Red cell distribution width as a predictor for the presence, severity, and complexity of coronary artery disease in patients with chronic coronary syndrome using the syntax score

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Back ground
Raised red cell distribution width (RDW) values have been associated with poor prognostic outcome in certain cardiac diseases. Our aim was to examine the relationship between RDW and the severity of coronary artery disease (CAD).

Patients and methods
Our current study included 199 patients who had coronary angiography for chronic coronary syndrome. RDW was measured for all patients. Classification of patients was done according to the syntax score into three groups: low (1–22), moderate (23–32), and high syntax score (>32).

Results
This study revealed that obstructive CAD patients had higher RDW than nonobstructive CAD (14.81 ± 1.3 vs. 12.95 ± 1.2) (P < 0.001). Moreover, RDW of high syntax-score patients (16.52 ± 0.7) was higher than that of patients with moderate syntax score (RDW = 15.77 ± 1.1) and low syntax-score patients (RDW = 13.91 ± 1.4). Also, a statistical significant relation was detected between RDW levels and syntax score (r = 0.778, P < 0.001). Multivariate analysis illustrated that smoking, hypertension, dyslipidemia, diabetes, obesity, and elevated RDW (odds ratio = 3.175, 95% confidence interval = 2.020–4.917, P < 0.001) were predictors of CAD.

Conclusions
RDW values were higher among high syntax-score patients. Also, the degree of severity of CAD has been correlated with higher levels of RDW.

Keywords:
chronic coronary syndrome, red blood cell distribution width, syntax score

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Background

Red cell distribution width (RDW) is the measurement of the variation in both size and volume of red blood cells (RBCs). RDW is calculated by dividing the SD of erythrocyte volumes for the mean corpuscular volume (i.e. RDW = SD/mean corpuscular volume). The causes that increase RBC size include iron deficiency, decreased vitamin B12 level, decreased RBC lifespan, and impaired erythropoiesis, leading to increased RDW% [1].

Moreover, RDW may be elevated in many medical conditions, such as heart failure, hypertension, atrial fibrillation, myocardial infarction, peripheral arterial disease, and cerebrovascular stroke [2]. Also, chronic inflammation can cause elevated heterogeneity of RBCs, leading to high RDW levels [3].

The causes of increased RDW in cardiovascular diseases have been attributed to the effective stimulation of erythropoiesis by erythropoietin hormone, which is secreted during hypoxic events and promotes the release of enlarged RBCs from bone marrow [4]. Another hypothesis is that elevated RDW may be due to a reduction of RBC turnover. More specifically, since the size of RBCs gradually reduces with aging of the cells, a decreased rate of RBC turnover would allow smaller cells to persist for a longer time in the circulation [5]. Moreover, chronic inflammatory state, which often accompanies acute and chronic cardiovascular diseases, may be another powerful erythropoiesis modulator [6]. In line with this hypothesis, a number of proinflammatory cytokines are effective to inhibit erythropoietin hormone secretion and RBC maturation, thus enhancing anisocytosis and elevating RDW [7].

The increased RDW is highly correlated with adverse clinical outcomes and higher mortality rates in many cardiovascular conditions, such as chronic stable angina [8] and heart failure [9].

The syntax score is a method of classification of the severity of coronary artery disease (CAD). Also, the

syntax score is used for prognosis of the severity of CAD [10].

As raised RDW may lead to adverse prognostic outcomes in cardiac events, we conducted our study to detect the correlation between RDW and the complexity of coronary artery disease in chronic coronary syndrome patients.

Aim

To detect the correlation between RDW level with the severity and complexity of coronary artery diseases in chronic coronary syndrome patients.

Patients and methods

This study included 199 patients who attended the Cardiology Department, Assiut University Hospital, to have elective coronary angiography for chronic CAD, during the period between January 2018 and January 2019. All patients signed informed consent. IRB number is 17100193 and Assiut Faculty of Medicine approved the study.

The inclusion criteria included chronic coronary syndrome patients who had stable angina and had symptoms such as (chest pain increased by exercise and relieved by rest) and/or clinical signs of CAD (abnormal resting ECG or positive exercise ECG).

Exclusion criteria were acute coronary syndrome, prior revascularization procedure, coronary artery bypass grafting, valvular or congenital heart disease, atrial fibrillation, decompensated heart failure, end-stage renal disease, anemia (hemoglobin <10 g/dl), malignancy, presence of thalassemia traits, active or chronic inflammatory disease, autoimmune diseases, and pregnancy.

