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# Red Blood Cell Distribution Width and Mortality in ICU Patients; A Cross Sectional Retrospective Analysis Red Blood Cell Distribution Width and Mortality in ICU Patients

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## Abstract

### Introduction

The red blood cell distribution width (RDW) is a predictor of mortality in many conditions. We investigated the prognostic value of RDW in the general ICU population.

### Methods

Two hundred and seventy-four patients were enrolled into this retrospective, cross sectional study in general full range ICU. Patients with history of recent blood transfusion, hematologic disorder and length of stay (LOS) ≤ 48 hours in ICU were excluded. The identification of these patients was performed via the central medical database of our hospital retrospectively. The patients were classified according to their age, LOS and clinical outcomes. The RDW values were recorded upon ICU admission (RDW-0) on 4th, 10th, 20th and 30th days respectively in ICU. The RDW value of the last blood sample was termed as RDW-last, and RDW-last% was defined with the percentage of RDW-last/RDW-0.

We used Student's t test and Mann Whitney U test to compare the groups. Repeated measures and parameters were analyzed using ANOVA and paired t tests. Logistic regression and ROC tests were also performed to determine the efficiency of the parameters for prognosis.

### Results

There were no differences in the RDW values between survivors and non-survivors as expected with RDW-last and RDW-last% values. The RDW values were higher in non-survivors (in tandem to LOS) compared to the initial values.

### Conclusions

The changes in RDW values to RDW-0 are more valuable for the estimation of lethal prognosis in hospitalized or critically ill patients.

### Keywords

Red blood cell distribution width (RDW); Mortality; ICU

## Introduction

The red blood cell distribution width (RDW) is a remarkable parameter of complete blood count (CBC) and is a quantitative measure for variability circulating erythrocytes in size [1,2]. The RDW test results are often assessed together with the mean corpuscular volume (MCV) to determine the possible causes of anemia. RDW is mainly used to differentiate anemia with mixed causes from anemia with a single cause. Anemia with iron deficiency is associated with increased RDW and decreased MCV. Anemia with folate and vitamin B12 deficiency usually exists with high RDW and MCV. Recent hemorrhage leads to high RDW values [3].

Recently, RDW has become an indirect predictor of prognosis for various diseases. Previous studies demonstrate the prognostic value of RDW in patients with liver disease [4], coronary disease [5], heart failure [6,7], community acquired pneumonia [8], metabolic syndrome [9] and Alzheimer's disease [10]. RDW has also been used as a mortality predictor in hip fracture [11], pulmonary embolism [12], acute dyspnea [13], stroke [14], geriatric patients [3,15,16], trauma [17] and cardiovascular diseases [18,19]. In intensive care unit (ICU) patients, RDW is associated with the risk of death [20] and is an independent prognostic marker [1,21].

The prognostic value of RDW in medical, general and coronary ICU patients has been studied previously [1,6,7,20,21]. RDW indicated the mortality risk in patients with multiple organ failure besides the isolated disease. Therefore in our retrospective study, we investigated the relationship between RDW and mortality in ICU patients including surgical patients.

## Materials and Methods

This retrospective study was conducted in the general ICU at single center. Upon ethics committee approval, 274 ICU patients, with varied age from 19 to 101, were enrolled into this study. All patients, including surgical, were identified retrospectively via the central medical database of the hospital. Patients with a history of recent blood transfusion, hematologic disorders, and patients who died or were discharged from the ICU within 48 hours were excluded. The patients were classified according to age, length of stay (LOS) in the ICU and clinical outcomes. The changes in RDW values depending on age and length of stay in the ICU were evaluated.

RDW values on day 0 (ICU admission) and the 4$^{th}$, 10$^{th}$, 20$^{th}$ and 30$^{th}$ days in the ICU were recorded. (All blood samples were collected in K3EDTA (BD vacutainer® tubes). If the test could not be performed at the appointed time, the results within ± 2 days were considered. The last blood samples of the patients in ICU were accepted as RDW-last. The RDW-last% value was calculated as follows:

$$RDW-last\% = 100 \times \left( \frac{RDW-last}{RDW-0} \right)$$

## Statistical Analyses

Statistical analyses were performed for Windows 11.5 statistical program with SPSS. The value changes in RDW were analyzed with repeated ANOVA measures and paired t tests depending on the length of ICU stay. The correlation analyses between RDW values and the data related to hospitalization and age was found using Pearson correlation test. Student's t test was used for normally distributed variables, and the Mann Whitney U test was used for non-normally distributed variables to evaluate the patients' values in the different groups. Logistic regression analysis was performed to determine the efficiency of the parameters for patient prognosis. Calculating the receiver operating characteristic (ROC) curves, discriminative power of the tests for mortality was assessed. The ROC curve statistics were reported as the area under the curve (AUC). Statistical significance was set at $p < 0.05$.

