

Correlation Between Red Cell Distribution Width (RDW) and Sequential Organ Failure Assessment (SOFA) Score in Sepsis Patients

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ABSTRACT

Background: There are an estimated 31.5 million cases of sepsis per year, and approximately 61% end up in sepsis shock, with a potential mortality rate of 5.3 million per year. In addition to the sequential organ failure assessment (SOFA) score, several biomarkers have been used to assess severity and predict mortality, including red cell distribution width (RDW). RDW is increased in conditions of ineffective red blood cell production or destruction that occur in inflammation or infection. RDW above 15.5% is associated with rigid and indestructible red blood cells, which can impede microcirculation and contribute to organ dysfunction, a part of the SOFA score.

Objective: The aim of this study was to determine the correlation between RDW and SOFA score in sepsis patients admitted to the intensive care unit (ICU) of Rumah Sakit Umum Pusat Haji Adam Malik Medan.

Methods: This study used a cohort-prospective study design with a consecutive sampling technique of the population that met the inclusion criteria. The samples were sepsis patients who were admitted to the ICU of Rumah Sakit Umum Pusat Haji Adam Malik Medan in April–June 2023. The data was analyzed by a Pearson or Spearman analysis test.

Result: There was a significant correlation between RDW and SOFA score ($r = 0.471$; $p < 0.05$) in ICU sepsis patients. There was a significant correlation ($p = 0.003$) between RDW values and SOFA scores on the third day, where there was a moderate degree of correlation ($r = 0.471$), but there was no significant correlation ($p = 0.103$) between RDW values and SOFA scores on the first day. The sensitivity, specificity, and cut-off values of RDW were found to be 76.5%, 75%, and 14.75%, which compared to SOFA were 76.5%, 75%, and 10.5.

Conclusion: There is a statistically significant relationship between RDW and SOFA, with a moderate correlation.

Keywords: ICU; infection; RDW; sepsis; SOFA score

INTRODUCTION

The size variability of red blood cells, also known as red cell distribution width (RDW), is routinely monitored in peripheral blood examinations. The size variability of red blood cells, also known as RDW, is routinely monitored in peripheral blood tests. An increase in RDW generally occurs in conditions of insufficient red blood cell production or faster blood cell destruction, which often occurs in inflammatory conditions or viral infections. The acute systemic inflammatory response that occurs in sepsis can also impact erythropoiesis and erythrocyte maturation. Elevated levels of RDW can indicate how much oxidative stress and inflammation are occurring, which can help predict the prognosis regarding mortality risk. Elevated RDW generally occurs in conditions where there is insufficient red blood cell production or more rapid blood cell destruction, which often occurs in inflammatory conditions or viral infections. The acute systemic inflammatory response that occurs in sepsis can also impact erythropoiesis and erythrocyte maturation. Elevated levels of RDW can indicate how much oxidative stress and inflammation are occurring, which can help predict the prognosis regarding mortality risk.¹

RDW levels in infectious states can be a good indicator for predicting sepsis. The relationship occurs when pro-inflammatory mediators are released into the circulatory system due to endotoxins produced by gram-negative bacteria. These mediators will trigger the sepsis cascade, beginning with the activation of macrophages that produce inflammatory mediators. The increased production of pro-inflammatory cytokines includes TNF- α , IL-1, IL-6, and NO. These cytokines will also trigger the release of other mediators such as prostaglandins,

leukotriens, platelet activating factor, and phospholipase A2. All of these mediators will change the structure of the endothelial lining of the blood vessels, which will then increase the permeability of the blood vessels. Changes in blood vessel structure will cause changes in shape and disruption of erythrocyte destruction and formation. In addition, the inflammatory mediators that appear can cause a surge in hormones such as adrenaline, noradrenaline, and angiotensin in the body. With the help of erythropoietin (EPO), these neurotransmitters can then stimulate the proliferation of red blood cells, causing the disruption of erythrocyte shape.² Erythrocyte variability will increase due to the disruption of erythrocyte shape, as measured by an increase in RDW. In addition, the formation of reactive oxygen species (ROS) in sepsis can also interfere with erythrocyte deformability, or the ability of erythrocytes to return to their original shape. In this condition, the RDW value in the blood tends to increase, indicating that the various situations have increased the variability of erythrocytes in the blood. Elevated RDW can also be a sign of cytomembrane instability, which can lead to multiple organ damage, worsening the health of sepsis patients, compromising their prognosis, and increasing their risk of death.³

