The Egyptian Journal of Hospital Medicine (October 2017) Vol.69 (2), Page 1838-1848

The Relation Between Red Cell Distribution Width (RDW) And Coronary Artery Calcium Score(CACS) in The Diabetic Patients Undergoing Coronary CT Angiography

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ABSTRACT

Background: red cell distribution width is a marker associated with increased mortality and morbidity in cardiac patients, however it's relation with coronary artery calcium score (CACS) is not well studied yet.

Aim of the work: this study aimed to assess the relation between red cell distribution width (RDW) and coronary artery calcium score (CACS) in the diabetic patients undergoing coronary CT angiography.

Patients and methods: this study was conducted on 60 patients presented for assessment of coronary artery disease (CAD) by coronary CT angiography and they were categorized into 2 groups, group (A) diabetics(30 patients),group(B)non-diabetics (30 patients), All patients included in this study were subjected to: History Taking, complete physical examination, multi-slice CT coronary angiography (MSCT) including calcium score(CACS), laboratory investigations including complete blood count (CBC) including RDW(SD&CV), serum calcium level(total and ionized), erythrocyte sedimentation rate (ESR), lipid profile. **Results:** higher RDW(SD) was associated with the presence of greater coronary complexity of CAD and higher calcium score. In our study total serum calcium and RDW (SD) were found to be independent predictors of high Ca score more than 100, while ionized calcium and systolic blood pressure(SBP) were independent predictors of high Calcium score more than 400. Cut off value of RDW to predict high calcium score (more than 100) was RDW(CV) more than 13.45 & RDW(SD) more than44.45, while Cut off value of RDW to predict high calcium score (more than 400) was RDW(SD) more than 45.1.

Conclusions: a greater baseline RDW(SD) value was independently associated with the presence of a greater coronary complexity of CAD and higher calcium score.

Keywords: MSCT, CACS, RDW (SD and CV), CA, OR,CI.

INTRODUCTION

Over the last decade, cardiovascular disease (CVD) has become the largest cause of death worldwide. Chronic coronary artery disease (CAD) was estimated to affect 16.8 million people in the United States; of these, 9.8 million had angina pectoris and nearly 8 million had a myocardial infarction (MI). In 2002, cardiovascular deaths were about 57 millions worldwide, and 80% of these cardiovascular deaths were in the developing world [(1)]. Many tools can help in diagnosis like electrocardiogram, echocardiography, stress testing, nuclear cardiology and cardiovascular magnetic resonance imaging. However, multi-slice CT coronary angiography is becoming one of the most important tools which can help greatly in detection of cardiac diseases and evaluating coronary artery disease (CAD) noninvasively [(2,3)]. In the 1950_s, heart disease became more recognized as a significant cause of mortality in the United States.

Red cell distribution width(RDW) is a measure of the variability in circulating erythrocyte size that is often used in the differential diagnosis of anemia [(4)]. the increased red cell distribution width (RDW) was found to be associated with a poor prognosis and increased mortality rate in several cardiovascular diseases such as stable coronary artery disease [(5)] heart failure[(6)] and peripheral arterial disease[(7)] and also with poor TIMI flow following primary percutaneous coronary intervention[(8)] and poor outcome of trans catheter aortic valve implantation. The RDW is also elevated in some subclinical states of atherosclerosis. Coronary artery calcification (CAC) is a well-established marker of the total burden of coronary atherosclerosis [(9)].

Some studies demonstrated that higher CAC scores are associated with increased risk for coronary artery disease (CAD) related events[(10)], and that addition of CAC score to traditional risk factors improves risk stratification[(11)].Diabetes mellitus (DM) represents a strong risk factor for CAD, albeit its association with CAC is controversial. While a number of studies have found significant relationship between high CAC and DM [(12)].

AIM OF THE STUDY

this study aimed to assess the relation between red cell distribution width (RDW) and coronary artery calcium score (CACS) in diabetic patients undergoing coronary CT angiography.

PATIENTS AND METHODS

Patients: this study included sixty consecutive patients whom were undergoing multi-slice CT

Received: 20 / 7 /2017
Accepted: 29/7 /2017
DOI : 10.12816/0040611

coronary angiography (MSCT) for the purpose of evaluation of chest pain from February 2016 to February 2017 who fulfill the inclusion criteria, and were divided into two groups:a)Diabetic(30patients),b)Non-diabetics(30 patients).

Patient's inclusion criteria

1- Both genders, either male or female.

2- Any age.

Exclusion criteria:

1- Systemic inflammatory disease.

2- Any Hematological disorder.(eg: RDW correlates negatively with the hemoglobin level, i.e. anemia is associated with increased RDW).

3- Thyroid disease. (Hyperthyroidism is associated with increased RDW, while hypothyroidism do the reverse).

4- Pregnancy.

5- Patients not suitable for MDCT like those with renal failure, allergy to the contrast & those with tachycardia.

6- Poor general condition.

7- Patient refusal.

8- Previous CABG or PCI.

9- Evidence of heart failure.

Methodology

- **Provision to maintain privacy:**

All participant names were hidden & were replaced by code numbers to maintain privacy of the patients.

- **All patients included in the study were subjected to:**

1- Through History Taking

- The risk factors for Coronary artery disease (age, smoking, status hypertension and diabetes mellitus).
- Chest pain which will be thoroughly analyzed regarding its character, associated symptoms, increasing factors, decreasing factors and severity.
- Special consideration to medical treatment & chronic drugs given to the patient.
- Furthermore past medical and cardiac history and history for diabetes mellitus, hypertension and other chronic diseases will be thoroughly taken and family history of coronary artery disease (CAD).

