality

[Table 4 & 5] 46 out of 52 patients (88.5 %) who died during the initial 5 days had an elevated RDW>

14.8 % whereas the remaining 6 (11.5 %) had RDW ≤ 14.8 %. Among the 48 patients survived more than 5 days, 28 had elevated RDW > 14.8 % (58.3 %) and the remaining 20 (41.7 %) had normal RDW. The mean RDW among the first group was 16.32 ± 1.52 and in the second group was 14.95 ± 0.99. The p value was 0.001 which was statistically significant. Odds ratio was found to be 5.476. 95% confidence interval is between 1.963 and 15.281

A RDW score of 15.15 was associated with a sensitivity of 76.9%, a specificity of 70.8%, and an area under an ROC curve (AUROC) of 0.789 for mortality.

Receiver Operator Characteristic (ROC) curve *

DISCUSSION

Patients who were hospitalised to the critical care units of different departments at Holy Cross Hospital in Kottiyam, Kollam, Kerala, were the subjects of this study. The goal of the current study was to determine if RDW was a significant prognostic factor in predicting 5-day mortality in patients hospitalised with sepsis, severe sepsis, or septic shock. It was a single centre prospective observational study. Retrospectively, the patients were divided into groups based on 5-day mortality. Our study's key finding is that the subgroup with RDW greater than 14.8 had a higher 5-day mortality.

Numerous plausible explanations of link between RDW and mortality have been proposed in earlier researchs, despite the fact that the exact mechanism underlying the association between increased RDW and death in septic patients is not yet fully known. Pro-inflammatory cytokines have been discovered to block erythropoietin-induced erythrocyte maturation and proliferation and to downregulate erythropoietin receptor expression, which are related with increases in RDW. Systemic inflammatory response affects bone marrow function and iron metabolism.[11-13] Oxidative stress may also play a role in the relationship between RDW and mortality. Reactive oxygen species are produced by activated leukocytes, and this causes significant oxidative stress.[14] According to a theory, oxidative stress promotes the release of large premature erythrocytes into the circulation while decreasing RBC lifespan.[15]

Malnutrition may be a factor in yet another reason. It is thought that nutritional indicators like albumin and total cholesterol have a strong relationship with RDW.[16] Given the aforementioned characteristics, it is plausible to suppose that higher RDW may serve as an integrative indicator of the several detrimental pathologic processes, such as inflammation, oxidative stress, and starvation, that are present at the same time in critical disease. In light of the findings of this study, we thus propose that rising RDW is a reflection of the escalation of oxidative stress, inflammation, and nutritional

inadequacies. Further research is necessary to ascertain the mechanism behind the relationship between RDW levels and mortality as inflammation, oxidative stress, and nutritional deficits may not fully account for why higher RDW is linked to higher mortality.

In order to identify the independent risk factors of mortality, factors that were found significantly linked with mortality among patients with sepsis, severe sepsis, or septic shock by univariate analysis with a p value of < 0.005 were subjected to a multivariate analysis of binary logistic regression. Multivariate analysis of binary logistic regression was used despite the fact that factors such respiratory distress, palpitations, oliguria, organ failure, metabolic acidosis, RDW, changed mental status, body temperature, etc. were shown to be statistically significant and the analysis demonstrated that the only independent indicators predicting death in these individuals are high RDW and impaired mental state. RDW might be integrated with other clinical and laboratory indicators to help predict how patients with confirmed sepsis would fare. RDW and altered mental state were shown to be separate prognostic indicators in the research. RDW integration with the other factors, however, could have had a better predictive value.

The cut-off point for the RDW score to predict mortality was found using the ROC curve. In our investigation, we used a cut-off of 14.8. Moreover, a cut-off point of 15.15 was connected to a sensitivity of 76.9%, specificity of 70.8%, and an AUC (area under the receiver operator characteristic curve) of 0.789 for mortality (p 0.001, 95% CI - 0.699 - 0.878).

