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Red blood cell distribution width (RDW) and adverse outcomes in acute coronary syndrome patients

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ABSTRACT

Background and objectives. Red blood cell distribution width (RDW) is an early biomarker indicative of the inflammatory process. Elevated levels of systemic and local inflammation are integral to the pathophysiology of acute coronary syndromes (ACS). This study aims to examine the correlation between increased RDW and various severe prognostic factors associated with ACS.

Materials and methods. This cross-sectional descriptive study was conducted on a cohort of 60 patients diagnosed with acute coronary syndromes (ACS). The diagnostic threshold for elevated RDW-CV was established at 15%. Accordingly, the study population was stratified into two groups: group 1 (RDW-CV≤15%), and group 2 (RDW-CV15%).

Results. The range of RDW-CV (%) distribution is from 11.2% to 16.9%, with a mean value of 14.2±1.3. A negative correlation exists between RDW-CV (%) and ejection fraction (EF%) (r=-0.4, p<0.01). Univariate linear regression analysis indicates that a 1% increase in RDW-CV (%) corresponds to a 3.3% decrease in EF (%) (Coefficient=-3.3, p<0.01). Furthermore, univariate logistic regression analysis reveals that patients with RDW >15% have a 9.3-fold increased risk of heart failure with reduced EF (OR=9.3, p<0.01) and a 4.5-fold increased risk of having damage to 2-3 coronary vessels (OR=4.5, p<0.05) compared to those with RDW≤15%. ROC curves demonstrate that RDW has a good predictive ability for reduced EF (AUC=0.779, 95% CI 0.626-0.932, p=0.006).

Conclusions. There is a significant relationship between elevated RDW and severe prognostic factors in acute coronary syndromes (ACS), including reduced ejection fraction (EF) and the extent of coronary vessel damage. Monitoring this straightforward hematological marker can enhance prognostic accuracy and inform appropriate treatment strategies.

Keywords: acute coronary syndrome' prognosis, coronary artery lesions, reduced EF, Modified Gensini score

Abbreviations (in alphabetical order):

ACS – Acute coronary syndrome
EF – Ejection fraction
MGS – Modified Gensini Score
NSTEMI – Non ST-elevation myocardial infarction
RDW – Red blood cell distribution width
STEMI – ST-elevation myocardial infarction
TIMI – Thrombolysis in Myocardial Ischemia

INTRODUCTION

Acute coronary syndrome (ACS) represents a critical medical emergency necessitating prompt diagnosis and aggressive treatment. To decrease mortality and rehospitalization rates associated with ACS, it is crucial to accurately predict the disease's severity and progression risk [1]. To achieve this, clinicians and scientific researchers must actively identify additional biomarkers with prognostic significance [2]. In recent years, hematological indices such as white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and red blood cell distribution width (RDW)

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have garnered significant interest. Among these, the RDW index is considered one of the most promising markers.

Red blood cell distribution width (RDW) is a numerical measure of the variability in the size of circulating erythrocytes [3]. Consequently, higher RDW values indicate greater heterogeneity in red blood cell size (anisocytosis), typically resulting from disruptions in erythrocyte maturation or degradation [4]. RDW is recognized as an early biomarker for the inflammatory process, and elevated systemic and local inflammation is crucial in the pathophysiology of chronic diseases in general, and cardiovascular diseases in particular [5]. This theory forms the basis for numerous studies investigating the relationship between elevated RDW and the incidence or severity of cardiovascular diseases, including acute coronary syndromes (ACS) [6]. High RDW has been demonstrated to significantly and independently predict adverse outcomes in patients with these conditions. Furthermore, it has been linked with mortality in patients with coronary artery disease [7], heart failure, ischemic stroke, and pulmonary hypertension [8].

However, limited studies have specifically examined the relationship between RDW and adverse outcomes in ACS. Therefore, this study aims to evaluate the clinical utility of RDW values in patients with ACS.

