ORIGINAL INVESTIGATION

J Crit Intensive Care 2021;12:15–19
https://doi.org/10.37678/dcybd.2020.2571

Simple Prognostic Markers to Predict Mortality in Intensive Care Unit: Red Cell Distribution Width

Ahmet ERDOGAN[1], Kazim SENOL[2], Deniz ERDEM[3], Enes Malik UCKAN[4], Mesut TEZ[4]

[1]Kahramanmaraş Elbistan State Hospital, General Surgery, Kahramanmaras, Turkey

[2]Uludag University, Faculty of Medicine, General Surgery, Bursa, Turkey

[3]Ankara City Hospital, Anesthesia and Reanimation, Ankara, Turkey

[4]Ankara City Hospital, General Surgery, Ankara, Turkey

Cite this article as: Erdogan A, Senol K, Erdem D, Uckan EM, Tez M. Simple Prognostic Markers to Predict Mortality in Intensive Care Unit: Red Cell Distribution Width. J Crit Intensive Care 2021;12:15–19

Corresponding Author: Ahmet Erdogan
E mail: erdogannumune@hotmail.com

©Copyright 2020 by Turkish Society of Medical and Surgical Intensive Care Medicine - Available online at www.dcyogunbakim.org

Received: Nov 21, 2020
Accepted: Dec 10, 2020
Available online: Jan 12, 2021

ABSTRACT

Background: We tried to examine association between the prognostic intensive care unit (ICU) scores and red cell distribution width (RDW) for prediction of mortality in a cohort of ICU patients at a single centre in Turkey.

Methods: This is a retrospective cohort study conducted in a 9-bed mixed ICU of a tertiary hospital from January to December 2013. One hundred and nine ICU patients requiring intensive care following an elective or emergent surgical procedure, trauma or medical severe disease were enrolled in the study. Demographic data, admission clinical parameters and Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) II scores were collected. The primary outcome was ICU mortality which is defined as death before hospital discharge for any reason. Receivers operating characteristic (ROC) curves were used to examine the performance of variables in predicting ICU mortality.

Results: There were significant positive correlations between RDW and APACHE II, SOFA and SAPS II scores. RDW levels were significantly higher in non-survivors (16.94±3.05 versus 15.62±2.82, p<0.001). The optimal cutoff value of RDW for prediction of mortality according to ROC analyses was 14.5. ICU mortality rate was 18.9% if RDW level was less than 14.5%; and 81.1 % if RDW level was greater than14.5%.

Conclusions: We found that ICU mortality was higher RDW was greater than 14.5%. We also found positive correlation between RDW and ICU mortality scores.

Key words: Red cell distribution width (RDW), intensive care unit (ICU), mortality scoring systems, accuracy

Introduction

Red cell distribution width (RDW) level is a hemogram test parameter that reflects the measurement of red cell dimensions. RDW generally increases in cases of ineffective erythropoiesis or increased red cell destruction. Studies conducted in recent years have revealed the usefulness of RDW as a new prognostic marker in varied conditions, including cardiovascular, thromboembolic and neurological diseases; sepsis, trauma; and acute and chronic inflammatory disorders (1-10). Furthermore, studies have shown the relationship between high RDW levels and high mortality rates at the time of admission to the intensive care unit (11-14). Clinicians need models to estimate the mortality of patients in the intensive care unit (ICU). ICU scoring systems use a large number of variables that are often observed only among critically ill patients (e.g., arterial blood gas measurements). It is not known which of these scores provide the best performance for patients in the ICU. The Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, and Sequential Organ Failure Assessment (SOFA) scores are the most commonly used scoring systems for ICU patients (15-17).

In this study, we examined a cohort of ICU patients to determine association between the prognostic scores and RDW for prediction of mortality at a single centre in Turkey.

Methods

This retrospective cohort study was conducted in a 9-bed mixed ICU of a tertiary hospital from January to December 2013. Patients with hematologic disorders, severe anemia, inflammatory disease, iron supplementation

therapy, venous thrombosis, red blood cell transfusion, hepatitis B or C, untreated thyroid disease, and severe liver and/or renal insufficiency and trauma patients with excessive blood loss, were excluded from the study.

