ORIGINAL ARTICLE

Red blood cell distribution width as a predictor of outcome in Intensive Care Unit: a retrospective cohort study

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ABSTRACT

Aim To evaluate the predictive significance of the red blood cell distribution width (RDW) >14.5 at admission to the Intensive Care Unit (ICU) on outcome parameters: length of hospital stay (LOHS), incidence of hospital mortality, 30-day mortality and 30-day survival after hospital discharge in unselected (surgical and non-surgical) critically ill patients.

Methods A total of 325 surgical and non-surgical critically ill patients were divided based on the RDW value at admission to the ICU into two groups: Group 1 (RDW >14.5) and Group 2 (RDW ≤14.5). Demographic and clinical parameters, laboratory findings, treatment and outcome parameters were compared between the groups. The predictive significance of RDW>14.5 on outcome parameters was analysed using linear regression analysis and univariate and multivariate logistic regression analysis, as appropriate.

Results In Group 1, LOHS was higher (19.77±15.15; p<0.000) as was the prevalence of hospital mortality (46.6%; p<0.0523), while 30-day survival after hospital discharge was lower (52.9%; p>0.026) compared to Group 2. RDW >14.5 was positively linearly related (r=0.64; r^2=0.40; p=0.000) with LOHS. RDW >14.5 predicted the prevalence of in-hospital mortality with a 73.7% positive predictive value (AUC 0.62; sensitivity 70.1%; specificity 59.5%; p<0.05) and 30-day survival after hospital discharge with a 34.5% negative predictive value (AUC 0.45; sensitivity 58.3%; specificity 68.7%; p<0.05).

Conclusions RDW value >14.5 at admission to the ICU can predict prolonged hospital stay, higher mortality and lower survival rate. RDW >14.5 may be an inexpensive and widely available early warning to redirect diagnostic and therapeutic decisions and improve outcomes.

Key words: critically ill patients, erythrocytes, logistic regression, survival rate

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INTRODUCTION

Red blood cell distribution width (RDW) reflects the degree of heterogeneity of the erythrocyte volume and is calculated as the standard deviation of red blood cell size divided by the mean corpuscular volume (1). The result of the equation is multiplied by 100 to express the results as a percentage. The reference range of red blood cell distribution width (RDW) value is between 11.5-14.5% (2). RDW is a simple, readily available parameter, routinely included in the automated analysis of the complete blood count with other haematological indices at no additional cost.

Erythrocytes have variations in size, becoming smaller over a lifespan of approximately 120 days (3). An increase in the RDW indicates a profound imbalance in erythrocyte homeostasis, resulting in ineffective erythropoiesis and abnormal survival of red blood cells. Many clinical conditions are associated with RDW >14.5% such as inflammatory and haematological diseases, cardiovascular and thrombotic disorders, oxidative stress, obesity or smoking (1). Elevated RDW is a predictor of all-cause and cause-specific mortality in the general adult population (4).

Previous studies have analysed the predictive value of RDW in critically ill patients (5-9). The study conducted in a cohort of 602 non-surgical critically ill patients in China found that elevated RDW was associated with mortality in the intensive care unit (ICU) (5). A large study from the USA confirmed the predictive value of RDW bloodstream infection in the ICU (6). Recent studies have revealed a relationship between increased RDW value and prognosis in critically ill patients with severe pancreatitis (7), acute kidney injury (8), and acute respiratory distress syndrome (ARDS) (9).

Despite these findings, RDW is not often used in routine clinical practice. Moreover, it remains unclear from the previous studies whether RDW can improve state-of-the-art risk prediction in unselected (surgical and non-surgical) critically ill patients (5-9). Since it is very important to find and use inexpensive and accessible routine tools that can improve the scoring and selection of patients at ICU admission, we conducted a retrospective cohort study.

The aim of this study was to evaluate the predictive significance of the RDW >14.5 at ICU admission on outcome parameters: length of hospital stay, prevalence of hospital mortality, 30-day mortality and 30-day survival after hospital discharge in unselected (surgical and non-surgical) critically ill patients. We hypothesized that a RDW value >14.5 at ICU admission can predicts serious outcomes in critically ill patients (prolonged hospital stay, higher mortality and lower survival rate).

PATIENTS AND METHODS

Patients and study design

This observational, retrospective, cross-sectional, single-centre study was conducted at the Department of Anaesthesiology and Intensive Care Unit of the Cantonal Hospital Zenica from 1 January 2022 to 31 December 2022.

