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Original Article EMERGENCY MEDICINE

The role of red cell distribution width in predicting 7-day in-hospital mortality in patients with acute ischemic stroke

Mustafa Ahmet Afacan,[1] Ismail Tayfur,[2] Sinem Dogruyol,[1] Burcu Genc Yavuz,[1] Burcu Bayramoglu,[2] Abdullah Algin,[3] Ozlem Tataroglu,[4] Kaan Yusufoglu[1]

[1]Department of Emergency Medicine, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkiye

[2]Department of Emergency Medicine, University of Health Sciences, Sancaktepe Sehit Prof. Dr. Ilhan Varank Research and Training Hospital, Istanbul, Turkiye

[3]Department of Emergency Medicine, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Türkiye

[4]Depermant of Emergency Medicine, University of Health Science, Kartal Dr Lutfi Kirdar Training and Research Hospital, Istanbul, Türkiye

ABSTRACT

OBJECTIVE: Red cell distribution width (RDW) is a hematological parameter that is routinely obtained as part of the complete blood count analysis. An increased RDW level, which helps identify erythrocyte anisocytosis, is also a good indicator of the severity and outcome of some other diseases. The aim of this study was to investigate the predictive power of the serum RDW level for determining (seven-days mortality) of patients with acute ischemic stroke (AIS).

METHODS: A total of 527 adult patients with AIS presenting to our emergency department of tertiary-care hospital were retrospectively enrolled. The baseline characteristics, National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores, reflecting stroke severity and neurological outcome, and serum RDW values were recorded retrospectively. An univariate and multivariate logistic regression analyses were performed to identify independent predictors of seven-days mortality, including serum levels of RDW, age, NIHSS and mRS values.

RESULTS: Serum RDW levels were significantly lower in patients who survived longer than seven-day compared with those who died within the first seven-days (15.36±1.04% v.s 16.61±1.28%, p=0.001). Furthermore, the mean NIHSS score was significantly lower in patients who survived longer than seven-days compared with those who died within the first seven-days. Additionally, the mean mRS score was significantly lower in patients who survived longer than seven-day compared with those who died within the first seven-day (p=0.001). Receiving operator characteristic analysis revealed a cut-off RDW level of 16.2%, with 66.1% sensitivity and 78% specificity, for distinguishing patients who survived longer than seven-days from who died within the first seven-day.

CONCLUSION: The serum RDW level may serve as a guide in diagnostic decision-making to predict neurological outcome and determine the short-term survival of patients with AIS.

Keywords: Acute ischemic stroke; red cell distribution width; hort-term survival.

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Correspondence: Mustafa Ahmet AFACAN, MD. Saglik Bilimleri Universitesi, Haydarpasa Numune Egitim ve Arastirma Hastanesi, Acil Tip Anabilim Dali, Istanbul, Turkiye.
Tel: +90 505 526 79 74 e-mail: drmustafaahmet@hotmail.com

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In 2015, 24.9 million patients worldwide were diagnosed with acute ischemic stroke (AIS), and there were 3.0 million deaths due to this disease [1]. According to the projections for 2030, an additional 3.4 million adults in the USA, representing 3.88% of the adult population, will have had a stroke. This means a 20.5% increase in prevalence from 2012 [2]. An ideal marker for the prediction of mortality and poor prognosis in this disease should be inexpensive, sensitive, specific, and easily accessible. It is an active research field to seek a parameter through blood tests to identify prognostic biomarkers for the mortality prediction in stroke cases. Red cell distribution width (RDW) is a measure of changes in the size of the erythrocyte life span of approximately 120 days [3]. Oxidative and inflammatory processes that have an effect on erythrocytes are considered to be the biological pathways that alter RDW [4]. This parameter is measured automatically as part of a complete blood count (CBC) analysis using Beckman Coulter electrical impedance method. The normal range of RDW can be a very useful clinical marker to demonstrate a healthy state. In-hospital mortality and morbidity are associated with the severity of diseases at admission, although it is also related to duration [5]. In patients with AIS, the timely detection and intervention of the severity of the disease is critical to delay its progression. AIS preserves its position as a paramount cause of in-hospital mortality and morbidity despite all advances in treatment. The determination of early and reliable estimation of functional loss after ischemic stroke should be seen as a precious approach to achieve accurate clinical and treatment management. The National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS) scores are used to determine the severity of AIS. These scores have been improved to predict the mortality and degree of neurologic disability in AIS patients [6]. The uncertainty of biochemical parameters which can be used as an objective in the determination of the severity of AIS patients and the prognosis is one of the most important clinical issue. Therefore, we aimed to investigate the predictive power of the serum RDW level for determing the neurological outcome and the short-term prognosis (seven-day mortality) of patients with AIS.