Medical history and complete examination were done to patients. Also, patients were asked about history of smoking, diabetes, hypertension, and any previous cardiac event. The following investigations were done, including complete blood count (hemoglobin level, RDW, and white blood cells' count), lipid profile (including serum total cholesterol, low-density lipoprotein, and high-density lipoprotein), 12-lead ECG, and echocardiography.

Coronary angiography was done for every patient with calculation of the syntax score by syntax-score algorithm. Every coronary lesion with a diameter of stenosis minimally 50%, within each vessel at least 1.5 mm, was scored and each of them was separately then added together to give the overall syntax score. The syntax score was calculated online at the website (www.syntaxscore.com) [10].

Statistical methods

Data were entered and analyzed using IBM-SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York, USA), version 21.0. χ^2 was used to compare between the differences in the distribution of frequencies between different groups. *t* test analysis was used for the comparison between the means of dichotomous data. Analysis of variance test was calculated to measure the mean differences of all data that follow normal distribution. Bonferroni correction was used to calculate post-hoc test. The association between variables (Pearson's correlation) was tested by correlation analysis. The demographic and clinical data with statistical significance from the univariate analyses were included in the multivariate analysis. Receiver operating characteristic curve was used to assess the diagnostic performance of RDW in the diagnosis of CAD, analyzed by 95% confidence interval, SE, and area under the curve. Specificity, sensitivity, negative, and positive predictive values were calculated to validate RDW for diagnosis of CAD. *P* value is significant if less than 0.05.

Results

The study included 199 patients who were classified into two groups: the first group: obstructive CAD (139 patients) and the second group: nonobstructive CAD (60 patients) according to their epicardial coronary angiography.

Clinical characteristics of obstructive coronary artery disease versus nonobstructive coronary artery disease patients

Males were higher than females in the two groups (P = 0.047). Regarding the RDW, higher RDW level was detected in obstructive CAD than the nonobstructive CAD patients and this shows the significant correlation between CAD and high RDW (P < 0.001) (Table 1).

Logistic regression analysis for prediction of coronary artery disease

Hypertension, diabetes mellitus (DM), obesity, smoking, and age were significantly correlated with an elevated RDW (Table 2).

Clinical characteristics of syntax score groups

As regards the RDW, a positive correlation was detected between syntax score and RDW in the

studied patients (P < 0.001). Moreover, higher RDW% value (16.52 ± 0.7) was detected in high syntax-score patients than moderate syntax-score patients (RDW%=15.77 ± 1.1) and higher than low syntax-score patients (RDW%=13.91 ± 1.4) (Fig. 1 and Table 3).

Table 1 Clinical data of obstructive coronary artery disease group versus nonobstructive coronary artery disease

Parameters	Nonobstructive CAD (*n*=60) [*n* (%)]	Obstructive CAD (*n*=139) [*n* (%)]	*P*
Age (years)	51.97±8.11	57.13±7.91	0.001
Sex			
Male	33 (55)	82 (59)	0.047
Female	27 (45)	57 (41)	
Smoking	16 (26.7)	64 (46)	0.011
Obesity	16 (26.7)	97 (69.8)	<0.001
Diabetes mellitus	19 (31.7)	75 (54)	0.004
Hypertension	27 (45)	88 (63.3)	0.016
Dyslipidemia	28 (46.7)	103 (74.1)	<0.001
Family history	20 (33.3)	42 (30.2)	0.663
Hb (mg/dl)	13.33±1.3	13.38±1.2	0.772
WBCs $\times 10^3$	7.06±2.1	9.14±1.9	0.008
RDW %	12.95±1.2	14.81±1.3	<0.001
SYNTAX score			
SS (1-22)	0	106 (76.3)	<0.001
SS (23-32)	0	25 (18)	
SS (>32)	0	8 (5.9)	

CAD, coronary artery disease; Hb, hemoglobin; RDW, red blood cell distribution width; SS, syntax score; WBC, white blood cells. P<0.05.

Relationship between red cell distribution width and syntax score in the studied patients

A statistical positive relation has been detected between RDW and syntax score among the studied patients (r = 0.778 and P < 0.001) as high RDW level was associated with elevated syntax score as shown in Fig. 2.