MATERIALS AND METHODS

Study population

A cross-sectional descriptive study on 60 patients diagnosed with ACS.

Inclusion criteria

Adult patients aged ≥18 years who presented to the Department of Cardiovascular Internal Medicine at the University of Medicine and Pharmacy, Hue University, and were diagnosed with acute coronary syndrome (ACS) by a cardiologist according to the latest European Society of Cardiology (ESC) guidelines [9] from March 2021 to March 2022, were included in this study.

Exclusion criteria

Exclusion criteria included refusal to participate in the study, incomplete clinical assessment, or incomplete diagnostic testing.

Patients were also excluded if they had severe concomitant diseases (e.g., severe heart valve disease, stroke, severe renal failure, severe liver failure) or conditions affecting the RDW index (e.g., hematological diseases, blood product transfusion, use of drugs affecting RBC, and non-hematological diseases such as cirrhosis, hypo/hyperthyroidism, Behcet's disease) [10].

Clinical diagnosis

According to clinical presentation, 12- lead ECG and serum cardiac markers, ACS was classified into (9):

1. Unstable angina (UA)
2. Non-ST-elevation myocardial infarction (NSTEMI)
3. S-T elevation myocardial infarction (STEMI)

Laboratory measurements

During the study period, RDW and other laboratory tests were analyzed in a central laboratory, using standardized, automated kit (XNL – 550 Sysmex). Data collection was approved by the hospital ethics committee. Patients were stratified based on baseline RDW levels, which were obtained from the initial complete blood count, into two groups: those with RDW levels of 15% or less, and those with RDW levels greater than 15%.The normal range for RDW in our laboratory is ≥12% and ≤15%.

Transthoracic echocardiographic examination

Undertake extensive M-mode and 2-D Transthoracic echocardiographic examinations and Doppler studies employing conventional parasternal and apical perspectives, in accordance with the guidelines established by the American Society of Echocardiography (ASE) [11]. Measurements of:

1. Left ventricular ejection fraction was estimated by EF=(EDV-ESV/EDV)×100. The study population was divided into 3 groups based on the value of EF index: Reduced EF (EF≤40%); Mild reduced EF (41%≤EF≤49%); Preserved EF (EF≥50%) [12].
2. As per the 16-segment model proposed by the American Society of Echocardiography (ASE), the left ventricle (LV) was divided into segments for the purpose of analyzing wall motion. For each segment, the presence of hypokinesis, akinesis, or dyskinesis was used to determine if there was an abnormality in wall motion.

Coronary angiography

All patients in our study underwent diagnostic coronary angiography. The main result was the number of injured vessels. Then, the study population was stratified into two subgroups based on the number of injured vessels (0-1 injured vessel and 2-3 injured vessels). Additionally, the severity of stenosis of the coronary artery can be objectively assessed by assigning points according to the modified Gensini

score (MGS). The higher the MGS, the more severe the damage to the coronary artery or the more branches of the coronary artery are damaged (13).

Statistical analysis

Continuous variables were assessed for normal distribution using the Kolmogorov-Smirnov test. Results were presented as mean and standard deviation for normally distributed data, and as median and interquartile range for non-normally distributed data. Categorical variables were expressed as percentages. Patients were divided into quartiles based on their RDW values.. Differences in baseline characteristics were compared using analysis of variance (ANOVA) or the t-test for normally distributed continuous variables, the Mann-Whitney U test for non-parametric continuous variables, and the chi-square test for categorical variables. The correlation between two normally distributed quantitative variables was evaluated using Pearson correlation, with the correlation coefficient (r) reported. Univariate linear regression was used to analyze the relationship between two quantitative variables, and univariate logistic regression was used to examine the relationship between two categorical variables. A Receiver Operating Characteristic (ROC) curve was used to evaluate the predictive performance of RDW for heart failure with reduced EF.