## Results

In total 274 ICU patients (154 male, 120 female), ages varying from 19 to 101 (65.4 ± 16.8) were retrospectively analyzed. The length of ICU stay, varied from 2 to 145 days (11.9 ± 14.3). One hundred and seventy two patients (62.8%) were recovered and were discharged from the ICU. The total ICU mortality (death before ICU discharge) rate was 37.2% (102). The patients died were significantly older to the patients alive. The LOS of the patients died was significantly longer to the LOS of the patients alive. There was no difference in the RDW values among the patients died or survived with the exception of RDW-last and RDW-last% values (Table 1). There were no significant differences in the repeated RDW values. A significant but weak correlation was observed (r: 0.131, p: 0. 031) between RDW-0 and patient age while there was no correlation with age in survival patients, a stronger correlation was found in non- survivors (r: 0.304, p: 0. 002). The values of the RDW-last and RDW-last% did not correlate with age in any groups (total, survivors and non-survivors). The length of ICU stay did not correlate with any RDW values. The AUC levels were 0.572, 0.651 and 0.621 for RDW-0, RDW-last and RDW-last%, respectively. The age AUC levels (0.651) were comparable with the RDW values. In logistic regression analysis, age, RDW-last and RDW-last% were significant independent variables for predicting ICU mortality ($p < 0.05$). Yet, RDW-0 was not a significant variable.

| | Total group | Subgroups | | P* |
|---|---|---|---|---|
| | | Survivor | Non survivor | |
| **LOS (day)**<br>**n** | 11.88 (14.31)<br>274 | 10.15 (10.27)<br>172 | 14.81 (18.99)<br>102 | 0.02344 |
| **Age (year)**<br>**n** | 65.37 (16.76)<br>274 | 62.27 (16.96)<br>172 | 70.60 (15.11)<br>102 | 0.00004 |
| **RDW-0**<br>**n** | 15.57 (3.04)<br>274 | 15.47 (3.34)<br>172 | 15.73 (2.46)<br>102 | NS |
| **RDW-4**<br>**n** | 15.88 (3.11)<br>251 | 15.66 (3.21)<br>162 | 16.29 (2.89)<br>89 | NS |
| **RDW-10**<br>**n** | 16.14 (2.83)<br>123 | 16.11 (3.34)<br>68 | 16.18 (2.05)<br>55 | NS |
| **RDW-20**<br>**n** | 16.35 (2.88)<br>41 | 16.51 (2.96)<br>21 | 16.18 (2.85)<br>20 | NS |
| **RDW-30**<br>**n** | 16.56 (3.61)<br>17 | 15.50 (3.08)<br>9 | 17.76 (3.97)<br>8 | NS |
| **RDW-last**<br>**n** | 15.98 (2.99)<br>274 | 15.53 (3.01)<br>172 | 16.73 (2.82)<br>102 | 0.00126 |
| **RDW-last%**<br>**n** | 103.39 (12.11)<br>274 | 101.35 (11.57)<br>172 | 106.83 (12.28)<br>102 | 0.00026 |

Table 1. The red cell distribution width (RDW) values of the patients. Mean (SD)

*: P values related to the comparison of the survivor and non survivor subgroups were determined using the Student's t test or Mann Whitney U test

LOS: Length of stay

RDW-0, RDW-4, RDW-10, RDW-20, RDW-30 values: On ICU admission, 4th, 10th, 20th and 30th days in ICU, respectively

RDW-last: The last blood sample

RDW-last%: The percentage of RDW-last/RDW-0

NS: Non significant

## Discussion

In this paper we evaluated the significance of RDW in ICU patients, including surgical patients. In contrast to previous studies we found no difference in the RDW values between survivors and non-survivors. However, the RDW-last and RDW-last% values were significantly higher in non-survivors.

Several prognostic markers have been used for the evaluation and management of ICU patients who have high morbidity and mortality risk. Because none of the current markers are perfect and the search for a more reliable marker will be continued. RDW studies have been performed in medical patients, including coronary ICU patients and the results demonstrate that RDW has the clinical utility to predict mortality [1,5-7,18-21,24]. The main mechanisms of the RDW and mortality association are explained below:

1. Erythropoiesis, circulating red blood cell half-life and red blood cell membrane deformability may be affected by chronic subclinical inflammation. Proinflammatory cytokines inhibit the proliferation of erythroid progenitor cells and erythropoietin receptor expression. RDW is increased by inflammation as a result of impaired iron metabolism and modulation of the bone marrow's response to erythropoietin. Oxidative stress and reduced serum antioxidant levels are also associated with increased RDW values. Inflammation and oxidative stress disrupts erythropoiesis and increase anisocytosis [3,9,16,19-23].

2. Pathological changes in the erythrocyte membrane lead to the deposition of free cholesterol to atherosclerotic plaque and extension of the necrotic core of the atherosclerotic lesion in atherosclerosis [19].

Former studies have demonstrated that RDW values increased with age [1]. The mechanism of age and RDW relationship has not been defined yet. This relationship could be dependent on several other factors including inflammation, anemia, nutritional status and age associated diseases [9,25]. In our study, the correlation between RDW-0 and age in all patients was significant but weak (r: 0.131, *p*: 0. 031). This correlation was more powerful among the patients who died (r: 0.304, *p*: 0. 002). Because of these results, we hypothesized that the correlation between RDW and age may originated from the patient's general health condition.

