



Özgün Araştırma / Original Article

Evaluation of the effect of red cell distribution width on the development of acute renal failure in patients with sepsis

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Received: 27.12.2016; Revised: 17.04.2017; Accepted: 04.05.2017

Abstract

Objective: Acute kidney injury (AKI) is an important clinical entity that is known to increase mortality in patients with sepsis. Erythrocyte maturation and proliferation are inhibited by pro-inflammatory cytokines; these cytokines exert effects on red cell distribution width (RDW) well. Based on this knowledge; our aim in this study was to evaluate the impact of RDW on acute kidney injury in patients with sepsis.

Methods: 120 patients diagnosed with sepsis and admitted to intensive care unit (ICU) and treated between 2009-2013 were retrospectively evaluated. Patients were divided into two groups as follows: group 1 (RDW \geq 16.8) and group 2 (RDW $<$ 16.8). Multiple logistic regression analysis was used to determine the association between RDW and AKI and mortality.

Results: There was a statistically significant relationship between AKI and RDW ($p<0.001$, OR=11.52) but there were no statistically significant relationship between AKI and sex, age, serum lactate levels as well as SOFA score. Also, there were statistically significant relationship between mortality and RDW ($p=0.044$, OR=5), serum lactate levels ($p=0.030$) and SOFA score ($p<0.001$). RDW was found associated with both AKI and mortality.

Conclusions: Results suggest that RDW is an important parameter for predicting development of AKI and mortality in ICU patients with sepsis.

Keywords: Acute kidney injury, Sepsis, Red cell distribution width

DOI: 10.5798/dicletip.319769

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Eritrosit dağılım genişliğinin sepsisli hastalarda akut böbrek hasarı gelişimi üzerine etkisinin değerlendirilmesi

Özet

Amaç: Akut böbrek hasarı (AKI) sepsisli hastalarda mortaliteyi arttırdığı bilinen önemli bir klinik tablodur. Eritrosit maturasyonu ve profilerasyonu, proinflatuar sitokinler tarafından inhibe edilir. Bu sitokinler eritrosit dağılım genişliği üzerinde etkilidirler. Bu ilgiye dayanarak sepsisli hastalarda eritrosit dağılım genişliğinin (rRDW) akut böbrek hasarı gelişimi üzerine etkisini değerlendirmeyi amaçladık.

Yöntemler: 2009-2013 yılları arasında sepsis tanısı olan ve yoğun bakım ünitesine kabul edilen 120 hastayı retrospektif olarak inceledik. Hastaları grup 1 (RDW \geq 16.8) ve grup 2 (RDW<16.8) olarak iki gruba ayırdık. RDW, akut böbrek hasarı ve mortalite arasındaki ilişkiyi belirlemek için multiple lojistik regresyon analizi kullandık.

Bulgular: Akut böbrek hasarı ve RDW arasında istatistiksel olarak anlamlı ilişki tespit ettik (p<0.001, OR=11.52) ancak akut böbrek hasarı ve cinsiyet, yaş, serum laktat seviyeleri ve SOFA skoru arasında anlamlı ilişki yoktu. Aynı zamanda, mortalite ve RDW arasında (p=0.044, OR=5), mortalite ve serum laktat seviyeleri arasında (p=0.030) ve mortalite ve SOFA skoru arasında (p<0.001) anlamlı ilişki gösterildi. RDW nin hem akut böbrek hasarı hem de mortalite ile ilişkili olduğu gösterildi.

Sonuç: Bulgular RDW nin yoğun bakım ünitesindeki sepsisli hastalarda mortalite ve akut böbrek hasarını tahmin etmede önemli bir parametre olduğunu göstermiştir

Anahtar kelimeler: Akut Böbrek Hasarı, Sepsis, Eritrosit dağılım genişliği

INTRODUCTION

Sepsis is a fatal infectious disease that can cause hemodynamic changes, multiple organ dysfunction and shock¹. Sepsis has high mortality rates, therefore, requires early diagnosis and treatment in intensive care units. Sepsis develops due to the interaction between the causative organism and the immunologic, inflammatory and coagulation responses of the host. The target tissue is the vascular endothelium, and almost all mediators are effective on the vascular endothelium. Endothelial cells secrete important molecules that regulate both coagulation and inflammation^{2,3}. In addition, shunts have been detected in the microvascular circulation in severe sepsis and septic shock⁴. These shunts may occur due to microvascular lumen obstruction, which is caused by endothelial cell swelling, by disruption of flow, caused by the binding of activated leukocytes to the endothelium, or by the deterioration of the elasticity of the wall⁵.