RESULTS

Baseline characteristics of research participants

The mean age of the study population was 70.8 ± 10.5 years. The majority of patients in our study were diagnosed with non-ST-elevation myocardial infarction (NSTEMI), comprising 38.3% of the total. The average ejection fraction (EF) among the study participants was 53.1±10.2%. The largest proportion of patients in the study had preserved EF, constituting 61.7% of the population. Approximately 45% of patients exhibited damage to ≥2 coronary branches. The mean MGS among the study population was 13±7.1, with the high-risk group (MGS >13) comprising the majority at 45.0%. Nearly 45% of patients were categorized as high-risk based on the TIMI score.

Characteristics of RDW index

Following statistical analysis, RDW-CV was characterized as a continuous variable displaying normal distribution, with values ranging from 11.2% to 16.9% and a mean of 14.2±1.3%. Given the normal range of RDW in our laboratory (≥12% and ≤15%), the study cohort was stratified into two subgroups based on a cut-off of 15%. Group 1 (RDW≤15%) accounted for 71.7% of the population, while Group 2 (RDW>15%) comprised the remaining 28.3% (Table 1 and Figure 1). When comparing the average RDW value among various subgroups of ACS's clinical classification, EF, MGS, and TIMI, we observed some differences in the mean RDW values between the mentioned subgroups. However, most of these differences did not reach statistical significance, except for variations observed within the EF subgroups (Table 2).

TABLE 1. Baseline characteristics of research participants

Age (mean ± SD)	70.8 ± 10.5	**Complete blood count**	
Age subgroup (n, %)		RBC (T/L)	4.4±0.5
< 65 year-old	19 (31.7)	HGB (g/dL)	13.2±1.6
≥ 65 year-old	41 (68.3)	**RDW-CV (%)**	14.2±1.3
Sex (n, %)		**RDW subgroup (n, %)**	
Male	36 (60.0)	Group 1 (RDW ≤ 15%)	43 (71.7)
Female	24 (40.0)	Group 2 (RDW > 15%)	17 (28.3)
Vital sign (mean ± SD)		**Echocardiography**	
Pulse (bpm)	85.6±22.9	**LVEF% (mean ± SD)**	53.1±10.2
Systolic BP (mmHg)	131.8±25.1	**EF subgroups (n, %)**	
Diastolic BP (mmHg)	77.9±11.3	Preserved EF	37 (61.7)
Killip classification (n, %)		Mildly reduced EF	13 (21.7)
Class I	42 (71.7)	Reduced EF	10 (16.7)
Class II, III, IV	17 (28.3)	**Wall motion abnormalities (n, %)**	
Clinical classification (n, %)		No	26 (43.3)
UA	19 (31.7)	Yes	34 (56.7)
NSTEMI	23 (38.3)	**Number of injured vessels (n, %)**	
STEMI	18 (30.0)	0-1 vessels	33 (55.0)
Laboratory testing		2-3 vessels	27 (45.0)
Ure (mmol/L)	5.8±2.0	**MGS subgroups (n, %)**	
Creatinine (μmol/l)	83±23.4	1-6 score	13 (21.7)
Glucose (mmol/L)	7.1±2.9	7-13 score	20 (33.3)
hs-TnT (ng/mL)	1.5±3.2	>13 score	27 (45.0)
Total cholesterol (mmol/l)	4.7±1.1	**TIMI score subgroups (n, %)**	
HDL-cholesterol (mmol/l)	1.3±0.3	Low-risk	12 (20.0)
LDL-cholesterol (mmol/l)	3.2±1.1	Moderate-risk	22 (36.7)
Triglyceride (mmol/l)	1.8±1.4	High-risk	26 (43.3)

RDW and left ventricular systolic function

The average RDW value was significantly higher in the reduced EF group compared to the preserved EF group (15.3±1.1 vs. 13.9±1.3), with a statistically significant difference observed ($p<0.01$) (Table 2). Moreo-