Only a small percentage of ICU patients suffer from an isolated disease. ICU patients are a heterogeneous group including metabolic disorders, atherosclerotic vascular and heart diseases in varying degrees, particularly in elderly patients. Although the primary reason for ICU admission varies, some associated diseases may also have significance. Infections are often observed in ICU patients and presents either as a primary reason or as a coexisting pathology. Thus, separating the ICU patients into specific disease subgroups is difficult because of concomitant multi-organ dysfunctions.

In our study we found that the initial RDW values on admission were not a significant prognostic predictor in ICU patients. However, the RDW-last and RDW-last% values were significantly higher in died patients. These findings indicated that RDW values were increased in patients whose conditions worsened during their ICU stay. When cut-off values were used for RDW-0 and RDW-last,14.85 % and 16.10 % respectively, both parameters predicted the mortality with 80% sensitivity and 75% specificity in the patients who had LOS $\geq$ 30 days.

The mean RDW levels in survival and non-survival patients are not sufficient solitary prognostic markers. Higher RDW levels may predict the risk of mortality, but RDW is insufficient to determine who will die or remain alive, individually. The sensitivity and specificity of RDW values for predicting survival and death have not been investigated with the exception of a few limited studies [1,10]. Currently, any useable boundary value for the sensitivity and specificity of RDW has not been determined due to many factors affecting each other and RDW values. The relationship between RDW and mortality was meaningfully demonstrated in a study performed by Bazick and co-workers in which a much more number of patients were investigated compared to our study. The receiver operating characteristic area under the curve for RDW was 0.67, in spite of the significant results. This AUC level had moderate discriminative power for mortality [20]. Despite our low patient numbers, the AUC levels were 0.572, 0.651 and 0.621 for RDW-0, RDW-last and RDW-last%, respectively. The age AUC levels (0.651) were comparable with the RDW values. All these AUC levels remained under the discriminative power of the scores commonly used in the ICU such as the Acute Physiology and Chronic Health Evaluation II (APACHE-II) or the Simplified Acute Physiology Score II (SAPS-II). In a study related to the prediction of hospital mortality [26], the AUC was calculated as 0.84 for APACHE-II score and 0.85 for SAPS-II. Although the RDW value alone is a weak prognostic marker, its power may be increased when combined with these scores.

The other limitations of the RDW value are the differences in calculation and analyzer techniques. The same blood sample results can be varying due to different hematology analyzers. Reference ranges of the RDW value differ considerably among instruments. For this reason, the results from different analyzers cannot be compared with each other. The cut-off RDW value is only valid for the instrument used [27]. The same machine was used for blood counts during the study period.

Despite a limited number of patients, the overall results of our study solely helped us to reach up an outcome. The increase in RDW values during the ICU period, especially in non-survivors, showed that this increase resulted from the patient's health status upon admission and also the progress of the disease. While RDW-0 was not a robust predictor, in contrast to similar studies, the RDW-last and RDW-last% values were significant. The RDW-last and RDW-last% values should be considered because these parameters increased more in non-survivors than survivors, and had higher AUC levels. Furthermore, the RDW-last and RDW-last% were strong and independent discriminative markers for mortality with logistic regression analysis.

Despite these significant results, the RDW-last and RDW-last% were not adequate for clinical practice use or prognosis. However, these results confirm that the changes in RDW values are the indicators of patient's health condition. We hypothesize that assessment with one RDW value is not accurate, because RDW can be affected by pre-analytic variables and the differences in analysis methods. The studies, in which RDW was found to be a strong prognostic marker had different cut-off values, supporting our hypothesis. A significant cut-off value for one study may be insignificant for other studies. Subsequent RDW measurements in addition to the first measurement may be useful in patients, especially with long term care.

Our study has some drawbacks: 1.The number of patients was not more enough to analyze them in subgroups and to verify some statistics. 2. This study was retrospectively designed. Thus other factors that could influence RDW levels, such as iron and vitamin B-12 deficiency values, could not be included. 3. Further grouping of patients, regarding primary pathology could not be performed.

## Conclusion

RDW is a component of the complete blood cell count, and it is widely available without any additional costs. Various factors, including nonspecific pathologic conditions, such as inflammation, oxidant stress, and nutritional status, affected RDW levels. Moreover, age and RDW values are correlated. The healthy patient may have some of these factors. RDW values can actually represent the whole body health condition. Currently, RDW does not appear to have strong sensitivity and specificity in spite of increasing in parallel with morbidity and mortality, owing to this complexity.

In the light of these results, we believe that the changes in RDW values (sequential measurements during ICU stay) should be investigated, especially in ICU patients. These results may participate to establish a single approach to predict mortality in future ICU patients.

## Conflicts of interest

The authors declare no conflicts of interest.

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