The study included 325 adult, critically ill patients, who met the study criteria. Inclusion criteria were the first admission to the ICU and availability of all study data in medical records. Exclusion criteria were: age <18 years, pregnancy, history of haematological, inflammatory, immunological and liver disease, hospitalisation in the ICU <48 hours, readmission to the ICU, and incomplete medical records.

The patients with RDW value below the range of normality (11.5-14.5) at ICU admission were excluded from the study.

The patients were divided into two groups based on the value of RDW at admission to the ICU. An RDW value of 14.5 was used as a cut-off value, according to previous studies and clinical significance (9). Group 1 included patients with a RDW value >14.5 at admission to the ICU and Group 2 patients with a RDW value 11.5-14.5

The Institutional Ethics Committee approved the study (No. 00-03-35-286-11/23). All study procedures were in accordance with the Declaration of Helsinki. The data used in the study were anonymous, thereby, an informed consent was waived.

Methods

All study data were extracted from the ICU electronic database. Demographic and clinical parameters, laboratory findings, treatment and outcome parameters were collected. Demographic parameters included age and gender. Clinical parameters involved comorbidities and reasons of ICU admission.

Laboratory findings included: RDW value, haemoglobin, white blood cells (WBC), platelets, glucose, urea, creatinine, C-reactive protein (CRP), albumin and lactate. Laboratory findings were monitored in three time points: within 24 hours of admission to the ICU (T1), on the day of discharge from the ICU (T2), and on the day of discharge from hospital (T3).

Treatment parameters included the prevalence of mechanical ventilation, vasopressors therapy, surgical procedures, transfusion therapy, renal replacement therapy and non-surgical treatment of polytrauma. The observed outcome parameters were length of hospital stay (LOHS), incidence of hospital mortality, 30-day mortality after hospital discharge and 30-day survival after hospital discharge.

Demographic and clinical parameters, laboratory findings, treatment and outcome parameters were compared between the group of patients with RDW value >14.5 and the group with RDW value ≤14.5 at admission into the ICU.

In addition, the predictive significance of the RDV >14.5 at admission to the ICU on outcome parameters was determined: length of hospital stay (LOHS), prevalence of hospital mortality, 30-day mortality after hospital discharge and 30-day survival after hospital discharge.

Statistical analysis

The normality of the distribution data was tested by the Kolmogorov-Smirnov test. Qualitative variables were presented as the frequency (percentages) and compared with Parson's $\chi 2$ test. Quantitative variables were presented as the means (± standard deviation) and tested by Student's *t* test and Levene's Test for equality of variances for repeated measurements. The relationship between RDW1 (at ICU admission) and the length of hospital stay was determined by linear regression analysis. The predictive accuracy of RDW1 on the incidence of hospital mortality, 30-day mortality and 30-day survival was analysed using univariate and multivariate logistic regression analysis. Area under curve (AUC) with 95% confidence interval (CT), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. All tests were considered statistically significant with a two-sided p value <0.05 for difference.

RESULTS

Among 611 patients admitted to the Department of Anaesthesiology and Intensive Care Unit of the Cantonal Hospital Zenica from 1 January 2022 to 31 December 2022, 286 patients did not meet the eligibility criteria and were excluded leaving 325 patients for the analysis: 206 patients in Group 1 (RDW >14.5) and 119 patients in Group 2 (RDW ≤14.5) (Figure 1). A statistically significant difference was found in the age (p<0.025) and gender (p<0.040) between the two groups. Patients in Group 1 were older and there were more women compared to Group 2. The average number of comorbidities per patient was higher in Group 1 (1.28±0.95) than in Group 2 (0.91±0.81) (p=0.061). A statistically