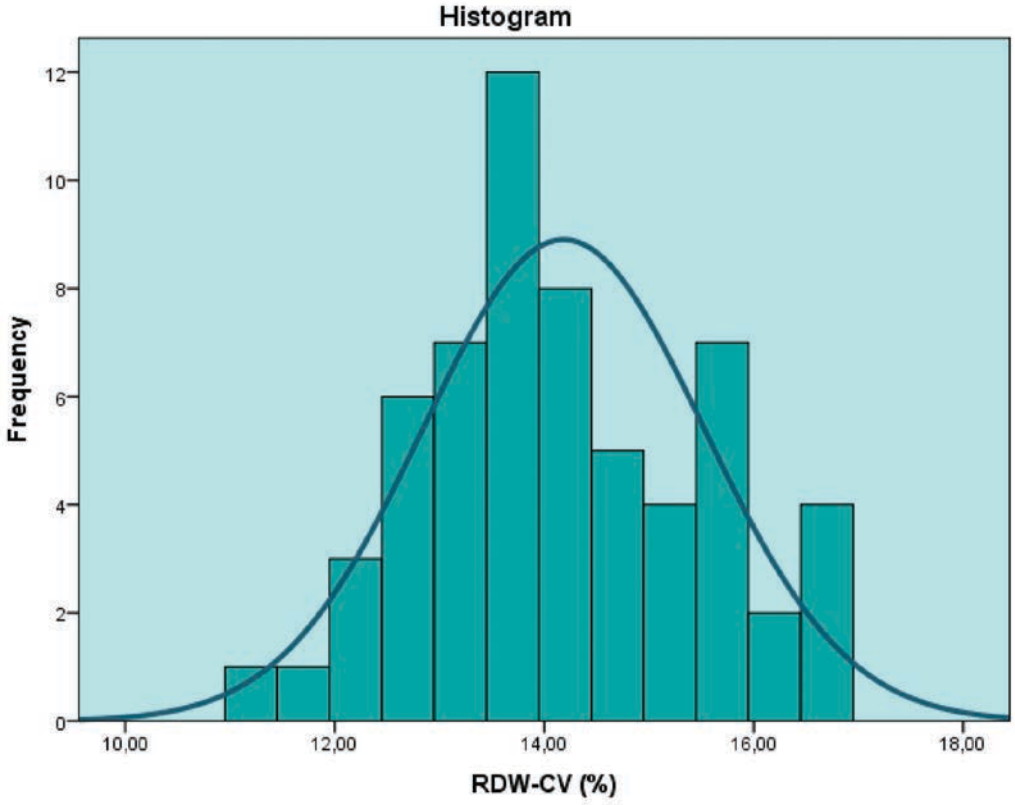
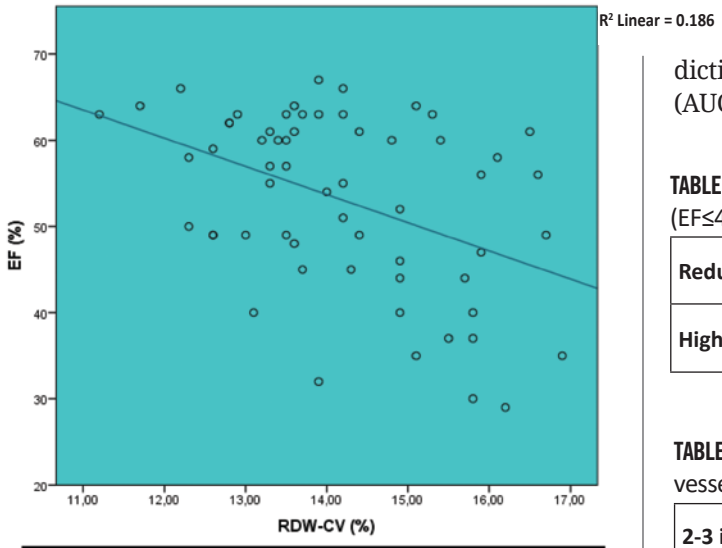