109 ICU patients were enrolled into the study requiring ICU admission following an elective or emergent surgical procedure, trauma and severe medical disease. Patient demographic data, etiology of ICU admission, length of ICU stay (LOS), mechanical ventilation (MV) support, continuous inotropic support, physiologic parameters including fever, heart rate, mean arterial pressure (MAP), daily urine output, presence of sepsis were abstracted from each patient record.

Laboratory data including hemoglobin, RDW, mean corpuscular volume (MCV), hematocrit level (Htc), white blood cell count (WBC), neutrophil ratio (Neu), platelet count (PLT), blood glucose, blood urea nitrogen (BUN), creatinine, calcium level, hepatic and cholestasis enzymes, lactate dehydrogenase (LDH) levels, arterial and venous blood gas analyses (partial pressure oxygen, pH, bicarbonate and base excess) were also collected on patient admission. The reference range for RDW in our laboratory is 11.5–14.5%. APACHE II, SOFA Score and SAPS II Score were calculated on admission.

The primary outcome measure was determined as ICU mortality, defined as death before ICU discharge for any reason.

Table 1. Univariate analyses of demographic and clinical parameters of survivor and non-survivor groups.

	Survivors (n=72, %)	Non-Survivors (n=37, %)	Total (n=109)	p value, Univariate Analysis
Male Sex	35 (48.61%)	20 (54.05%)	55 (50.5%)	0.369
Age (years)	62±19	73±16	72 (23-90 y)	0.005
APACHE II	12±5	22±8	15.34±7.74	<0.001
SOFA	3.49±1.94	9.16±3.42	5.41±3.69	<0.001
SAPS II	31.94±11.55	56.35±16.39	40.22±17.66	<0.001
Comorbidity				
None	38 (52.77%)	19 (51.35%)	57 (52.29%)	0.524
One	31 (43.05%)	16 (43.24%)	47 (43.11%)	0.552
Two and more	3 (4.16%)	2 (5.40%)	5 (4.58%)	0.572
Malignancy	10 (13.88%)	8 (21.62%)	18 (16.51%)	0.476
Admission Etiology				
Medical				
Emergent	16 (22.22%)	12 (32.43%)	28 (25.68%)	0.390
Others	30 (41,67%)	16 (43.24%)	46 (42.20%)	0.379
Postoperative				
Elective	21 (29.17%)	8 (21.62%)	29 (26.60%)	0.187
Trauma	5 (6.94%)	1 (2.70%)	6 (5.50%)	0.446
Length of ICU stay	5 (2-45)	10 (2-82)	6 (2-82 days)	0.001
Mechanical ventilator support	7 (9.72%)	33 (89.18%)	40 (36.69%)	<0.001
Inotropic support	2 (2.77%)	20 (54.05%)	22 (20.18%)	<0.001
Urine output, oligurie (<500cc/day)	4 (5.55%)	11 (29.72%)	15 (13.76%)	0.001
Sepsis	24 (33.33%)	25 (67.56%)	49 (44.95%)	0.001
Blood culture, positive	6 (8.33%)	19 (51.35%)	25 (22.93%)	<0.001
WBC (x10^3/µL)	10.99±4±.92	12.58±4.38	11.52±4.87	0.035
Hemoglobin (mg/dl)	12.20±2.32	11.33±2.86	11.9±2.35	0.019
Hematocrit (%)	37.17±6.58	36.15±9.18	36.82±7.53	0.207
Platelet (x10^3/µL)	203.96±83.95	213.57±109.58	207.2±93	0.977
RDW (%)	14.96±2.47	16.94±3.05	15.62±2.82	<0.001
Glucose (mg/dl)	136.61±59.99	151.32±87.89	141.6±70.6	0.595
BUN (mg/dl)	52.38±37.11	83.30±57.62	62.87±47.2	0.005
Creatinine (mg/dl)	1.14±1.11	1.42±0.89	1.23±1.04	0.010
Ca (mg/dl)	8.31±1.05	8.11±0.91	8.25±1.02	0.202
Albumin (g/L)	34.05±8.08	28.61±9.58	32.20±8.95	0.008
LDH (U/L)	443 (193-2400)	540 (261-15610)	479 (193-15610)	0.002
Bilirubin (mg/dl)	0.5 (0.1-5.2)	0.7 (0.3-14.1)	1.12 (0.1-14.1)	0.014
Bicarbonat (mmol/L)	24.74±4.47	20.90±7.42	23.39±5.93	0.013

APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, SAPS II: Simplified Acute Physiology Score, ICU: Intensive care unit, RDW: Red cell distribution width, WBC: White blood cell count, BUN: blood urea nitrogen, Ca: Calcium LDH: Lactate dehydrogenase

Table 2. Multivariate logistic regression model for prediction of ICU mortality.

Variables	Odds Ratio	95% Confidence Interval	p value
SAPS II	1.03	1.009-1.57	0.006
RDW	1.23	1.080-1.457	0.002

SAPS II: Simplified Acute Physiology Score, RDW: Red cell distribution width

Table 3. Correlations between RDW and ICU mortality predicting scoring systems

Variables	r	p value
APACHE II	0.010	0.001
SOFA	0.014	0.000
SAPS II	0.041	0.000

(APACHE II: Acute Physiology and Chronic Health Evaluation SOFA: Sequential Organ Failure Assessment, SAPS II: Simplified Acute Physiology Score)

Ethical approval were obtained from the Ankara Numune Training and Research Hospital (2015-1021)

Statistical Analyses

Skewness and Kurtosis test were used to assess normality. The normally distributed data was presented as mean ± SD (standard deviation) and non-normally distributed data was presented as median value (interquartile range). The Spearman's rank correlation was used to define a correlation between scoring systems, and RDW. Baseline characteristics between survivors and non-survivors were compared with an unpaired Student's t-test or the Mann-Whitney U test for continuous variables and a $\chi 2$ test or Fisher's exact test for categorical variables. Cox regression analyses was conducted to identify the independent risk factors associated with ICU mortality, including all variables with a p value <0.10 in the univariate analysis (using a stepwise forward regression model). Receivers operating characteristic (ROC) curves were used to examine the performance of variables in predicting ICU mortality. The area under the curve (AUC, also known as C-index) was calculated from the ROC curve. Hosmer-Lemeshow method was used to test the goodness-of-fit of the regression model. All statistical procedures were performed with SPSS 15.0 (SPSS Inc, Chicago, Illinois). The p-value for statistical significance was p<0.05.