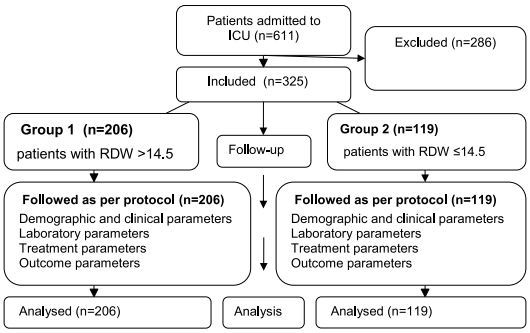

Figure 1. Flow chart of the study protocol

Table 1. Comparison of demographic and clinical parameters between the groups

Parameter	Patients group		p
	Group 1 (n=206)	Group 2 (n=119)	
Mean age (±SD) (years)	62.59 (±14.47)	58.42 (±16.89)	0.025
Female/Male No (%)	97/109 (47.1/52.9)	44/75 (37/63)	0.040
Comorbidities (Mean±SD)	1.28 (±0.95)	0.91(±0.81)	0.061
Comorbidities	**No** (%)		
Hypertension No (%)	122 (59.2)	55 (46.2)	0.023
Diabetes mellitus	52 (25.2)	20 (16.8)	0.05
COPD	27 (13.1)	5 (4.2)	0.009
Coronary disease	42 (20.4)	23 (19.3)	0.818
Chronic renal disease	11 (5.3)	3 (2.5)	0.225
Cerebrovascular disease	13 (6.3)	3 (2.5)	0.125
Reasons of ICU admission (Mean±SD)	4.74 (±2.67)	4.46 (±2.83)	0.071
Reasons for ICU admission	**No** (%)		
Surgical intervention No (%)	100 (48.5)	48 (40.3)	0.007
Respiratory failure	53 (25.7)	41 (34.5)	0.005
Sepsis	18 (8.7)	5 (4.2)	0.128
Resuscitation	10 (4.9)	4 (3.4)	0.751
Neurological disease	12 (5.8)	9 (7.6)	0.643
Polytrauma	6 (2.9)	7 (5.9)	0.257
Acute coronary injury	5 (2.4)	4 (3.4)	0.804
Acute renal failure	2 (1)	1 (0.8)	0.981

Group 1, patients with RDW >14.5; Group 2, patients with RDW ≤14.5; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit

Table 2. Comparison of laboratory parameters between the groups

Parameter (range of normality)	Time	Patients group		95% CI	p
		Group 1 (n=206)	**Group 2** (n=119)		
	T1	16.51 (±2.65)	13.09 (±0.70)	2.9-3.9	0.000
RDW (11.5–14.5%)	T2	16.74 (±2.61)	13.38 (±0.73)	2.8-3.9	0.000
	T3	16.57 (±2.50)	13.15 (±0.82)	2.8-3.9	0.000
	T1	121.70 (±75.03)	132.01 (±22.62)	-24.2-3.5	0.145
Haemoglobin (138-157 x10^9/L)	T2	107.85 (±18.59)	120.92 (±17.29)	-17.1- -8.9	0.000
	T3	114.38 (±16.51)	126.86 (±15.42)	-17.0- -7.9	0.000
	T1	12.92 (±6.66)	13.76 (±6.23)	-2.3-0.6	0.267
WBC (3.4-10 x10^9/L)	T2	12.28(±10.18)	12.35 (±5.37)	-2.0-1.9	0.944
	T3	8.98(±4.10)	9.10 (±3.28)	-1.2-0.9	0.819
	T1	232.23 (±119.73)	233.23 (±90.67)	-25.9-23.9	0.938
Platelets (150-400 x10^9/L)	T2	217.71 (±126.31)	219.37 (±86.04)	-27.3-23.9	0.899
	T3	293.64 (± 155.55)	286.29 (±110.39)	-32.1-46.8	0.714
	T1	8.78 (±3.71)	8.69 (±3.77)	-0.7-0.9	0.845
Glucose (3.3-6.1 mmol/L)	T2	7.44 (±3.53)	7.61 (±3.48)	-0.9-0.6	0.662
	T3	6.23 (±2.68)	6.28 (±2.05)	-0.6-0.7	0.787
	T1	11.10 (±9.38)	8.55 (±6.23)	0.6-4.4	0.009
Urea (1.7-8.3 mmol/L)	T2	12.71 (±11.00)	9.02 (±6.79)	1.4-5.8	0.001
	T3	6.85 (±5.86)	6.22 (±3.01)	-0.7-2.0	0.374
	T1	130.84 (±134.08)	90.20 (±62.50)	14.9-66.3	0.002
Creatinine (59-106 mmol/L)	T2	123.92 (±117.83)	76.15 (±54.03)	25.2-70.2	0.000
	T3	80.54 (±103.71)	61.56 (±21.02)	-4.2-42.1	0.108
	T1	70.80 (±79.65	41.50 (±51.09)	13.3-45.2	0.000
CRP (<5.0 mg/L)	T2	70.52 (±74.44)	32.29 (±33.19)	24.0-52.4	0.000
	T3	28.50 (±32.35)	9.14 (±8.60)	12.0-26.6	0.000
	T1	29.48 (±6.89)	33.34 (±5.58)	-5.3- -2.3	0.000
Albumin (35-48 g/L)	T2	28.11(±4.15)	31.18 (±4.73)	-4.0- -2.0	0.000
	T3	31.25 (±3.75)	35.10 (±3.63)	-4.8- -2.7	0.000
	T1	2.95 (±1.80)	2.51 (±1.09)	0.0-0.8	0.015
Lactate (0.36-1.39 mmol/L)	T2	2.83 (±2.13)	2.37 (±1.25)	0.0-0.8	0.036
	T3	1.86 (±1.07)	1.41 (±0.63)	0.1-0.7	0.001