Highlight key points

- Serum RDW level is an independent predictor of 7-day in-hospital mortality in patients with acute ischemic stroke (AIS); non-survivors had significantly higher RDW values compared with survivors (16.61±1.28% vs. 15.36±1.04%).
- An RDW cut-off value of 16.2% demonstrated strong discriminative ability for early mortality, with an AUC of 0.772, 66.1% sensitivity, and 78% specificity; patients with RDW ≥16.2% had nearly a 7-fold increased risk of 7-day mortality (OR: 6.912).
- Age, NIHSS score, mRS score, and RDW were identified as independent prognostic factors in multivariate analysis, indicating that incorporating RDW into early risk stratification may enhance clinical decision-making in AIS.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the Ethics Committee of the Haydarpasa Numune Training and Research Hospital Faculty of Medicine, University of Health Sciences, HNEAH- KAEK (trial registration no. 2019/71-884). The study population in this retrospective, cross-sectional study consisted of 527 adult patients admitted to the emergency department (ED) of our tertiary care university hospital between January 2015 and June 2018, where they were diagnosed with AIS.

Using the medical record database, we retrospectively reviewed the baseline demographic characteristics, related clinical information, and CBC results (including RDW as a parameter). The baseline demographic characteristics and related clinical information had been obtained from each patient at the time of ED admission. Inclusion criteria; being over 18 years old and diagnosed as AIS in the emergency department. Patients with missing data, those with cancer or anemia (hematocrit <30% or hemoglobin <12 mg/dl for women, hemoglobin <13 mg/dl for men), those receiving ongoing anemia treatment at the time of admission, and those with a previous ischemic stroke within the last year were excluded in order to provide standardization and test the effect of the RDW level for in-hospital mortality. All CBC analyses were conducted using Mindray equipment (model BC-6800). Artificial intelligence–based computer programs were not used in this study.

Statistical Analysis

The Number SPSS 25 Cruncher Statistical System (Stanford University, USA) was used for statistical analysis. Numerical data (e.g. stroke scores; NIHSS; mRS value; and RDW level) are expressed as means±standard deviations (SD), and categorical variables (gender and age) as numbers (n). The suitability of the quan-

Table 1. Distribution of 527 adult patients according to the descriptive characteristics

Variables (%)	Value
Female	43.3 (n=228)
Male	56.7 (n=299)
Age (mean±SD)	68.21±13.51
7-day mortality	22.4 (n=118)
Hypertension	69.3 (n=365)
Atrial fibrillation	11
Coronary artery disease	25.4 (n=134)
Diabetes mellitus	41.7 (n=220)
Smoking	19.5 (n=103)

SD: Standard deviation.

Table 2. Distribution of RDW values, NIHSS score at admission – discharge, Modified Rankin Score and Modified Rankin prognosis

RDW	
Min–Max (Median)	12.3–18.9 (15.6)
Mean±SD	15.65±1.22
NIHSS entry score	
Min-Max (Median)	0-19 (4)
Mean±SD	5.36±4.07
Entry NIHSS ≤ exit NIHSS, n=527	
Good prognosis (%)	82.4
Poor prognosis (%)	17.6
Modifiye rankin score	
Min–Max (Median)	0–6 (2)
Modifiye rankin prognosis, n=527	
Good prognosis (%)	63.8
Poor prognosis (%)	36.2

RDW: Red cell distribution width; NIHSS: The National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale; SD: Standard deviation; Min: Minimum; Max: Maximum.