FIGURE 1. Characteristics of the RDW-CV (%) value distribution

TABLE 2. Comparison of mean RDW-CV values (%)

Clinical classification (n, %)		p-value	MGS subgroup (n, %)		p-value
UA	13.8±1.1	>0.05	1-6 score	14.3±1.2	>0.05
NSTEMI	14.5±1.5		7-13 score	13.7±1.3	
STEMI	14.2±1.4		>13 score	14.5±1.4	
EF subgroups			**TIMI score subgroup (n, %)**		
Preserved EF	13.9±1.3	**<0.05**	Low-risk	13.7±1.4	>0.05
Mildly reduced EF	14.3±1.3		Moderate-risk	14.0 ±1.2	
Reduced EF	15.3±1.1		High-risk	14.5±1.4	



EF (%)	r-Pearson	p-Pearson	Coef	p
RDW-CV (%)	-0.4	<0.01	-3.3	<0.01

FIGURE 2. Correlation between RDW-CV (%) and EF(%)

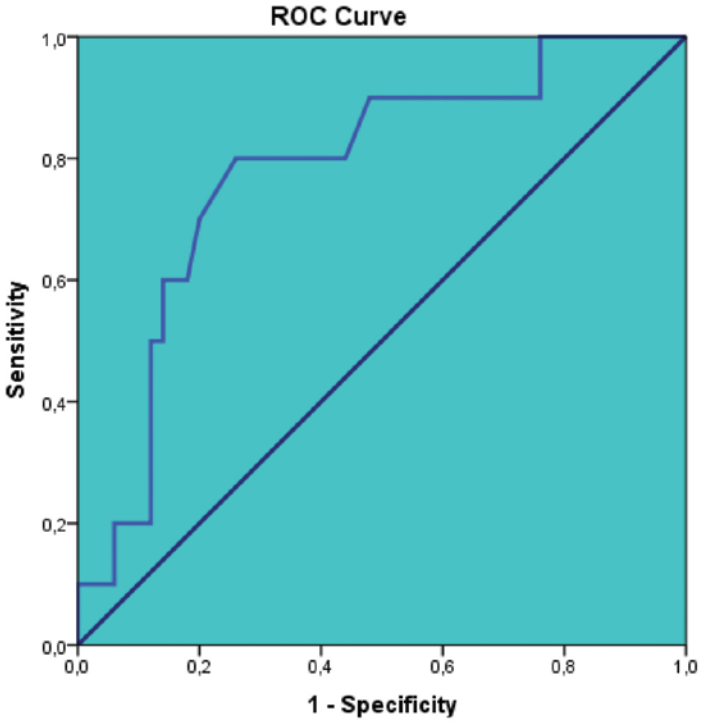
ver, a negative correlation between RDW and EF was identified (r=-0.4, p<0.01). Additionally, for each 1% increase in RDW-CV (%), there was a corresponding 3.3% decrease in EF (Coef=-3.3, p<0.01) (Figure 2). Furthermore, in the univariate logistic regression model examining the association between heart failure with reduced EF (EF≤40%) and high RDW (RDW>15%), it was determined that patients with high RDW had a 9.3-fold increased risk of heart failure with reduced EF compared to those without high RDW (OR=9.3, p<0.01) (Table 3). Additionally, RDW exhibited good predictive accuracy for identifying reduced EF (EF≤40%) (AUC=0.779, 95% CI 0.626-0.932, p=0.006) (Figure 3).