RDW scores were significantly higher in patients with sepsis shock and in non-survivors compared to survivors. There is a strong correlation between SOFA and RDW scores in predicting disease outcome. This was seen in a study conducted by Jain et al. in 2022. According to a study conducted by Lorente et al. Research in 2014 showed a possible relationship between increased RDW and SOFA scores in sepsis patients and the role of

inflammatory processes and oxidative stress states. Pro-inflammatory cytokines and oxidative stress themselves are associated with increased mortality in septic patients.⁴ Because of the above background, researchers are interested in examining the relationship between red cell distribution width (RDW) and Sequential Organ Failure Assessment (SOFA) scores in sepsis patients admitted to the intensive care unit (ICU) of Rumah Sakit Umum Pusat Haji Adam Malik Medan.

METHOD

This study is an observational study with a cohort-prospective research design to analyze the relationship between RDW in sepsis patients admitted to the ICU of Rumah Sakit Umum Pusat Haji Adam Malik Medan, and SOFA scores. The study was conducted after the research ethics were approved by the medical committee of faculty of medicine Sumatera Utara University—Rumah Sakit Umum Pusat Haji Adam Malik Medan with letter number 310/KEPK/USU/2023. The study was conducted at the Department of Anesthesiology and Intensive Therapy,

Faculty of Medicine, Sumatera Utara University/Rumah Sakit Umum Pusat Haji Adam Malik Medan, from April 2023 to June 2023. The study population was patients with sepsis who were admitted to the ICU of Rumah Sakit Umum Pusat Haji Adam Malik Medan from April 2023 to June 2023. The research subjects were patients with sepsis who were admitted to the ICU of Rumah Sakit Umum Pusat Haji Adam Malik Medan, with data collection techniques carried out consecutively to all the affordable population who met the inclusion criteria. The collection of research subjects was stopped when the sample size was reached.

RESULT

Based on Table 1, there were 20 samples of males (52.6%) and 18 samples of females (47.4%), with a mean + SD age of 53.08+10.72. Mortality data showed 4 samples (10.5%) survived and 34 samples (89.5%) did not survive. In addition, the mean +SD data of body weight, height, and BMI of the study samples were 64.49+9.27 kg, 164.35+4.50 cm, and 24.02+3.50.

Table 1. Characteristics of patients in this study

Characteristics	n (%)	Mean±SD	Median	Min – Maks
Gebder				
- Male	20 (52.6)	-	-	-
- Female	18 (47.4)			
Mortality Rate				
- Survivor	4 (10.5)	-	-	-
- Non-survivor	34 (89.5)			
Age (years)		53.08±10.72	56	24 – 64
Weight (kgs)		64.49±9.27	65	50 – 90
Height (cms)		164.35±4.50	165	145 – 170
BMI		24.02±3.50	23.88	18.37 – 34.72

BMI = Body Mass Index

Based on the normality test analysis, it is known that the RDW data is not normally distributed, so a non-

parametric statistical analysis is carried out using the Wilcoxon test between T0 and T3.

Table 2. Changes in RDW

Data	Mean	SD	P-value ^c
RDW T0	15.592	2.459	0.001
RDW T3	16.403	2.888	

^cUji Wilcoxon

Based on Table 2, the initial RDW value was 15.592+ 2.459%, and the third day RDW was 16.403+2.888 ≥%. After statistical analysis using the Wilcoxon test, it was found that there was a significant change (p = 0.001) between the initial RDW and the third day where there was an increase in the percentage value of RDW, which means that there is an increase in the variation in the size of

red blood cells compared to normal conditions.