titative data for normal distribution was tested using the Shapiro-Wilk test. Student-t test was used to compare normally distributed age, cholesterol, hematocrit, leukocyte, platelet, and RDW variables between two groups with and without mortality. The Mann-Whitney U test was conducted to compare NIHSS score and mRS at admission between the two groups. The Pearson chi-square test was used to compare the qualitative data. The Spearman correlation analysis was performed to evaluate the relationship between the NIHSS and mRS scores at admission and RDW, which were not normally distributed. Diagnostic screening tests (sensitivity, specificity) and the receiver operating characteristic (ROC) analysis were used to determine the predictive value for these parameters. The backward logistic regression analysis was undertaken to determine the risk factors affecting seven-day mortality. Confidence intervals were given at the 95% level and a value of $p<0.05$ was considered to indicate significance.

RESULTS

This study was conducted with 527 patients with AIS, of whom 43.3% (n=228) were female and 56.7% (n=299) were male. The ages of the subjects included in the study ranged between 23 and 98, and the mean age was 68.21±13.51 years. It was observed that 22.4% (n=118) of the cases died within seven days of admission. Hypertension was observed in 69.3% (n=365), atrial fibrillation (AF) in 11%, chronic artery disease in 25.4% (n=134), and diabetes mellitus in 41.7% (n=220). It was determined that 19.5% (n=103) of the subjects were smokers. The length of hospital stay ranged from 1 to 120 days with a median value of 8 as shown in Table 1. The RDW measurements of the subjects ranged from 12.3 to 18.9, with an average of 15.65±1.22. The NIHSS scores at entry range from 0 to 19, with a median value of 4. According to NIHSS the prognosis was good for 82.4% (n=434) of cases and poor for 17.6% (n=93). The mRS score of the cases ranged from 0 to 6, with a median value of 2. According to mRS a good prognosis was observed in 63.8% (n=336) and a poor prognosis in 36.2% (n=191) (Table 2). The in-hospital mortality group was significantly older and had a significantly higher frequency of diabetes mellitus ($p<0.001$ and $p=0.023$, respectively). The NIHSS and mRS scores of the patients with seven-day mortality were significantly higher than those without mortality ($p<0.001$ and $p<0.001$, respectively) (Table 3). The RDW values of seven-day mortality were significantly higher than those without mortality ($p<0.001$) as shown in Figure 1. The RDW values of the patients with a poor prognosis were significantly higher than those with a good prognosis according to the NIHSS scores ($p<0.001$). A weak significant correlation was found between the RDW values and the NIHSS scores at admission (the NIHSS score

Table 3. Evaluation of seven-day mortality according to descriptive characteristics

	7-day mortality (-) (n=409)	7-day mortality (+) (n=118)	P
Age, Mean±SD	65.41±12.80	77.91±11.29	[a]0.001**
Gender (%)			[b]0.210
Female	75.0	25.0	
Male	79.6	20.4	
Smoking (%)			[b]0.420
-	76.9	23.1	
+	80.6	19.4	
HT (%)			[b]0.537
-	75.9	24.1	
+	78.4	21.6	
AF (%)			[b]0.507
-	77.2	22.8	
+	81.0	19.0	
CAD (%)			[b]0.472
-	78.4	21.6	
+	75.4	24.6	
DM (%)			[b]0.023*
-	81.1	18.9	
+	72.7	27.3	
Hematocrit, Mean±SD	40.57±4.67	40.41±5.17	[a]0.738
Leukocyte, Mean±SD	8929.07±2916.97	9312.20±2893.39	[a]0.209
Platelets, Mean±SD	239792.91±71686.20	244092.37±76902.82	[a]0.573
NIHSS entry score, Median (Q1–Q3)	4 (2–6)	7 (4–12)	[c]0.001**
Modified rankin score, Median (Q1–Q3)	1 (1–3)	5 (2–6)	[c]0.001**
RDW, Mean±SD	15.36±1.04	16.61±1.28	[a]0.001**