Data are presented as mean and standard deviation (±); Group 1, patients with RDW >14.5; Group 2, patients with RDW ≤14.5; T1, at admission to intensive care; T2, on discharge from intensive care; T3, on discharge from hospital; CI, confidence interval of the difference; RDW, red blood cells distribution width; WBC, white blood cells; CRP, C-reactive protein;

significant higher prevalence of hypertension (p<0.023), diabetes mellitus (p<0.05) and COPD (p<0.009) was recorded in Group 1. Regarding the reasons for ICU admission, surgical intervention (p<0.007) was more frequent in Group 1, while respiratory failure (p<0.005) was more common in Group 2 (Table 1).

Comparison of laboratory parameters between groups showed that the mean value of RDW remained higher in Group 1 during the entire time period (p=0.000). Increased RDW was accompanied by lower mean values of haemoglobin on the day of discharge from ICU (p<0.000) and on the day of discharge from hospital (p<0.000), as well as lower mean values of albumin at all time points (p<0.000). The mean values of urea and creatinine were higher at admission to the ICU (p<0.009 and p<0.002, respectively) and on the day of discharge from ICU (p<0.001 and p<0.000, respectively) compared to Group 2. Statistically significant higher mean values of CRP (p<0.000) and lactate (p<0.05) were detected during all observed time periods in Group 1 (Table 2). The use of vasopressors (63.1%; p<0.005), surgical procedures (58.3%; p<0.025), transfusions (68.0%; p<0.000) and renal replacement therapy (10.3%; p<0.01) were more frequent in Group 1. In terms of outcome parameters, LOHS

Table 3. Comparison of treatment parameters and outcomes between the groups

Parameter	No (%) of patients in the group		p
	Group 1 (n=206)	**Group 2** (n=119)	
Treatment No (%)			
Mechanical ventilation	158 (76.7)	96 (80.7)	0.404
Vasopressors	130 (63.1)	56 (47.1)	0.005
Surgical procedures	120 (58.3)	54 (45.4)	0.025
Transfusion	140 (68.0)	48 (40.3)	0.000
Renal replacement therapy	21 (10.3)	3 (2.5)	0.01
Polytrauma without surgery	9 (4.4)	7 (5.9)	0.543
Outcomes No (%)			
Incidence of hospital mortality	96 (46.6)	41 (35.5)	0.023
30-day mortality	1 (0.3)	0	/
30-day survival	109 (52.9)	78 (65.5)	0.026
LOHS (mean±SD) ((days))	19.77 (±15.15)	14.26 (±8.33)	0.000

Group 1, patients with RDW >14.5; Group 2, patients with RDW ≤14.5; LOHS, length of hospital stay

(19.77±15.15; p<0.000) and the prevalence of hospital mortality (46.6%; p<0.0523) were higher, while 30-day survival after hospital discharge was lower (52.9%; p>0.026) in Group 1.

The linear regression method revealed that the value of RDW >14.5 and LOHS were positively linearly related (r=0.64; r^2=0.40; 95% CI: 2.55-8.47; p = 0.000). An increase in RDW value by 1% meant an increase in LOHS by 5.11 days. A value of RDW >14.5 at admission to the ICU displayed 73.7% PPV on the prevalence of hospital mortality and 34.5% NPV on 30-day survival after hospital discharge (Table 4).

Table 4. Predictive significance of RDW>14.5 on outcome parameters

Variable (%)	Hospital mortality	30-day mortality	30-day survival
AUC	0.62	0.50	0.45
Sensitivity	70.1	100	58.3
Specificity	59.5	36.7	68.7
PPV	73.7	0.5	51.9
NPV	34.5	100	34.5
95% CI	0.45-0.65	0.32-1.00	0.30-0.65
p	0.05	0.526	0.05

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; CI, Confidence interval

DISCUSSION

Timely prediction of serious outcomes is essential for clinicians to optimize patient triage and treatment strategy for multiple conditions in critically ill patients. The present retrospective, cross-sectional, single-centre study investigated the predictive significance of RDW >14.5 at ICU admission on outcome parameters: LOHS, incidence of hospital mortality, 30-day mortality and 30-day survival after hospital discharge in unselected (surgical and non-surgical) critically ill patients. In this study, RDW >14.5 was associated with prolonged LOHS. A 1% increase in RDW prolonged LOHS by 5.11 days. RDW >14.5 at ICU admission predicted prevalence of hospital mortality with 73.7% PPV and 30-day survival rate after hospital discharge with 34.5% NPV.