Based on the normality test analysis, it was found that the SOFA score data was not normally distributed, so a non-parametric statistical analysis was performed using the Wilcoxon test between T0 and T3.

Table 3. Changes of SOFA score

Data	Mean	SD	P-value ^c
SOFA T0	9.079	3.559	P<0.001
SOFA T3	11.711	3.791	

^cUji Wilcoxon

Based on Table 3, the initial SOFA score was 9.079+ 3.559, and the third-day SOFA score was 11.711+3.791. After statistical analysis using the Wilcoxon test, there was a significant change (p<0.001) between the initial SOFA score and the third day, where there was an increase in SOFA score.

Based on the normality test analysis, it is known that the RDW value data and SOFA scores are not normally distributed, so non-parametric statistical analysis is carried out using the Spearman correlation test.

Table 4. The correlation of RDW score with SOFA score.

Data	r	P-value ^d
RDW – SOFA T0	0.269	0.103
RDW – SOFA T3	0.471	0.003

^dUji Spearman

Based on Table 4, statistical analysis using the Spearman test showed a significant correlation (p = 0.003) between RDW values and SOFA scores on the third day, where there was a

moderate degree of correlation (r = 0.471), but there was no significant correlation (p = 0.103) between RDW values and SOFA scores on the first day.

In this study, ROC curves were analyzed to determine the sensitivity, specificity, and cut-off values of RDW with SOFA scores. The first analysis was carried out using the ROC curve using SPSS

software, then the analysis was continued to determine the cut-off value using MS Excel software. In this study, the cut-off was used to determine the risk of mortality in sepsis patients.

Table 5. Sensitivity, specificity, and cut-off values of RDW with SOFA

Data	Area	Std Error	P-value	Cut Off	Se	Sp
RDW	0.901	0.067	0.010	14.75	0.765	0.750
SOFA	0.930	0.062	0.005	10.5	0.765	0.750

Based on table 5, it is known that RDW has an AUC value of 0.901, or 90.1%, with a p-value of 0.010 and a sensitivity value of 76.5%, a specificity of 75%, and a cutoff of 14.75. It is also known that the SOFA score has an AUC value of 0.930, or 93%, with a p-value of 0.005 and a sensitivity value of 76.5%, a specificity of 75%, and a cutoff of 14.75.

DISCUSSION

A retrospective cohort study by Xu et al. in 2019⁵ analyzed 6,134 adult patients with sepsis in the intensive care unit at Beth Israel Deaconess Medical Center from 2001 to 2012. In the study, male patients tended to be admitted to the ICU more than female patients, with 2,677 (43.6%) female patients and 3,457 (56.4%) male patients. Compared to females, male patients with sepsis had a higher mortality rate (55.6% vs. 51.4%, p = 0.001).⁵ A study by Yuan et al.⁶ from August to December 2018 included 434 sepsis patients. Among the 434 patients, 259 (59.6%) were male, with a mean age of 67.6 years.⁶ The study by Feng et al. (2017) also found that male sepsis patients tended to outnumber female sepsis patients (107 vs. 68 out of a total of 175 sepsis patients).⁷ The prevalence rate of sepsis and its complications (i.e., septic shock) is significantly higher in men than women.⁸

Zhou et al. (2017) identified 1,716 sepsis patients with a mean age of 80 years, and 57.6% were male.⁸ The sepsis patients treated in this study were between 24 and 64 years old, with a mean±SD age of 53.08±10.72. Furthermore, based on the literature, of the eleven cohort studies that evaluated the effect of age on sepsis rates in critically ill patients, only two studies found a significant association between older age and sepsis rates in intensive care patients.⁹