Diagnostic criteria of red cell distribution width as a predictor of coronary artery disease

Three cut-off values of RDW (13.25, 14.05, and 15.25) were used to detect the role of RDW as a predictor for diagnosis of CAD. The diagnostic accuracy of RDW values was measured and it was detected that raised RDW level was correlated with high risk of having CAD, as demonstrated by the high specificity and the higher positive predictive value as shown in Table 4 and Fig. 3.

Higher RDW level was detected in the obstructive CAD group than the nonobstructive CAD patients, and this indicates the positive correlation between high RDW and CAD (P < 0.001) (Fig. 4).

The role of red cell distribution width value for diagnosis of coronary artery disease, determined by area under the curve

In a receiver-operating characteristic curve analysis, a cut point of 13.25 was identified in patients with

Table 2 Predictors of coronary artery disease by univariate and multivariate logistic analysis.

Factor	Univariate regression analysis			Multivariate regression analysis		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI*	*P*
Age (years)	1.086	1.042-1.132	<0.001	1.065	1.010-1.123	0.020
Sex (males)	1.177	0.639-2.169	0.601	1.142	0.579-2.121	0.687
Smoking	2.347	1.210-4.551	=0.012	3.341	1.331-8.846	=0.011
Obesity	6.351	3.227-12.500	<0.001	2.925	1.171-7.305	=0.022
Diabetes	2.529	1.336-4.786	=0.004	2.541	1.636-5.734	=0.039
Hypertension	2.109	1.141-3.899	=0.017	1.161	0.449-3.002	=0.758
Dyslipidemia	3.270	1.736-6.161	<0.001	2.369	1.009-5.563	=0.048
RDW%	3.693	2.476-5.509	<0.001	3.175	2.020-4.917	<0.001

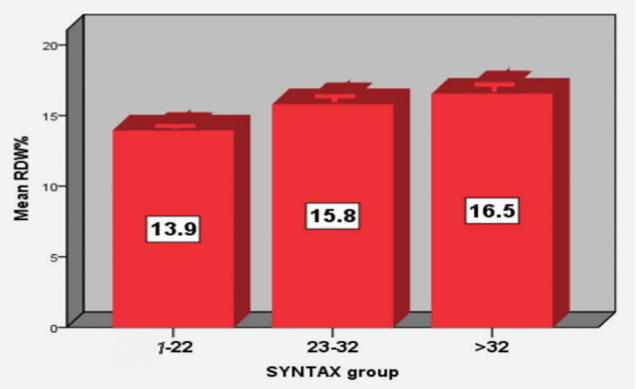
CI, confidence interval; RDW, red cell distribution width. P<0.05.

Table 3 Clinical profile according to syntax-score level

	SS (1-22) (*n*=166) [*n* (%)]	SS (23-32) (*n*=25) [*n* (%)]	SS (>32) (*n*=8) [*n* (%)]	*P*
BMI	25.31±2.5	28.68±2.4	30.75±2.3	<0.001
DM	71 (42.8)	17 (68)	6 (75)	=0.006
HTN	91 (54.8)	19 (76)	5 (62.5)	=0.124
Dyslipidemia	103 (62)	20 (80)	8 (100)	=0.007
Family history	49 (29.5)	9 (36)	4 (50)	=0.191
Hb (mg/dl)	13.33±1.3	13.50±1.2	13.70±1.6	=0.610
P	*P*1=0.522	*P*2=0.704	*P*3=0.420	
WBCs $\times 10^3$	7.08±1.9	7.16±2.1	7.66±2.4	=0.708
P	*P*1=0.839	*P*2=0.534	*P*3=0.413	
RDW%	13.91±1.4	15.77±1.1	16.52±0.7	<0.001
P	*P*1<0.001	*P*2=0.164	*P*3<0.001	

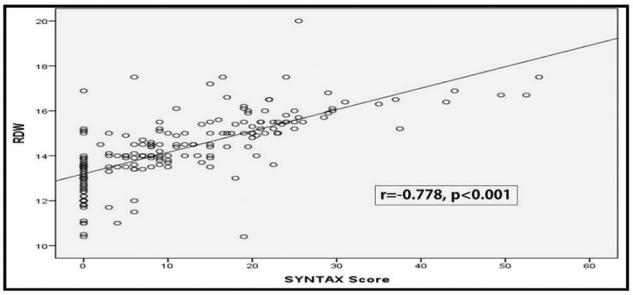
DM, diabetes mellitus; Hb, hemoglobin; HTN hypertension; RDW, red blood cell distribution width; SS, syntax score; WBCs, white blood cells. *P*1 (GI vs. GII), *P*2 (GII vs. GIII), and *P*3 (GI vs. GIII). *P* is significant if less than 0.05.