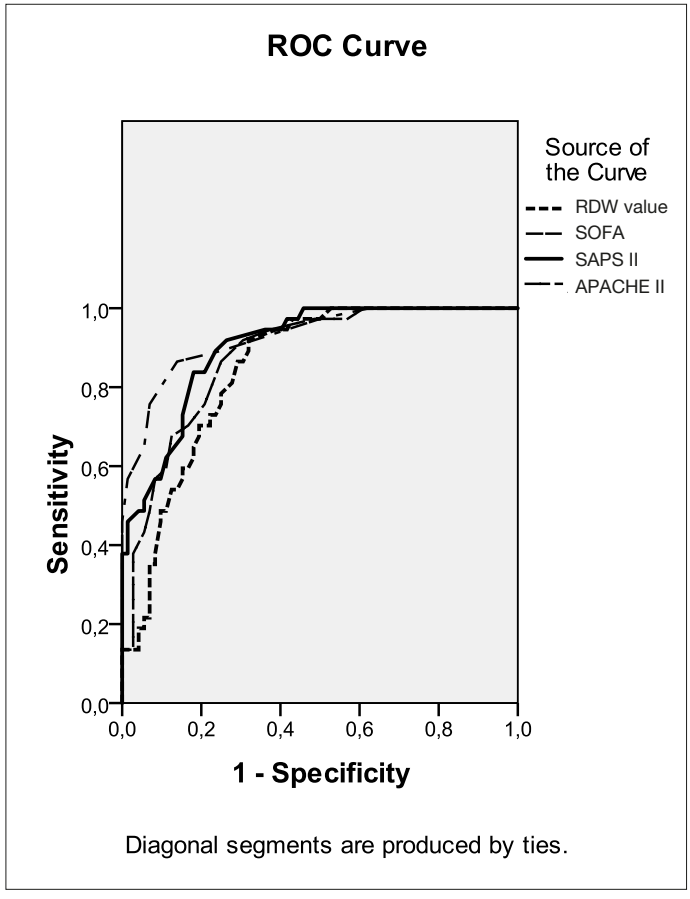

Figure 1. Diagnostic performances of RDW and mortality predicting scoring systems

Results

Median age of the patients was 72 years (23-90). Male-female ratio was 1.01 (55/54). ICU admissions etiology was medical in 74 (67.9%) patients including cerebral vascular disease in 16 (14.7%), pneumonia in 11 (10.1%), sepsis in 7 (6.4%), drug intoxication in 4 (3.7%), acute renal failure in 5 (4.6%), chronic obstructive pulmonary disease in 8 (7.3%), cardiovascular diseases in 3 (2.7%), malignancy in 5 (4.6%), poor general condition in 15 (13.8%) and was postoperative in 35 (32.1%) patients who were admitted to ICU over 24h following an emergent or elective procedure.

Fifty-two (47.7%) of the patients had co-morbid diseases, including hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease and malignancy. Eighteen patients (16.5%) had malignancy, 3 (2.8%) patients had heart failure, 7 (6.4%) patients had chronic obstructive pulmonary disease, 8 (7.3%) patients had diabetes mellitus, 14 (12.8%) patients had hypertension, 3 (2.8%) patients had diabetes mellitus and hypertension, 4 (3.7%) patients had coronary artery disease, 2 (1.8%) patients had diabetes mellitus, hypertension and coronary artery disease, 9 (8.3%) patients had Alzheimer's disease and 2 (1.8%) patients had epilepsy.

Mean APACHE II, SOFA, and SAPS II scores on admission were 15.34±7.74, 5.41±3.69, and 40.22±17.66, respectively.

The demographic, clinical characteristics of the patients and etiology of ICU admissions were demonstrated in Table 1. Median length of ICU stay was 6 (2-82) days. Thirty seven (33,9%) patients died during ICU stay. There were significant positive correlations between RDW and APACHE II, SOFA and SAPS II scores (Table 2).

RDWs were significantly higher in non-survivors (16.94±3.05 versus 15.62±2.82, p<0.001). The optimal cutoff value of RDW for prediction of mortality according to ROC analyses was 14.5. Mortality rate was 18.9% if RDW≤14.5 and 81.1% if RDW >14.5.

Regression models for short-term mortality

Univariate analyses demonstrated admission APACHE II, SOFA, and SAPS II scores, WBC, Hb level, RDW, LDH, albumin level, blood BUN, creatinine, bilirubin level, age, presence of sepsis, mechanical ventilation support and cardiac inotropic support were associated with mortality. In multivariate model, RDW and SAPS II score were independent significant factors for ICU mortality (Table 3). The Hosmer-Lemeshow goodness of fit test demonstrated a good model (x^2=1.936, p=0.983). Discriminating power of each mortality predicting score and RDW was identified by area under the curve (AUC) with ROC curve analyses. APACHE II, SOFA, SAPS II scoring systems and RDW values showed similar diagnostic performance to identify the non-survivors (AUC were 0.879, 0.928, 0.903 and 0.846, respectively) (Figure 1).

Discussion

There are studies showing that initial high RDW values are associated with mortality in intensive care patients (14,18). Our results are consistent with previous studies showing that ICU mortality was higher when increased RDW was present. Our results are in compliance with previous studies showing that ICU mortality was higher when increased RDW was present.