The rate of sepsis shock admitted to intensive care increases disproportionately in the elderly. Shock sepsis is more likely to occur in people with chronic obstructive pulmonary disease, cancer, chronic kidney and liver disease, and diabetes. In the study, the average age of patients was quite old, presumably because the ICU level of the sampling hospital was the final provincial referral hospital, so the incoming samples were thought to have passed screening from primary and secondary level health facilities. Other risk factors include long-term care, malnutrition, and the use of immunosuppressants and ventilators. These disorders may be secondary to chronic disease or old age.¹⁰

The results of this study showed that the mean±SD of body weight, height, and BMI of the study sample were 64.49±9.27 kg, 164.35±4.50 cm, and 24.02±3.50 kg/m², respectively. A study by Li et al. (2019) on 5563 patients with sepsis showed that obese patients (>30 kg/m²) were more than normal patients (18.5–24 kg/m²) (1910 vs. 1726). Obese patients with sepsis received more aggressive treatment than those with a normal weight.¹¹

In this study, there were 4 samples (10.5%) of survivors, and 34 samples (89.5%) experienced mortality. A 2018 study by Sakr et al. involving 10,069 patients from Europe (54.1%), Asia (19.2%), America (17.1%), and other continents (9.6%) found sepsis incidence rates varied from 13.6% to 39.3% in different regions. Overall, hospital and ICU mortality rates were 25.8% and 35.3% in sepsis patients, respectively. Risk factors for mortality included old age, comorbid cancer, chronic heart failure, cirrhosis, ventilator use or renal replacement therapy, and nosocomial infection with *Acinetobacter spp.*¹² In this study, it was also found that samples who experienced mortality had equally high RDW and SOFA values, with cut-off values of 14.75% and 10.5%, respectively. Jiang et al. also found that day 1 and 3 RDW values were significantly higher in sepsis non-survivors (14.2% and 15.4%, $p < 0.05$) compared to sepsis survivors (13.3% and 14.0%, $p > 0.05$).¹³

The red blood cell distribution width (RDW) value on days 1 (T0) and 3 (T3) showed significant changes ($p = 0.001$) with an increase in the RDW percentage value, namely, an increase in changes in erythrocyte size compared to normal conditions. Research by Jiang et al. (2019), which examined 198 sepsis

patients to observe changes in anemia parameters associated with inflammation to evaluate their relationship with 28-day mortality, found that there was a significant increase in the RDW value of sepsis patients on the first day (13.5%) and the third day (14.6%) after ICU admission ($p < 0.05$).¹³

The exact pathophysiological mechanisms underlying RDW and clinical findings are currently poorly understood. Increased RDW is associated with inflammatory biomarkers and increased oxidative stress. Inflammation impairs iron metabolism, increases erythrocyte apoptosis, decreases erythropoietin production, and has myelosuppressive effects. In previous studies, RDW has been reported to be associated with increased mortality in critically ill patients, suggesting that RDW may be a potential biomarker for assessing sepsis severity.¹⁴

An increase in RDW from baseline during the first three days after ED admission was associated with mortality in sepsis shock. In the study by Kim et al., the average age of the population was below 65 years.¹⁵ In elderly patients, malnutrition and multiple comorbidities, such as chronic heart failure and chronic renal failure, are associated with increased RDW.¹⁶ This may affect the ability of the RDW effect in sepsis.¹⁴

There was a significant change between the SOFA score on day 1 (T0) and day 3 (T3) ($p < 0.001$), where the mean SOFA score at T0 was from 9.079±3.559 to 11.711±3.791 at T3. An increase in SOFA score of 2 or more in adults with suspected infection admitted to the intensive care unit has higher prognostic accuracy for in-hospital mortality.¹⁷ Sepsis patients who experienced

mortality had an increase in SOFA score from day 1 (T0) of 6.5 to 7 at the next 24-hour evaluation (T1). Non-survivor sepsis patients had a higher Δ SOFA compared to survivor sepsis patients (0.37 ± 2.15 vs -0.28 ± 1.88 , $p < 0.0001$).¹⁸