TABLE 3. Univariate logistic regression between reduced EF (EF≤40%) and High RDW (RDW>15%)

Reduced EF	B	SE.	OR	CI - 95%	p-value
High RDW	2.2	0.8	9.3	2.0 - 42.7	**<0.01**

TABLE 4. Univariate logistic regression between 2-3 injured vessels and high RDW (RDW>15%)

2-3 injured vessels	B	SE.	OR	CI - 95%	p-value
High RDW	1.5	0.6	4.5	1.3 - 15.1	**<0.05**



Variable	Cut-off point	AUC	Sensitivity	Specificity	PPV	NPV	p-value
RDW-CV	14.85	0.779	0.8	0.74	0.381	0.949	0.006

FIGURE 3. ROC curve analysis between RDW & reduced EF (EF≤40%)
AUC: area under curve; PPV: Positive predictive value; NPV: Negative predictive value

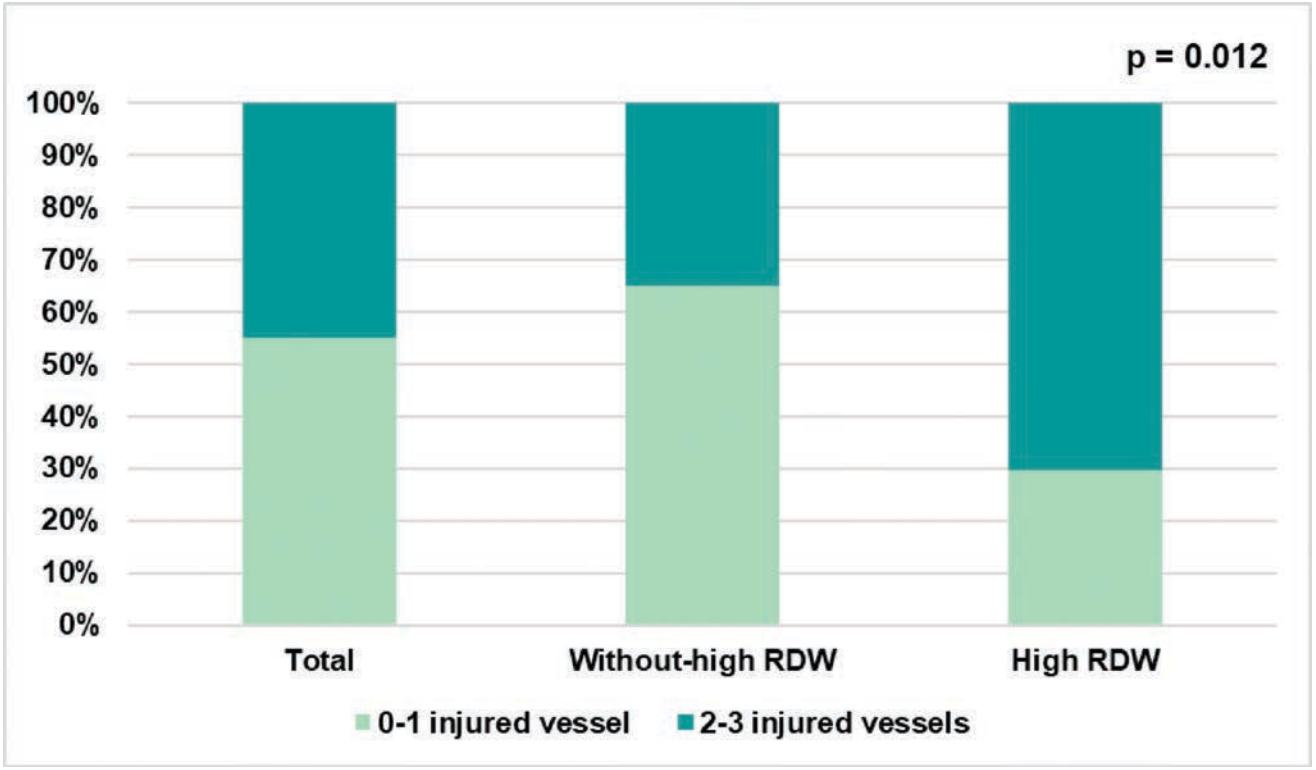


FIGURE 4. Comparison of the number of injured vessels among subgroups of RDW

RDW and the severity of coronary artery damage

The proportion of ≥2 coronary branches damaged in the high RDW group was statistically significantly greater than that of the group without high RDW (approximately 71% compared to nearly 35%, with $p<0.05$) (Figure 4). Moreover, in the univariate logistic regression analysis investigating the association between ≥2 coronary branches damaged and

high RDW (RDW >15%), it was observed that patients with high RDW-CV (>15%) had a 4.5-fold increased risk of having ≥2 coronary branches damaged compared to those without high RDW (OR=4.5, p<0.05) (Table 4).