The most common causes of sepsis are bacteria, fungi, viruses and parasites, respectively⁶. However, microbiological evidence is unnecessary for the diagnosis of sepsis⁷. It has been reported that etiological factors cannot be determined in 30-50 % of patients with sepsis^{8,9}.

Acute kidney injury (AKI) is one of the key factors determining morbidity and mortality in sepsis¹⁰. Due to the recent progress made in cell biology, the pathophysiology of sepsis has become better understood. Mediators and cytokines involved in the pathophysiology of sepsis has been determined and their effects on metabolic changes in the body and other mechanisms of action have been defined^{11,12}. Sepsis and especially septic shock are important causes of AKI. AKI due to sepsis is one part of multi organ failure and has a significant effect on mortality¹³.

Erythrocyte distribution width (RDW), which is determined by the complete blood count (CBC), is an important index showing the distribution of the sizes of circulating red blood cells. RDW within normal limits indicates that the sizes of

the erythrocytes are in a regular distribution. RDW is used in the diagnosis of anemia, and increases in RDW are observed in hemolysis and erythrocyte production disorders¹⁴.

The systemic inflammatory response affects the function of bone marrow and iron metabolism^{15,16}. It is known that pro-inflammatory cytokines, which are related to increases in RDW inhibit erythrocyte maturation and proliferation induced by erythropoietin and down-regulate erythropoietin receptor expression¹⁷. Furthermore, it is thought that oxidative stress causes increased RDW by shortening the lifetime of erythrocytes and thus enhancing the release of large, premature erythrocytes to the peripheral circulation¹⁸. Increased RDW indicates an increased diversity in the size of the erythrocytes, which is a situation that is also known as anisocytosis. Increased RDW occurs especially in nutritional deficiency such as iron, folate and vitamin b12. Increased RDW is not only observed in hematological diseases, but has also been observed in pulmonary embolism¹⁹, acute renal failure²⁰, pulmonary arterial hypertension²¹, stroke²² and peripheral arterial diseases²³. Increased RDW levels increase the risk of death due to any cause in addition to the increased risk of cardiovascular death. The aim of this study is to evaluate the impact of RDW on acute kidney injury in patients with sepsis.

METHODS

The records of 120 patients with a diagnosis of sepsis who were admitted to the internal medicine intensive care unit and treated between 2009-2013 in Dicle University Faculty of Medicine Research and Application Hospital were retrospectively evaluated. This study was approved by the local ethics committee (357).

The study inclusion criteria were as follows: patients between the ages of 18-70, patients who had two or more systemic inflammatory response syndrome (SIRS) findings with the clinical and/or bacteriological evidence of

infection (fever>38 C or fever<36 C), heart rate >90/min, respiratory rate>20/min or PaCO₂<32 mmHg or mechanical ventilation requirement, WBC>12000/mm³ or <4000/mm³, platelet count<100000/mm³ or sepsis induced coagulopathy, and hypoperfusion findings, including oliguria (<0.5 ml/kg/h), variable mental status or serum lactate level>2.2 mmol/L.

The study exclusion criteria were as follows: fasting>15 days, blood products transfusion the week prior to ICU admission, bleeding>10%, history of hematological disease, recent history of chemotherapy, cardiogenic shock, hepatic cirrhosis, pregnancy or drug usage, which can change red blood cell morphology.

The files of 565 patients with a diagnosis of sepsis were reviewed retrospectively. 445 patients were excluded from the study according to aforementioned criteria. The demographic characteristics, sepsis etiology and comorbid conditions of 120 patients who meet the criteria were obtained from the patient files. The values of RDW, Hgb, Htc, MCV, CRP and creatinine at ICU admission and at 48 hours after admission were recorded from the patient files. The SOFA score for each patient was calculated. These values, including the SOFA score, were also recorded at ICU follow up. Patients were divided into two groups as follows: group 1 (RDW≥16.8) and group 2 (RDW<16.8). AKI was investigated in both groups; patients with a 0.3 mg/dl or greater increase in serum creatinine within 48 hours were considered as having AKI.

SPSS (Statistical Package for Social Sciences for Windows version 16) was used for statistical analysis. A Student's *t* test and multiple logistic regression analysis were used. Data were expressed as means±SD. Odds Ratio values were calculated to evaluate the relationship between RDW and AKI. P values <0.005 were considered statistically significant at the 95% confidence interval.