In several previous studies of ICU and ED patients, the mean and highest SOFA scores were correlated with mortality.^{19,20} The study by Jones et al. confirmed that the prognostic value of SOFA score changes assessed during the first 72 hours is too long a time to treat patients in the emergency room. The study by Innocenti et al. (2017)¹⁸ found non-survivor patients showed significantly higher lactate concentrations and lower clearance compared to survivor patients. However, lactate levels at sepsis diagnosis, adjusted for the SOFA score, showed no independent prognostic value.¹⁸

At the time of initial diagnosis, elevated lactate levels have a multifactorial pathogenesis, including increased production and decreased clearance, and this is not always related to hypoperfusion. High lactate levels after 24 hours are independently associated with a worse prognosis. Despite the heterogeneity of the populations involved and the different measurement time points, many studies have shown that changes in lactate levels during the first hours of treatment are a valuable tool in the evaluation of critically ill patients. The persistence of high lactate concentrations may indicate a poor response to treatment.¹⁸

The increase in RDW T0 and T3 is in line with the increase in SOFA scores T0 and T3. This study found that there was a significant correlation between RDW and the increase in SOFA scores ($r = 0.471$; $p < 0.05$) in ICU-treated sepsis

patients. This result is in line with research conducted by Jiang et al. (2019),¹³ which found that SOFA scores had a positive correlation with RDW ($p < 0.05$).¹³ Another study by Nurtadjudin et al. (2023)²¹ also found a significant correlation between RDW and SOFA score ($r = 0.206$, $p = 0.031$). Elevated RDW due to systemic inflammation may predict disease progression. Proinflammatory cytokines inhibit erythrocyte proliferation and maturation induced by erythropoietin, leading to changes in erythrocyte structure and function. So infection and increased inflammatory cytokines can lead to increased RDW.²¹

A retrospective study by Jing et al. (2020)²², confirmed the prognostic importance of RDW in sepsis patients. Jing et al. showed that increased RDW in sepsis patients was not only associated with an increased risk of death 30 days after admission, but also with the development of septic shock and ICU admission. In addition, the significantly higher SOFA score in the high RDW group may be related to impaired microcirculation, organ ischemia, or decreased physiological reserve, leading to more severe organ dysfunction.²²

The potential mechanisms underlying the association between increased RDW and higher mortality risk remain unknown. Several mechanisms have been described to explain why increased RDW leads to adverse outcomes in sepsis patients. Firstly, the association between increased RDW and increased levels of acute phase reactants has been well demonstrated in previous studies, such as C-reactive protein (CRP), ESR, interleukin-6 (IL-6), and tumor necrosis factor (TNF). This suggests that RDW may reflect an inflammatory response, which may negatively affect bone

marrow function, iron metabolism, and red blood cell homeostasis, and subsequently lead to anemia, play a positive role in the emergence and progression of various pathologies, and may also negatively affect systemic inflammatory reaction syndrome (sepsis).^{23,24}

Secondly, high oxidative stress, one of the pathophysiological entities of sepsis, can reduce erythrocyte viability and increase premature erythrocyte release into the circulation, which directly leads to increased RDW. Thirdly, sepsis can alter glycoproteins and ion channels on the erythrocyte inner membrane, which contributes to such changes in erythrocyte morphology. Finally, RDW has been shown to be associated with renal dysfunction, which is closely related to malnutrition and inflammation. Considering all the above factors, it can be suspected that the increase in RDW may be a reflection of various harmful disease processes, including oxidative stress, inflammatory response, renal dysfunction, and malnutrition, which may occur in conjunction with sepsis.²³