Figure 1



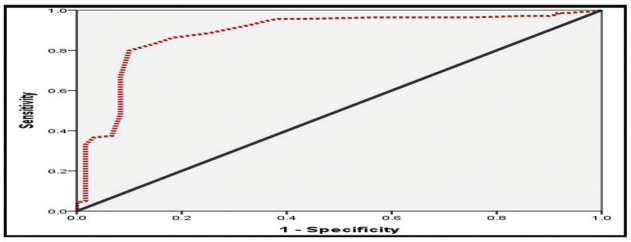
Differences in the mean RDW among SYNTAX groups

Figure 2



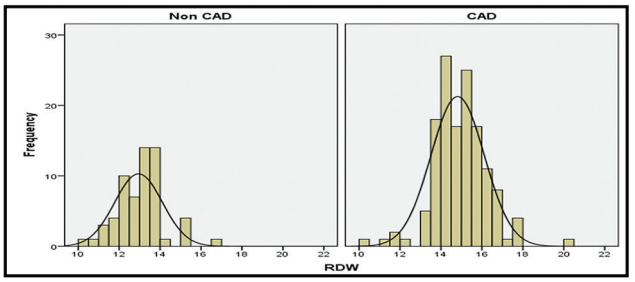
Correlation between RDW% and SYNTAX Score

Figure 3



ROC curve for diagnosis of CAD by RDW%.

Figure 4



RDW Distribution in CAD vs. Non-CAD patients

angiographic CAD (area under the curve = 0.855, 95% confidence interval 0.830–0.941). RDW value more than 13.25 demonstrated a sensitivity of 80%, a specificity of 90%, a positive predictive value of 88.9%, and a negative predictive value of 81.8% (Table 5).

Discussion

RDW is a nonexpensive and available test that can be done for predicting the degree of severity of CAD, depending on the syntax score. Our study was conducted to detect the correlation between the level of RDW and the severity of CAD. The current study included 199 patients who were referred to elective coronary angiography for stable angina in the Cardiology Department of Assiut University Hospital. Our study showed that the mean value of RDW in nonobstructive CAD patients was 12.95 ± 1.2, while in obstructive CAD patients, the mean RDW was 14.81 ± 1.3 ($P < 0.001$) and this reflects the significant association between the level of RDW with the degree of complexity of CAD as correlated with the higher levels detected in obstructive CAD patients than patients with nonobstructive CAD.

Identification and controlling of the risk factors that may increase the severity of CAD may provide a good prognostic role for management of those patients. Some of those risk factors are elevated inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-a [11]; neurohumoral factors such as BNP [12]; also, any associated comorbidities such as peripheral arterial disease [13]; pulmonary conditions such as chronic obstructive pulmonary disease [14]; other risk factors that may be associated with atherosclerosis, such as advanced age, smoking, hypertension, and DM [15,16]. Moreover, a strong association was detected in many recent studies between the level of RDW and the presence of complications in patients having CAD [17–19].

The current study included 199 patients who were referred to elective coronary angiography for stable angina in the Cardiology Department of Assiut University Hospital. Our study showed that the mean value of RDW in nonobstructive CAD patients was 12.95 ± 1.2, while in obstructive CAD patients, the mean RDW was 14.81 ± 1.3 ($P < 0.001$) and this reflects the significant association between the level of RDW with the degree of complexity of CAD, as correlated with the higher levels detected in obstructive CAD patients than patients with nonobstructive CAD.

This study was in line with many other studies that illustrated that RDW is strongly correlated with the clinical outcomes and the complications of coronary

Table 4 Diagnostic criteria of red cell distribution width % value for prediction of coronary artery disease

	Diagnostic criteria RDW% value		
AUC		0.855	
Cutoff	13.25	14.05	15.25
Accuracy (%)	80	85	74
Sensitivity (%)	96	80	50
Specificity (%)	64	90	98
PPV (%)	72.7	88.9	96.2
NPV (%)	94	81.8	66.2

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; RDW, red cell distribution width.