Gender Distribution
In our study, of the total of 100 patients studied, 64 % were males and 36 % were females. Retrospectively, the patients were divided into groups based on 5-day mortality. Of the 100 patients, 52 died within the first five days, while 48 made it. In the first group, there were 59.6% men and 40.4% women, while in the second, there were 33 men and 15 women. Females (58.3%) had a greater 5-day mortality rate than males (48.4%). Statistically speaking, this was not significant. According to research by Anthony P. Piatropaoli et al., hospital mortality was greater in women (35%) than in males (33%) in cases of severe sepsis and septic shock. In their analysis, the p value was 0.008, which was statistically significant.[17]

Age and Outcome
In the mortality group, the mean age was 65.08 ± 19.35, whereas in the survival group, it was 52.23 ± 21.76. The difference was statistically significant, with a p value of 0.002. In research on the impact of age on sepsis outcomes, Martin GS et al. discovered that elderly sepsis patients died more quickly while hospitalised. In an adjusted multivariable model, age was a standalone predictor of death (odds ratio 2.26, 95% confidence interval 2.17 - 2.36).[18] This was in contrast to our analysis, which revealed that age was not a significant risk factor on its own.

Severity of Sepsis
According to the methodology, the study population was further divided into sepsis, severe sepsis, and septic shock depending on the severity of the condition. Sepsis was present in 48%, severe sepsis was present in 36%, and septic shock was present in 16% of the 100 cases, 37.1% of sepsis patients died within the first 5 days, whereas 62.9% survived. 63.9% of patients with severe sepsis died in the first 5 days, whereas the other patients recovered. Additionally, none of the 16 patients in septic shock lived longer than 5 days, with all 16 (100%) dying within the first 5 days. This comparison's p value was 0.001 (p <0.05), which indicates that it was statistically significant and had an impact on the result.

According to our research, mortality rises when the stage of sepsis advances from sepsis to septic shock. Greg S. Martin came to the conclusion that sepsis was one of the most common conditions they encountered in ICU, with more severely ill patients being maximum resource users and at high mortality risk. The study focused on changes in incidence, pathogens, and outcome in patients with sepsis, severe sepsis, or septic shock.[19]

Rough estimates of mortality rates according to the consensus conference definition are as follows,

Sepsis   :   10 – 30 %
Severe sepsis: 30- 50 %
Septic shock: 40-85 %

RDW and outcome
In the mortality group, the mean RDW was 16.32 ± 1.52; in the survival group, it was 14.95 ± 0.99. Students t test was 5.324 and the p value was 0.000 (<0.05) which was statistically significant (Odd's ratio and 95% CI were 5.476 and 1.963-15.2 respectively). This was analogous to research by Muhammad Aslam Shaikh et al., who found that RDW levels assessed upon admission can be utilised as a predictive marker in severe sepsis and septic shock. In their study, the mean RDW was 15.20 ± 2.29 in non-survivors and 13.86 ± 2.20 in survivors (p<0.001).[20]

74 patients had RDW of more than 14.8 % and the remaining 26 had RDW ≤ 14.8. The 5 day mortality was high (62.2 %) in the group with RDW > 14.8. Meanwhile, 5 day mortality was lower (37.8 %) in the group with RDW ≤ 14.8 %. The difference was statistically significant which influences the outcome. This was comparable with study done by Sejin Kim et al, which showed RDW was an independent predictor of 30 day mortality (hazardsratio 1.10; 95 % confidence interval, 1.04 – 1.17; p value <0.001).[21]

You Hwan Jo et al, studied the prognostic significance of RDW in cases of severe sepsis and septic shock. They found that higher RDW values are frequently linked with non survivors compared to survivors, (p<0.001).[22]

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A study done by Heidi S. Bazick et al which showed that compared to those with RDW < 13.4%, the adjusted risk of bloodstream infection was 1.40 and 1.44 times greater in patients with RDW values of 14.7-15.8% and > 15.8%, respectively.[23]

Limitations of our study

The small sample size was one of the study's shortcomings. No investigation was done into the usage of erythropoetin, vitamin supplements, iron supplements, blood transfusions, etc., which might have altered RDW levels and hence reduced the interpretability of the study results.

CONCLUSION

Sepsis and septic shock are the major causes of death in hospitals. The current definition of sepsis describes it as a life-threatening organ malfunction resulting from a dysregulated host response to an infection. Red cell Distribution Width (RDW) is a strong predictive indicator for predicting mortality in sepsis, severe sepsis, and septic shock patients. Red cell Distribution Width (RDW) is readily available, inexpensive and is part of a standard blood test. As a result of greater awareness of the illness and continuous quality-improvement projects, we now have a better grasp of the evidence-based ways to addressing the problem, which has led to improved results. Therefore, RDW can be utilised as a regular biomarker for predicting patients' 5-day mortality.

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