Table 1: Demographic characteristics, laboratory results, SOFA scores and average lengths of stay in the intensive care unit for groups 1 (RDW>16.8) and 2 (RDW<16.8).

| Variables | Group 1 (n:66) | Group 2 (n:54) | P |
|--|----------------|----------------|------------------|
| Sex(m/f) | 37/29 | 32/22 | 0,724 |
| Age(years) | 50,66 ± 14,79 | 49,59 ± 13,93 | 0,685 |
| Hgb (g/dl) | 11,39 ± 2,05 | 12,28 ± 1,91 | 0,016 |
| MCV (fl) | 82,75 ± 7,70 | 87,52 ± 5,20 | <0,001 |
| CRP(mg/dl) | 14,43 ± 10,44 | 14,51 ± 11,85 | 0,972 |
| Creatinin (mg/dl) | 2,17 ± 1,95 | 1,38 ± 1,49 | 0,016 |
| SOFA score | 5,09 ± 4,39 | 3,14 ± 3,95 | 0,013 |
| Average length of stay in the ICU (days) | 18,16 ± 15,82 | 15,68 ± 10,02 | 0,320 |

RESULTS

Of the 120 patients with sepsis that were included in this study, 69 (57.5%) were male and 51 (42.5%) were female. The mean age of the patients was 50.18 ± 14.36 years. There were 66 patients in group 1 (RDW≥16.8) and 54 patients in group 2 (RDW<16.8). According to the etiology of sepsis of the patients in group 1, 38 had lung infection, 14 had urinary tract infection, 3 had gastrointestinal tract infection and 12 had other system infections. In group 2, 21 patients had lung infection, 13 had urinary tract infection, 3 had gastrointestinal tract infection and 18 had other system infections (p=0.292).

Table 2: Multivariate logistic regression analysis for AKI.

| Variables | OR | %95 CI | P |
|-------------------------|-------|------------|--------|
| RDW≥16.8% | 11.52 | 4.62-28.72 | <0.001 |
| Gender (Female vs Male) | 0.21 | 0.50-2.92 | 0.671 |
| Age>65 years | 0.72 | 0.20-2.57 | 0.619 |
| Lactate>2 mmol/L | 1.34 | 0.52-3.45 | 0.542 |
| SOFA score≥7 | 1.57 | 0.48-5.10 | 0.453 |

OR, odds ratio; CI, confidence interval

Table 3: Multivariate logistic regression analysis for mortality.

| Variables | OR | %95 CI | P |
|-------------------------|-------|------------|--------|
| RDW≥16.8% | 5.00 | 1.04-24.01 | 0.044 |
| Gender (Female vs Male) | 0.38 | 0.12-1.14 | 0.087 |
| Age>65 years | 2.34 | 0.58-9.47 | 0.232 |
| Lactate>2 mmol/L | 3.24 | 1.12-9.39 | 0.030 |
| SOFA score≥7 | 21.21 | 5.48-82.02 | <0.001 |
| AKI | 3.23 | 0.87-11.94 | 0.079 |

OR, odds ratio; CI, confidence interval

When we evaluated patients according to comorbid diseases accompanying sepsis, we have found that in group 1, 6 patients had congestive heart failure (9.09%), 5 had diabetes mellitus (7.57%), 3 had hypertension (4.54%), 12 had chronic obstructive pulmonary disease (18.18%), 4 had coronary artery disease (6.06%), 8 had neurological disease (12.12%), 2 had chronic kidney disease (3.03%) and 1 had chronic liver disease (1.51%). In group 2, 14 patients had diabetes mellitus (25.92%), 6 had hypertension (11.11%), 1 had coronary artery disease (1.85%), 8 had neurological disease (14.81%), and 1 had chronic liver disease (1.85%). All of the patients with congestive heart failure

and/or COPD were in group 1. In addition, there were 5 patients with coronary artery disease, and 4 of them were in group 1. We note that these three significant comorbid conditions may be associated with an increase in RDW. There was a statistically significant difference between groups 1 and 2 with respect to comorbid diseases ($p=0.016$).