DISCUSSION

It is established that RDW is conventionally utilized in the differential diagnosis of anemia as part of red blood cell indices. Recent years have seen numerous studies highlighting RDW's significance as a predictor of adverse clinical outcomes across various diseases, including acute coronary syndromes (ACS). Regarding the theoretical framework linking RDW and ACS, two primary mechanisms have been proposed: inflammation and oxidative stress. Theoretically, inflammation is responsible for a decrease in erythropoietin from the renal mesangial cells, which leads to anisocytosis and microcytosis of RBC, thereby increasing the RDW [14]. Another proposed mechanism involves oxidative stress, which induces early RBC damage, contributing to microcytosis and consequently elevated RDW. Furthermore, both oxidative stress and inflammation may contribute to endothelial dysfunction and macrophage accumulation, processes implicated in the development of atherosclerotic lesions. Atherosclerosis typically manifests in clinical scenarios such as ACS or sudden cardiac death due to coronary occlusion [15].

Baseline characteristics

The average age of the population in our study was 70.8±10.5 years, which was higher than in most related studies [10,16,17]. Regarding clinical classification, patients with NSTEMI accounted for the majority of our study population, at 38.3%; followed by the UA group, comprising 31.7%, and finally, the STEMI group, represented only 30%. In contrast to our findings, Khaled Elkhashab's study (2018) reported STEMI as the most prevalent group, comprising 37.5% [10]; research by Janaswamy Vibhav (2012) also concluded that the largest proportion was the group of STEMI (69%) [18]. The average EF value of our study participants was 53.1±10.2. Regarding wall motion abnormalities, more than half of the patients in our study exhibited signs of such abnormalities. This characteristic is similar to the research of T.T. Wu (2019) [19] but is higher than the research of author V.H. Contreras Gutiérrez (2016) [17]. Analyzing the number of damaged coronary branches, nearly 50% of patients with ACS in our study had ≥2 injured coronary branches. In addition, the average MGS score among study participants was 13±7.1, the high-risk group (MGS>13) comprised the largest proportion at 45.0%, followed by the moderate-risk group (MGS 7-13) and low-risk group (MGS 1-6), with rates of 33.3% and 21.7%, respectively. In contrast to our findings, Mohsin Shabir's study (2021) reported that the moderate-risk group represented the highest proportion (37.5%) [20].

Characteristics of RDW index

The distribution range of RDW-CV in our study is from 11.2% to 16.9%. This range is narrower compared to Ali Zorlu's study (2015) and Marcello Tonelli's study (2008) (12.1%-22.1% and 10.9%-23.2%, respectively) [21,22]. The average RDW-CV(%) value in our study was 14.2±1.3, which closely resembles that reported by Ali Zorlu (2015) (14.1±1.4), but is higher than the value reported by Marcello Tonelli (2008) (13.4±1.1) [21,22]. The difference in average RDW values among the three clinical subgroups in our study was not statistically significant (p>0.05). This finding aligns with the results reported by Khaled Elkhashab (2018) (p=0.3) [10]. The difference in the average RDW value among the MGS subgroups did not reach statistical significance (p>0.05). In contrast, Praveen Nagula's study in 2017 found a statistically significant difference, with the high-risk group exhibiting a higher average RDW-CV value compared to the other two groups (14.7±1.1 vs. 14.6±1.1 and 14.5 ±0.9, p<0.01) [16]. Regarding the evaluation of average RDW-CV values across TIMI score subgroups, our study did not identify a statistically significant difference (p>0.05).