Table 5 Diagnostic performance of RDW value for diagnosis of CAD, analyzed as area under the curve (95% CI)

	AUC	95% CI	SE	*P*
RDW	0.885	0.830-0.941	0.028	<0.001

AUC, area under the curve; CI, confidence interval; RDW, red cell distribution width. $P<0.05$ is significant.

artery disease. Tonelli *et al.* [19] studied the relationship between RDW and the adverse outcomes in patients having CAD and detected a positive correlation between RDW values and the complications in patients of chronic CAD. Later on, Ren *et al.* [20] detected a positive correlation between RDW and mortality in chronic stable CAD patients. Moreover, in agreement with our study, Isik *et al.* [21] detected that all patients with obstructive CAD had higher RDW levels than patients without CAD.

Also, our findings agree with Nagula *et al.* [22] who studied the relationship between RDW and CAD severity and reported a positive relation between the elevated RDW values and the risk of CAD. Also, this study agrees with that of Celik *et al.* [23] in which the RDW of the CAD patients was higher than the RDW of non-CAD patients. Consequently, we propose that the high RDW is strongly associated with the severity and complexity of CAD. Also, Zalawadiya *et al.* [24] detected that a high level of RDW was considered a strong predictor risk factor of CAD. In another study, Osadnik *et al.* [25] studied the prognostic role of RDW during the long-term follow-up period over 2 years in patients with chronic stable angina who had PCI, and it was detected that there was a high mortality rate among patients with elevated RDW.

CAD is caused by multiple mechanisms; one of them is inflammation, which is considered as a risk factor of atherosclerosis: as the atherosclerotic process begins with leukocyte migration and ends by plaque rupture. In most studies, high levels of inflammatory markers, such as C-reactive protein [11] and white blood cell count [26] are strongly associated with the incidence and severity of coronary artery disease. This finding agrees with our study that showed the higher level of white blood cell count in obstructive CAD patients than the nonobstructive CAD patients and this showed the significant correlation between inflammation with the risk of CAD.

It is well known that the risk factors of atherosclerosis, such as hypertension, DM, old age, obesity, and smoking, were considered important determinants for the incidence, complexity, and severity of CAD [27]. In the current study, diabetes, hypertension, and obesity were detected to be positively associated with high RDW values. In accordance with our results, Nagula *et al.* [22], Karaçağlar *et al.* [28], and Isik *et al.* [21] showed that DM, hypertension, smoking, and obesity were considered as risk factors of CAD and associated with high RDW level and high syntax score.

Furthermore, our study showed a positive correlation between the syntax score and RDW level among the studied patients ($P < 0.001$), and it was detected that high syntax-score patients had higher RDW (16.52 ± 0.7) than patients with moderate syntax score (RDW = 15.77 ± 1.1) and was higher than low syntax-score patients (RDW = 13.91 ± 1.4). So, RDW was considered as an important predictor of high syntax score among the studied patients. Also, all patients with obstructive CAD had higher syntax score than nonobstructive CAD patients.

Isik *et al.* [21] agree with this finding in which patients with higher syntax score had the highest level of RDW values and this showed the significant relationship between RDW and the syntax score. Moreover, this finding agrees with Sahin *et al.* [29] who studied the relationship of RDW with the severity of CAD and found that higher RDW was detected in patients with higher syntax score.

Conclusion

High RDW was positively correlated with high syntax score. Also, a positive relationship was detected between RDW and the incidence and severity of CAD based on the syntax score. Furthermore, risk factors of CAD (hypertension, DM, dyslipidemia, and smoking) were elevated in patients with high RDW levels.

Limitations of the study

Elevated RDW levels are observed in many clinical settings, such as hemolysis, increased red cell destruction after blood transfusion, and in case of iron, vitamin B12, or folate deficiency. RDW is also increased in pregnancy, thrombotic thrombocytopenic purpura, and inflammatory bowel diseases. Only hemoglobin levels

were measured in our study, and other factors including iron, vitamin B12, and folate, were not measured. None of our patients received blood transfusion, and conditions like pregnancy, inflammatory bowel diseases, and thrombotic thrombocytopenic purpura, were excluded from the study.

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Conflicts of interest
None declared.

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