Of the patients in group 1 ($RDW > 16.8$), 37 were male, 29 were female, the mean age was 50.6614 ± 79 years, the mean RDW was 19.38 ± 2.94 , the mean Hgb value was 11.39 ± 2.05 , the mean MCV was 82.75 ± 7.70 , the mean CRP value was 14.43 ± 10.44 , the mean SOFA score was 5.09 ± 4.39 , the mean creatinine value was 2.17 ± 1.95 and the average length of stay in the ICU was 18.16 ± 15.82 days. Of the patients in group 2, 32 were male, 22 were female, the mean age was 49.59 ± 13.93 years, the mean RDW was 15.70 ± 0.75 , the mean Hgb was 12.28 ± 1.91 , the mean MCV was 87.52 ± 5.20 , the mean CRP value was 14.51 ± 11.85 , the mean SOFA score was 3.14 ± 3.95 , the mean creatinine value was 1.38 ± 1.49 and the average length of stay in the ICU was 15.68 ± 10.02 days. There were statistically significant differences between groups with respect to RDW, Hb, MCV, SOFA score and creatinine values. The differences between the other variables were not statistically significant. The results are summarized in table 1. Thirty-seven patients in group 1 had AKI while 18 patients in group 2 had AKI ($p=0.013$). The distribution of the patients into subgroups with respect to RDW and AKI is shown in figure 1.

The mortality rate in group 1 was 39.4%, and their discharge rate was 60.6%. For group 2, the mortality rate was 16.7% and the discharge rate was 83.3%. The mortality rate was significantly higher in group 1 ($p=0.006$) (figure 2).

In multiple logistic regression analysis; there was a statistically significant relationship between AKI and RDW ($p < 0.001$, $OR=11.52$) but there were no statistically significant

relationship between AKI and sex, age, serum lactate levels and SOFA score (table 2). Also, there were statistically significant relationship between mortality and RDW ($p=0.044$, $OR=5$), serum lactate levels ($p=0.030$) and SOFA score ($p < 0.001$) (table 3). RDW was found associated with both AKI and mortality.

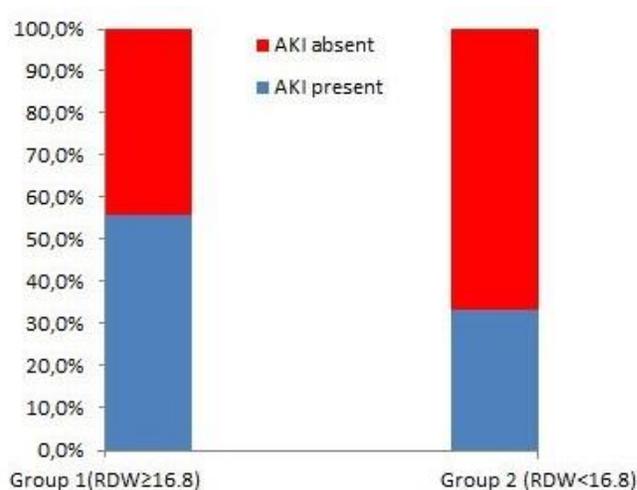


Figure 1. Distribution of the patients into subgroups with respect to RDW and AKI.

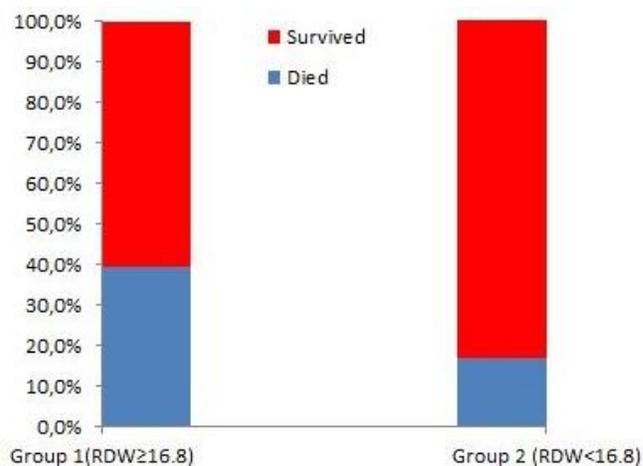


Figure 2. Distribution of the patients into subgroups with respect to RDW and mortality