RDW and EF

When comparing the average RDW-CV values across ejection fraction (EF) subgroups, our study found a statistically significant difference, with the reduced EF group exhibiting a higher average RDW value compared to the preserved EF group (15.3±1.1 vs. 13.9±1.3, p<0.01). When evaluating the relationship between RDW and EF value (%), our study observed a significant relationship between RDW and EF values (%), where the average EF value in the high RDW group was significantly lower than in the non-high RDW group (47.1±12.1 vs. 55.5±8.3, p<0.01). Similar findings were reported by Erhan Tenekecioglu in 2015, who also noted a statistically significant lower EF value (%) in the high RDW group compared to the non-high RDW group (49.3±9.6 vs. 54.6±8.3, p<0.01) [23]. Through Pearson correlation analysis, we recorded a negative correlation between RDW-CV and EF with r=-0.4, p<0.01. However, it is noteworthy that this correlation is moderate in strength, as r falls between -0.3 and -0.5. When further analyzing the linear regression relationship between RDW-CV and EF, we also observed that for every 1% increase in RDW-CV (%), there was a corresponding decrease of 3.3% in EF (Coef=-3.3, p<0.01). Similar findings were reported in studies by Khaled Elkhashab (2018) and

Rudrani Sharma (2015). Both studies documented a negative correlation between RDW and left ventricular ejection fraction EF (with r=-0.6, p<0.001 and r= -0.1; p<0.05) [10,24]. On the other hand, when analyzing the univariate logistic regression model, the analysis results showed that patients with high RDW (RDW >15%) will have an increased risk of heart failure with reduced EF (EF≤40%) by 9.3 times compared to the group without high RDW (OR=9.3, p<0.01). Furthermore, in our attempt to determine the optimal cut-off value of RDW for predicting reduced EF (EF≤ 40%) in patients with acute coronary syndrome (ACS), we established that RDW demonstrates robust predictive capability for identifying reduced EF (EF≤ 40%) (AUC=0.779, 95% CI 0.626-0.932, p=0.006). The best cut-off point is 14.85% with a sensitivity of 80% and a specificity of 74%, additionally, this cut-off has a positive predictive value of 38.1% and a negative predictive value of 94.9%. This analysis is quite the same as the analysis in the study of Ali Zorlu et al (2015), which performed ROC curve analysis between RDW & EF≤45% and found that the best cut-off point is 14 with a sensitivity of 70% and specificity of 62.5% [21].

RDW and the severity of coronary artery damage (as measured by the number of injured vessels)

When examining the association between RDW and the extent of coronary artery damage, the proportion of patients with 2-3 injured vessels in the high RDW group was approximately 71%, significantly higher than the approximately 35% observed in the non-high RDW group (p<0.05). A study by Erhan Tenekecioglu in 2015 reported similar findings, where the percentage of patients with damage to 2-3 coronary branches was significantly higher in the high RDW group compared to the non-high RDW group (69.1% vs. 51.5%, p<0.05) [23]. Moreover, in our univariate logistic regression analysis, it was determined that patients with high RDW (RDW > 15%) had a 4.5-fold increased risk of having damage to 2-3 coronary branches compared to those without high RDW (OR=4.5, p<0.05).

CONCLUSION

The primary findings of our study support the notion that the RDW index may serve as a predictor of adverse outcomes in patients with acute coronary syndrome (ACS). In our study, adverse outcomes were specifically characterized by the severity of left ventricular dysfunction, assessed based on left ventricular ejection fraction (LVEF), and the extent of coronary artery injury observed on angiography. Additionally, we identified a specific RDW cutoff point that demonstrates good predictive capability for identifying reduced EF (EF≤40%). These findings provide additional evidence supporting the idea that attention to this straightforward hematological marker can enhance prognostic assessment and guide appropriate treatment strategies for patients with ACS.

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The authors declare that they have no competing interests

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