Scoring systems have been developed to measure the severity of the disease and the prognosis of patients in the ICU. These measurements are beneficial in making clinical decisions, standardizing studies, and comparing the quality of patient care in different ICUs (16).

APACHE II (15), SAPS II (16), and SOFA (17) are widely accepted and used scoring systems. We have found a positive correlation between RDW levels and ICU mortality scores. The latest updates of these scores have acceptable discrimination and calibration. However, estimated scoring systems have important limitations in terms of data collection, mortality calculation, effectiveness and cost. RDW is a quantitative measure of anisocytosis and is calculated by dividing the standard deviation of the erythrocyte volume by MCV. It increases in various conditions. The relation between RDW and mortality is not known completely. Several hypotheses for this relation have been proposed and the most popular ones include inflammatory response and oxidative stress. In animal models, RDW is associated with the presence of certain oxidative stress-related molecules, such as reactive oxygen species (ROS), superoxide dismutase (SOD), and glutathione peroxidase (19).

Previously, Zhang et al. found that high RDW was associated with increased hospital mortality and a longer stay in the ICU. However, the ability of RDW to distinguish patients with a better survival prognosis is suboptimal and repeated RDW measurements did not offer additional clinical value in predicting results (13). Wang et al. and Bazick et al. also found that RDW had a strong relationship with all causes of mortality in ICU patients(11,20).

Including RDW in scoring systems can improve mortality estimates. Hunziker et al. found that RDW was a prognostic marker in ICU patients and it significantly improved the SAPS risk classification in a large group (21). As proved by Wang et al.(11) (from 0.832 ± 0.020 to 0.885 ± 0.017, P <0.05) and Meynaar et al. (12), combining the RDW and APACHE II score increases the area under the curve (AUC) to predict ICU mortality. Recently, Loveday et al. found that RDW is an independent mortality predictor in ICU patients and the inclusion of RDW in APACHE III increases the mortality estimate marginally (22). However, Lorente et al. could not find a correlation between RDW and WBC or C-reactive protein (CRP). The lack of correlation between RDW and WBC and RDW and CRP is consistent with the results of Meynaar et al.(12) and supports the conclusion that RDW does not stem from inflammation(23).

RDW is a part of routine complete blood count analysis and does not generate any additional costs. This feature of RDW makes it an easily accessible variable. If other studies can support our findings, RDW could become a part of more commonly used and more advanced disease severity scoring tests (e.g., APACHE IV, SAPS III), thus increasing their accuracy.

Our study has certain limitations. First, we did not examine the causes of high RDW, such as iron or vitamin B12 deficiency, which can disrupt the relationship between RDW and negative outcomes. Second, this is a single-center study. A study with multiple centers would reduce the concerns about the case mixture and benefit from a larger sample size.

Conclusion

We found that ICU mortality was higher when RDW was greater than 14.5%. We also found a positive correlation between RDW and commonly used ICU mortality scores. This might suggest that instead of using scoring systems which require computation of multiple variables we could utilize a single easily accessible laboratory value (ie RDW) to predict mortality in ICU patients.

Acknowledgements

We thank our colleagues from Ankara Numune Education and Research Hospital who provided insight and expertise that greatly assisted the research, although they may not agree with all of the interpretations/conclusions of this paper.

AUTHOR CONTRIBUTIONS:

Concept: AE, KS; **Design:** AE, KS; **Supervision:** DE, MT; Resources: AE, EMU, MT; **Materials:** AE, KS, EMU, MT; **Data Collection and/or Processing:** AE, EMU, KS; **Analysis and/or Interpretation**: AE, MT, DE; **Literature Search:** AE, KS, DE, EMU, MT; **Writing Manuscript**: AE, KS; **Critical Review:** AE, KS, DE, EMU, MT.

Ethics Committee Approval: Ethical approval were obtained from the Ankara Numune Training and Research Hospital(2015-1021) (Date: 22/07/2015).