SD: Standard deviation; HT: Hypertension; AF: Atrial fibrillation; CAD: Coronary artery diseases; DM: Diabetes mellitus; NIHSS: The National Institutes of Health Stroke Scale; RDW: Red cell distribution width; mRS: Modified Rankin Scale.

at admission increased as RDW increased) (r=0.194; p<0.001). The RDW values of the patients with a poor prognosis were statistically higher than those with modified prognosis with a good prognosis according to the mRS scores (p<0.001). A positive significant correlation was determined between the RDW values and the mRS scores, in which the latter increased in parallel to the former (r=0.254; p<0.001; p<0.001) (Table 4). When the variables that were considered to have an effect on seven-day mortality are evaluated by the backward (conditional) logistic regression analysis, it was seen that the model provided significant results, and the explanatory

Table 4. The correlation of RDW with NIHSS and Modified Rankin Scale scores

Variable	Correlation coefficient (r)	p
RDW vs NIHSS	0.194	<0.001
RDW vs mRS	0.254	<0.001

RDW: red cell distribution width; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale; Student's t-test; r = Spearman's correlation coefficient; P<0.01.

Table 5. Independent predictors of seven-day mortality in patients with AIS identified in univariate and multivariate logistic regression analysis

Variable	OR	95% CI	p
Age	1.074	1.045–1.103	<0.001
RDW	2.203	1.677–2.893	<0.001
mRS	2.021	1.704–2.396	<0.001

AIS: Acute ischemic stroke; OR: Odds ratio; CI: Confidence interval; RDW: Red cell distribution width; DM: Diabetes mellitus; RDW: Red cell distribution width; mRS: Modified Rankin Scale. The values of the last observed step are given in the model.

coefficient of the model (88.4%) was good (p<0.001; p<0.01). At the end of the fourth step, the effects of age, RDW and mRS scores on seven-day mortality were statistically significant (p<0.001; p<0.001; p<0.001). The remaining variables that were analyzed in the model were found to have non-significant effects although they provided significant or close to significant results in univariate evaluations (p>0.05). According to the model, the seven-day mortality risk was increased 1.074 times by one unit increase in age (95% confidence interval (CI): 1.045–1.103], 2.203 times by one unit increase in RDW (95% CI: 1.677–2.893), and 2.021 times by one unit increase in mRS (95% CI: 1.704–2.396) (Table 5). The cut-off point for RDW was calculated as 16.2, at which the sensitivity of this parameter was 66.1%, specificity was 78%, positive predictive value was 46.4%, and negative predictive value was 88.9%. The ROC curve obtained for RDW revealed 77.2%. The risk of seven-day mortality was 6.912 times greater (95% CI: 4.419–10.810) in patients with an RDW of 16.2 or above (Fig. 2).

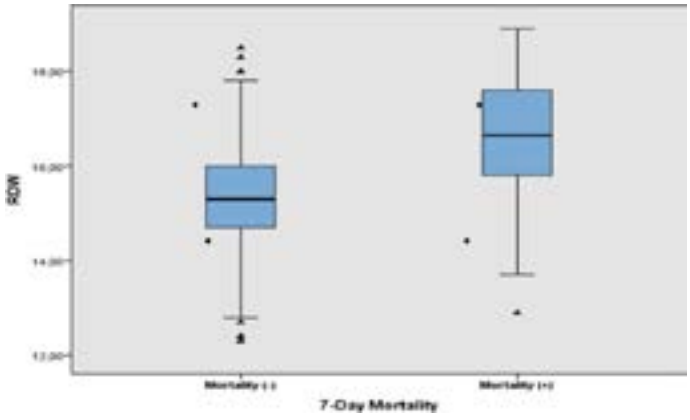

Figure 1. Distribution of RDW levels in patients who survived longer than seven-day (mortality-) and those who died within the first seven-day (mortality+).

RDW: Red cell distribution width.