This study found an insignificant correlation between RDW values and SOFA scores on day 1 (T0) ($p = 0.103$), in line with research by Ju et al. (2017)²⁵ in China, who found that day-1 RDW did not have a significant correlation with SOFA scores ($p > 0.05$).²⁵ Although it is commonly found that RDW is elevated in critically ill patients, the reasons for these elevated values are not fully understood. Increased RDW values have been reported in various conditions, such as liver disease, autoimmune disease, respiratory disease, stroke, and cardiovascular disease, as a marker of ongoing inflammation. Inflammation can impair erythropoiesis by reducing

erythrocyte precursor activity and erythropoietin production, inducing red blood cell apoptosis, and limiting the availability of iron available for hemoglobin synthesis. These effects lead to the incomplete maturation of red blood cells and the release of many reticulocytes into the circulation.²⁶

High RDW is also associated with increased oxidative stress, poor nutritional status, and renal dysfunction, all of which are very common in intensive care patients. Other causes of high RDW could be iron, vitamin B12, or folate deficiency and a decreased erythrocyte survival rate, but this study did not evaluate these variables. However, the presence of potential confounders (e.g., liver disease, diabetes) did not explain the difference in RDW in this study.²⁶

RDW in this study had an AUC value of 0.901, or 90.1%, with a p -value of 0.010 and a sensitivity value of 76.5%, a specificity of 75%, and a cutoff of 14.75. The SOFA score had an AUC value of 0.930, or 93%, with a p -value of 0.005 and a sensitivity value of 76.5%, a specificity of 75%, and a cutoff of 14.75. Some interesting results from Han et al.'s study (2018) are: first, RDW showed significant accuracy in predicting mortality after 4 years (AUC = 0.930, or 93%). mortality after 4 years (AUC = 0.64), providing diagnostic performance comparable to conventional disease severity scores, one of which is the SOFA score. Thereafter, RDW remained independently associated with 4-year mortality after adjustment for usual severity, even in non-anemic patients. Finally, and perhaps most importantly, RDW improved the accuracy of the 4-year prognosis of all-cause mortality from conventional severity scales.²⁷

The study by Karakike et al. 2019²⁸ included 448 patients divided into a derived group (i.e., patients with sepsis due to gram-negative infection) and 199 patients in the validation group (i.e., patients with sepsis due to ventilator-associated pneumonia). The mean SOFA scores at day 1 in each group were 6.06 ± 4.07 and 7.84 ± 3.39 , respectively, and mortality at day 28 was 22.8% and 29.6%, respectively. In the derived group, the earliest time point at which the Δ SOFA score predicted mortality was day 7 (AUROC 0.84 (0.80-0.89); $p < 0.001$). The best predictor was found with a 25% change (sensitivity: 78%, specificity: 80%).²⁸

In Li et al.'s study,²⁹ SOFA scores were used to analyze 28- and 90-day mortality in sepsis patients. In the 28-day group, the AUC of the SOFA score was significantly higher than that of the qSOFA score. Therefore, the sensitivity and specificity of the SOFA score for predicting the 28-day prognosis of sepsis patients were higher than those of the qSOFA score. However, for ICU patients with sepsis, qSOFA has been shown to be inferior to the Logistic Organ Disorders System (LODS) score and SOFA score for predicting prognosis at 28 and 90 days. However, the simplicity of qSOFA as a rapid identification of sepsis makes it more suitable for emergencies. Although the AUC value of the LODS score is superior to the SOFA score in predicting the 90-day prognosis of patients with sepsis, the LODS score is a more complex tool, and its AUC value is only slightly better than the SOFA scale. Therefore, the SOFA score is now the instrument of choice in the SEPSIS-3 criteria.²⁹

CONCLUSION

In this study, there was a statistically significant increase in RDW from $15.392 \pm 2.459\%$ to $16.403 \pm 2.888\%$ and a statistically significant increase in SOFA score from 9.079 ± 3.559 to 11.711 ± 3.791 in sepsis patients. There was a statistically significant relationship between RDW and SOFA, with a moderate degree of correlation. The sensitivity, specificity, and cut-off values of RDW were 76.5%, 75%, and 14.75%, which compared to SOFA were 76.5%, 75%, and 10.5%.

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