In the current study, the patients with RDW >14.5 were older than the patients with RDW ≤14.5. Age distribution among the groups confirmed the strong dependence of elevated RDW on age (10,11). Elevated RDW is associated with a natural decline in the physiological functions of erythropoiesis, reflecting the underlying aging process (12). The gender distribution of elevated RDW is not consistent across studies. In our study, elevated RDW was more common in men, supporting the findings of Yan et al. (13). Conversely, Li et al. found a higher RDW in women (14).

Regarding the average number of comorbidities per patients and reasons for ICU admission, the groups were comparable. Surgical intervention, respiratory failure and sepsis were the main reasons for ICU admission in both groups. Each of these conditions, as well as all other reasons for admission to the ICU, result in the process of stress erythropoiesis. Stress erythropoiesis is characterized by impaired bone marrow function, inhibited maturation of erythrocytes, inhibited erythropoietin, increased release of large premature erythrocytes into the peripheral circulation and increased RDW (15).

The mechanism of the association between increased RDW and serious outcomes is not clear.

Several conditions occurring simultaneously in critical illness are hypothesized to contribute to stress erythropoiesis but also multiple organ disfunction and mortality: inflammation (16), oxidative stress (17), nutritional deficiency and anaemia (18), neurohormonal responses (19), renal dysfunction (20) and arterial underfilling (1). In our study, many of these conditions were recognized in the group with RDW >14.5. A statistically significantly higher value of CRP and a lower value of albumin reflected a higher intensity of inflammation compared to the group with RDW <14.5. Lower levels of haemoglobin and albumin indicated anaemia (21) and nutritional deficiency (22). Elevated urea, creatinine and lactate, as well as more frequent use of renal replacement therapy were indicators of renal disfunction (23). Elevated lactate and more frequent use of vasopressor therapy were indicators of arterial underfilling (24).

Our study confirmed the association between RDW >14.5 and prolonged LOHS. A 1% increase in RDW value prolonged LOHS by 5.11 days. Similar to our results, Otero et al. found that RDW >14.5 at ICU admission resulted in 13% longer LOHS in mechanically ventilated patients (25). The present study displayed that RDW >14.5 at ICU admission predicted a higher incidence of hospital mortality with moderate discriminative power. It is clear that RDW >14.5 has a certain predictive value for critically ill patients. The

obtained discriminatory power is not optimal due to the heterogeneous clinical presentation and the characteristics of the sample in our study. Researchers reached a stronger discriminatory power of RDW (AUC 0.79) in patients with acute pancreatitis (7). A meta analysis by Zhang et al. included 17 961 patients with sepsis and confirmed that a 1% increase in basal RDW increased the mortality risk by 14% (26).

Our results showed no significant interactions of RDW with 30-day mortality rate in critically ill patients. Wang et al. reported no predictive value of RDW on 30-day mortality among ICU patients with ARDS (9). In the current study, RDW >14.5 predicted 30-day survival rate after hospital discharge with a negative predictive value of 34.5%. The practical significance of the presented results is the possibility of rapid prediction of serious outcomes based on RDW value at ICU admission. The APACHE II (Acute Physiology and Chronic Health Evaluation II) (27) and SOFA (Sequential Organ Failure Assessment) scores (28), commonly used to predict ICU mortality, require many routine variables and take at least 24 hours to calculate.

This study has several limitations. Considering the single-centre retrospective study design and the lack of sampling analysis, bias cannot be excluded. The prehospital RDW value was not considered. Causal relationship between RDW and ICU outcomes was not evaluated. We did not correlate the value of RDW with APACHE or SOFA scores at the admission in ICU. A future multi-centre prospective study with an accurate sample size analysis is needed to provide definitive clinical evidence.

In conclusion, elevated RDW value is a potential marker for severity and outcome assessment in unselected (surgical and non-surgical) critically ill patients. An RDW value >14.5 at ICU admission predicts prolonged hospital stay, higher hospital mortality and lower 30-day survival rate. RDW >14.5 may be considered an inexpensive and widely available early warning to redirect diagnostic and therapeutic decisions and improve outcomes.

FUNDING

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TRANSPARENCY DECLARATIONS

Competing interest: None to declare.

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