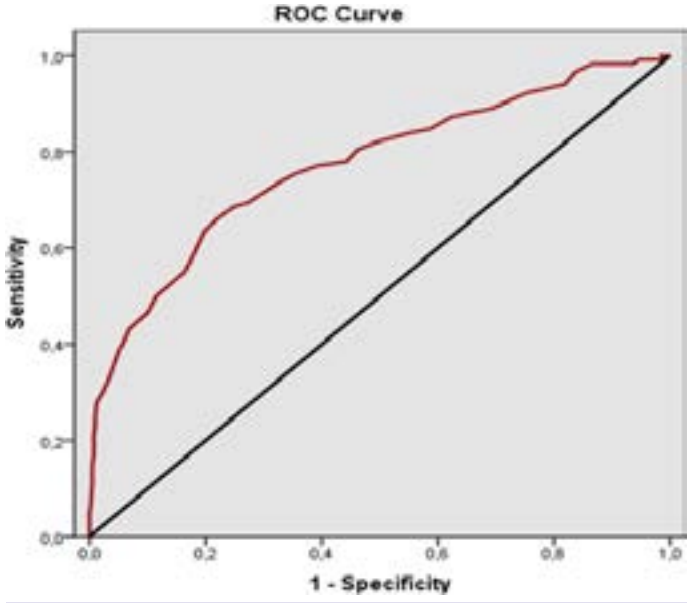

Figure 2. Receiver operating characteristic (ROC) curve of RDW for predicting 7-day mortality. Area under the curve (AUC)=0.772. Patients with RDW ≥16.2% had an odds ratio (OR) of 6.912 (95% CI: 4.419–10.810) for 7-day mortality.

DISCUSSION

In the present study, RDW emerged as a reliable biomarker for predicting seven-day mortality among patients with acute ischemic stroke (AIS). While previous research has demonstrated the prognostic value of RDW in estimating 28-day and one-year mortality in AIS populations [7, 8], our study is the first, to our knowledge, to establish its utility in forecasting early (within seven days) mortality. Accurate early prediction of stroke-related mortality holds significant clinical importance for optimizing patient management and resource allocation. Given its low cost and widespread availability, incorporating RDW measurement into the initial evaluation of AIS patients may offer a practical tool for risk stratification and potentially inform more tailored therapeutic strategies.

The RDW level has been shown to be effective in predicting cardiovascular diseases [9], acute kidney injury [10], trauma [11], and cancer [12]. However, the literature contains limited data on the relationship between the RDW level and in-hospital mortality in patients with AIS. At the same time, most available studies an-

alyzed RDW as a predictor of long-term mortality. In the long-term follow-up of patients, various factors, such as the quality of hospital care, uncontrolled chronic diseases, and post-stroke infections can have an effect on the mortal course of the disease, which interferes with the ability of RDW to predict AIS mortality [13]. Furthermore, RDW is severely affected by conditions, such as anemia and cancer, and less affected by environmental factors [14]. Elevated RDW has long been used in the classification of anemia or the diagnosis of iron deficiency anemia [15]. In a study examining cases with malignant and benign breast cancer, the RDW value was shown to be significantly increased in the former compared to the latter [16]. Similarly, another study evaluating cases with malignant and benign uterine lesions found RDW to be higher in patients with malignant lesions, although this parameter was increased in both groups [17]. In addition, malignancy is frequently accompanied by gastrointestinal dysfunction and malnutrition. This coexistence is considered to cause iron, folic acid and vitamin B12 deficiencies, which may lead to anemia and ultimately an increase in RDW [18]. In the light of these findings reported in the literature, in the current study, we excluded AIS cases with a diagnosis of anemia or cancer, which are known to alter RDW levels. In the literature, however, in studies investigating the efficacy of RDW in predicting 28-day and one-year mortality in AIS cases, diseases such as anemia and cancer that alter the level of RDW were not excluded [7–13]. In this context, we consider that by eliminating the effect of other diseases on the RDW level, we consider that our study provides clearer data about the isolated mortality outcomes. While several previous studies have explored RDW in predicting 28-day or long-term mortality in AIS patients [7–8, 13], there remains a gap in literature concerning its predictive utility for early-period mortality. This study uniquely addresses that gap by focusing on 7-day outcomes. From a clinical perspective, early identification of high-risk AIS patients based on RDW levels may assist emergency physicians in triage decisions, determining intensive monitoring needs, and possibly guiding early ICU admission.