DISCUSSION

The causes of sepsis are quite complex. Sepsis is a life-threatening disease associated with multiple organ failure, and its follow-up and

treatment are carried out in the intensive care unit. Due to the dissemination of bacterial infection and the endothelial response to this infection, sepsis often involves multiple organs. The kidney is one of the most targeted organs in sepsis. Acute kidney injury (AKI) occurs in 5% of hospitalized patients and in 30% of ICU patients, and it is one of the key factors determining morbidity and mortality²⁴. Approximately 15-20% of all patients hospitalized in the ICU will develop sepsis-induced AKI, and based on the severity of the damage the mortality of sepsis-induced AKI has been reported to vary between 20.9% and 56.8%²⁵⁻²⁷. Despite recent advancements in advanced renal replacement technologies, the mortality rate of sepsis remains high, and therefore, the early diagnosis of AKI is very important. The red cell distribution width (RDW) may increase in conditions other than hematological diseases, including anemia, hemolysis and erythrocyte production disorders. The inflammatory process is one of the conditions that may cause an increase in RDW. Based on this knowledge, in this retrospective study we investigated the effect of RDW on the development of acute kidney injury in patients with sepsis. The mean age of the patients evaluated in this study (50.18 ±14.36 years) was significantly younger than the mean age of the patients in most published studies regarding AKI and sepsis^{28,29}. There was no statistically significant difference between our groups (RDW≥16.8 and RDW<16.8) according to gender. In multiple logistic regression analysis; there was a statistically significant relationship between AKI and RDW (p<0.001) but there were no statistically significant relationship between AKI and sex, age, serum lactate levels and SOFA score (table 2). Also, there were statistically significant relationship between mortality and RDW (p=0.044), serum lactate levels (p=0.030) and SOFA score (p<0.001) (table 3). RDW was found associated with both AKI and mortality.

In the current study, we found multiple comorbid diseases in both groups of patients. When evaluating the etiologies of sepsis in our study groups, we found that pulmonary and urinary tract infections were among the most common causes, respectively, in both groups. These etiologic causes are consistent with the literature^{30,31}. RDW was increased in all of the patients with heart failure and/or chronic obstructive pulmonary disease. Four of the 5 patients with coronary artery disease had increased RDW values. All of the patients with heart failure and chronic obstructive pulmonary disease were in group 1 (RDW≥16.8). In addition, 4 of the 5 patients with coronary artery disease were in group 1. Therefore, the significantly increase in RDW values in group 1 may be due to the comorbidities of the patients in this group.

CRP is an important diagnostic and follow-up parameter in sepsis. In our study, CRP levels were elevated in both groups and there was no significant difference between the two groups, which is similar to previously published data^{20,31}. In addition, studies have reported that the mean CRP value was significantly higher in patients with elevated RDW³². In the current study, we found that in group 1, RDW was 19.38 ±2.94%, hemoglobin was 11.39±2.05 g/dl and MCV was 82.75±7.70 fl. In group 2, RDW was 15.70±0.75%, Hgb was 12.28±1.91 gr/dl and MCV was 87.52±5.20 fl. There was a statistically significant difference between the groups with respect to these three variables, and these differences were consistent with previously published data^{28,32}.

The SOFA score, which is used to assess the prognosis of patients with severe sepsis, is an important parameter that is highly related to mortality. In our study, there was a statistically significant difference in the SOFA scores between the groups, and the SOFA score was higher in group 1 (p=0.013). In a study by Esper R.C. et al, the RDW values were significantly higher in ICU patients with sepsis

than in those without sepsis. In addition, they have found that RDW values were higher in patients with elevated SOFA scores³³. In our current study, we found that patients with sepsis had elevated SOFA scores, which was similar to previously published data^{30,31}.

The results of the current study suggest that an increase in RDW is associated with the increase in the risk of developing AKI ($p < 0.001$, OR: 11.52). Lippi G. et al. reported similar findings. They found that GFR levels decrease progressively ($p < 0.001$, OR: 1.982) in accordance with an increase in RDW independent of age, gender, MCV and hemoglobin values²⁸. The results of the study by Lippi G. et al. have been supported by other studies^{31,34}. However, there are some published studies that show no correlation between RDW and renal function tests²⁰.

It is important to evaluate the relationship between RDW and mortality as well as the relationship between RDW and AKI. In our current study, there was a statistically significant difference in the mortality rate between the two groups ($p = 0.006$, OR: 3.250). We found that the mortality rate increased with increasing RDW levels, which is consistent with the literature^{29,30,35}. A meta-analysis by Patel K.V. et al found that for every 1% increase in RDW, there is a 14% increase in mortality³⁶. Our current study and the results of previously published studies support that an increase in RDW is closely related to mortality.

In conclusion, results of the current study indicate that an increase in RDW leads to an increase in the risk of developing AKI ($p < 0.001$, OR: 11.52). RDW can be an important parameter that is used to predict the development of AKI and mortality in ICU patients with sepsis. However, further large-scale studies relevant to this topic are needed.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received.

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