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Patel KV, Semba RD, Ferrucci L, et al. Red cell distribution width and mortality in older adults: a meta-analysis. J Gerontol A Biol Sci Med Sci 2010;65A:258–65. [CrossRef]
2. Perlstein TS, Weuve J, Pfeffer MA, et al. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med 2009;169:588–94. [CrossRef]
3. Ku NS, Kim HW, Oh HJ, et al. Red blood cell distribution width is an independent predictor of mortality in patients with gram-negative bacteremia. Shock (Augusta, Ga) 2012;38:123–7. [CrossRef]
4. Hong N, Oh J, Kang SM, et al. Red blood cell distribution width predicts early mortality in patients with acute dyspnea. Clin Chim Acta 2012;413:992–7. [CrossRef]
5. Fatemi O, Paranilam J, Rainow A, et al. Red cell distribution width is a predictor of mortality in patients undergoing percutaneous coronary intervention. J Thromb Thrombolysis 2013;35:57–64. [CrossRef]
6. Sadaka F, O'Brien J, Prakash S. Red cell distribution width and outcome in patients with septic shock. J Intensive Care Med 2013;28:307–13. [CrossRef]
7. Majercik S, Fox J, Knight S, et al. Red cell distribution width is predictive of mortality in trauma patients. J Trauma Acute Care Surg 2013;74:1021–6. [CrossRef]
8. Senol K, Saylam B, Kocaay F, et al. Red cell distribution width as a predictor of mortality in acute pancreatitis. Am J Emerg Med 2013;31:687–9. [CrossRef]
9. Kim CH, Park JT, Kim EJ, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care 2013;17:R282. [CrossRef]
10. Bilgic I, Dolu F, Senol K, et al. Prognostic significance of red cell distribution width in acute mesenteric ischemia. Perfusion 2014;30:161–5. [CrossRef]
11. Wang F, Pan W, Pan S, et al. Red cell distribution width as a novel predictor of mortality in ICU patients. Ann Med 2011;43:40–6. [CrossRef]
12. Meynaar IA, Knook AH, Coolen S, et al. Red cell distribution width as predictor for mortality in critically ill patients. Neth J Med 2013;71:488–93. http://www.njmonline.nl/getpdf.php?id=1376
13. Zhang Z, Xu X, Ni H, et al. Red cell distribution width is associated with hospital mortality in unselected critically ill patients. J Thorac Dis 2013;5:730–6. [CrossRef]
14. Han Y-Q, Yan L, Zhang L, et al. Red blood cell distribution width provides additional prognostic value beyond severity scores in adult critical illness. Clin Chim Acta 2019;498:62–7. [CrossRef]
15. Knaus WA, Draper EA, Wagner DP, et al. APACHE II. a severity of disease classification system. Crit Care Med 1985;13:818–29. [CrossRef]
16. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957–63. [CrossRef]
17. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/ failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intens Care Med 1996;22:707–10. [CrossRef]
18. Otero TMN, Canales C, Yeh DD, et al. Elevated Red Cell Distribution Width at Initiation of Critical Care Is Associated With Mortality in Surgical Intensive Care Unit Patients. J Crit Care 2016;34:7–11. [CrossRef]
19. Ghaffari S. Oxidative stress in the regulation of normal and neoplastic hematopoiesis. Antioxid Redox Signal 2008;10:1923–40. [CrossRef]
20. Bazick HS, Chang D, Mahadevappa K, et al. Red cell distribution width and all-cause mortality in critically ill patients. Crit Care Med 2011;39:1913–21. [CrossRef]
21. Hunziker S, Celi LA, Lee J, et al. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patients. Crit Care 2012;16:R89. [CrossRef]
22. Loveday S, Sinclair L, Badrick T. Does the addition of RDW improve current ICU scoring systems? Clin Biochem 2015;48:569–74. [CrossRef]
23. Lorente L, Martin MM, Abreu-Gonzalez P, et al. Red blood cell distribution width during the first week is associated with severity and mortality in septic patients. PloS ONE 2014;9:e105436. [CrossRef]