Although the underlying mechanisms linking elevated RDW to poor outcomes in AIS patients remain incompletely understood, several hypotheses have been proposed to clarify its prognostic relevance [4]. One prevailing theory centers on the role of systemic inflammation, which may contribute to increased RDW levels and heightened mortality risk in AIS. Inflammatory processes are known to disrupt iron metabolism and suppress bone marrow function, thereby impairing erythropoiesis. Furthermore, proinflammatory cytokines may interfere with normal erythrocyte maturation, resulting in a heterogeneous population of red blood cells with diminished deformability [19, 20]. These structurally compromised erythrocytes exhibit impaired flow dynamics, potentially promoting thrombotic events and contributing to the pathophysiology of acute ischemic stroke [21]. In most laboratories, the normal reference range of RDW is 11–15% [9]. In a study of ischemic stroke, the cut-off value of RDW in predicting stroke was determined as 14% [AUC: 0.760; CI: 0.676–0.844] [22]. Another previous study demonstrated the efficacy of an RDW of greater than 15% in predicting adverse neurological outcomes in patients with subarachnoid hemorrhage [23]. In another study conducted with acute pancreatitis cases, the RDW cut-off value for 30-day mortality was reported to be 14% (AUC: 0.842) [24]. A baseline RDW of >15.5% was also independently associated with mortality in patients undergoing aortic valve implantation (1.83, CI: 1.44–2.32) [25]. However, only few studies have been conducted to reveal the relationship between stroke-related mortality and RDW, and no data is available on the cut-off value of RDW in predicting mortality among the existing studies. Thus, our study is the first in the literature to specify a cut-off value for the RDW prediction of seven-day mortality in AIS patients. In this study, we calculated this value as 16.2 (AUC: 0.772) and found that the seven-day mortality risk was 6.912 times greater in patients with an RDW of ≥16.2 (95% CI: 4.419–10.810). In our study, in addition to RDW, age and NIHSS score, the mRS score was found to be an independent prognostic factor in mortality.

In this study, we investigated the link between poor prognosis and RDW in patients with high mRS and NIHSS scores, and found that elevated RDW was significantly correlated with cerebral ischemic complications. The present data are consistent with the results of a previous study in subarachnoid hemorrhage patients that showed a significant relationship between mRS and NIHSS scores and RDW in the univariate analysis [26]. Furthermore, Turcato et al. [27] revealed RDW, age and NIHSS score as the main determinants according to the nomogram. This was confirmed by our results and found to be important and independent determinants of unfavorable outcome. The measurement of RDW, which is a routinely obtained hematologic parameter in emergency department, together with the above mentioned scores can be more efficient than using the scores alone in evaluating the prognosis of patients with AIS.

Limitations

This study has several limitations, the foremost being its retrospective nature and single-center setting, which may limit the generalizability of the findings. Additionally, RDW levels were measured at a single time point—upon patient admission to the emergency department—which restricts the ability to assess dynamic changes in this parameter over time. These methodological considerations should be addressed in future prospective, multicenter studies involving AIS populations. Nevertheless, a notable strength of this study lies in the exclusion of patients with acute anemia and malignancies, which helped to minimize potential confounding factors and enhance the internal validity of the results.

Conclusion

The results of logistic regression analysis revealed that serum RDW level was independently associated with seven-day mortality in patients with AIS. Furthermore, the receiver operating characteristic analysis showed that the best cut-off value of RDW for the prediction of seven-day mortality was 16.2%, at which its sensitivity and specificity were 66.1% and 78%, respectively. For rapid and accurate clinical decision-making, the serum RDW level might help predict neurological outcomes and determine the short-term survival of patients with AIS. Further controlled clinical trials involving larger numbers of subjects are warranted.

Furthermore, our study did not include inflammatory biomarkers such as C-reactive protein (CRP) or ferritin, which could act as unmeasured confounders influencing RDW levels. Future studies should consider these factors to enhance model accuracy.

Ethics Committee Approval: The Haydarpasa Numune Training and Resarch Hospital granted approval for this study (date: 16.07.2019, number: 2019/71).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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