Calcium Score	Presence of CAD
0	No evidence of CAD
1-10	Minimal evidence of CAD
11-100	Mild evidence of CAD
101-400	Moderate evidence of CAD
Over 400	Extensive evidence of CAD

2- PHYSICAL EXAMINATION

- **Including general examination especially:**
- Recording ABP, pulse, JVP, general status of patient, presence of edema and auscultation of lung bases, and local cardiac examination.

3- Multi-slice CT Coronary Angiography (MSCT):

Cardiac imaging by multi-slice computer tomography (MSCT) was done for all patients using Toshiba aquilion one CT coronary angiography 320 slice with protocol used for calcium score: 114 su/ff.

Patient pre examination preparation protocol:

Subjects with a heart rate >60 beats per minute received oral ivabradine (in the form of 2 tablets of Procoralan 7.5mg in a single dose 2 days before the test) before the CT examination(as pre working protocol of our center).

The Technique

Usually, coronary CT angiography (cCTA) is performed as it contains data about coronary and cardiac anatomy. Due to recent innovations during the last two decades, new cCTA protocols allow for significant dose reductions.

However, each examination must be tailored to each patient depending on patient characteristics and clinical indication.

Calcium scoring When evaluating the heart for potential coronary artery disease, usually a non-enhanced calcium scoring sequence is first performed. This low-dose technique allows for a detection of calcifications of the coronary arteries. Although this technique does not give any information about potential hemodynamically relevant stenosis, an Agatston score can be calculated based on that data. The calculated Agatston score allows for an early risk stratification of patients with a high Agatston score (> 160) have an increased risk for a major adverse cardiac event (MACE).

Coronary CT angiography

In contrast to other CT angiography examinations, cCTA usually requires a rather high flow rate for the contrast media injection, usually between 4-5 mL/sec through an antecubital vein. Beta blockers and sublingual nitrates are usually administered before the examination to lower the heart rate, avoid arrhythmia and dilate the coronary arteries. To allow for an improved image quality and dose reduction, cCTA is usually ECG-triggered using prospective ECG gating to adapt the scan sequence to the patient's heartbeat.

Calcium score was assessed and severity was calculated using agataston score according to the following schedule:

The coronary CT angiography was used for assessment of coronary anatomy (Lesion severity).

4- Red Cell Distribution Width (RDW)

Red cell distribution width (RDW) is a parameter that measures variation in red blood cell size or red blood cell volume.

RDW is elevated in accordance with variation in red cell size (anisocytosis), i.e, when elevated RDW is reported on complete blood count, marked anisocytosis (increased variation in red cell size) is expected on peripheral blood smear review.

Reference ranges may vary depending on the individual laboratory and patient's age.

The reference range used was as follows:

- RDW-SD(standard deviation) 39-46 fL.
- RDW-CV(coefficient of variation) 11.6-14.6% in adults .

5- Other Laboratory Investigations

1- Serum Calcium level:

Venous blood sample { 2 cm of patient blood were collected in serum gel blood tube , centrifuged at rate of 5000 RPM (round per minute) were analyzed using Beckman coulter au 680 hematology analyze by using o-cresolphthalein complexone (o-cpc) .

2- Complete blood count (CBC):

Venous blood sample obtained and analyzed using sysmex xn 1000 hematology analyzer

3- Erythrocyte sedimentation rate (ESR):

Venous blood sample obtained and analyzed manually using ALI FAX analyzer.

ESR test results are measured in mm/hour, or millimeters per hour.

In our study we used first hour ESR.

4- Lipid Profile:

After 12 hours of fasting , venous blood sample were analyzed using architect plus c8000 chemistry analyzer. The blood sample was analyzed for triglycerides , cholesterol, high density lipoproteins cholesterol(HDL-C) and low density lipoproteins cholesterol(LDL-C) .

Optimal:

If the LDL is Less than 100 mg/dL (2.59 mmol/L); for those with known disease {Atherosclerotic Cardiovascular Disease(ASCVD) or diabetes}, less than 70 mg/dL (1.81 mmol/L) is optimal.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

RESULTS

This prospective analytical study conducted on sixty consecutive patients undergoing multi-slice CT coronary angiography (MSCT) for the purpose of evaluation of chest pain from February 2016 to February 2017 who fulfill the inclusion criteria, and were divided into two groups: diabetic and non-diabetic patients.

Descriptive analysis

1- **Age and Sex Distribution:**The study population included 60 patients 36 male patients (60.0%) and 24 female patients (40.0%) with a mean age of 52.28 years(± 11.15 years).

These data are tabulated and graphically represented in table 1and figure1.

Table 1: distribution of age and sex among the study population

Age & sex	Study Population
Males	36
Females	24
Mean age ± SD	52.28 ±11.15

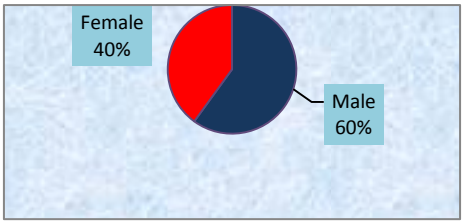

Figure 1: chart showing gender distribution among study population.

2-Risk factor distribution

Major risk factors were distributed among the study population as follow:

Dyslipidemia was the most prevalent being found in 40 patients {defined as total cholesterol mora than 200mg/dl} (66.7%) this was followed by Hypertension witch was found in 38 patients (63.3%) then diabetes witch was found in 30 patients (50.0%)and finally smoking witch was found in 22 patients (36.7%).

These data are tabulated and graphically represented in table 2 and figure 2.

Table 2: risk factors distribution among the study population:

Dyslipidemia	**Present**	**40**	**66.7%**
Hypertension	**Present**	**38**	**63.3%**
Diabetes mellitus	**Present**	**30**	**50.0%**
Smoking	**Present**	**22**	**36.7%**

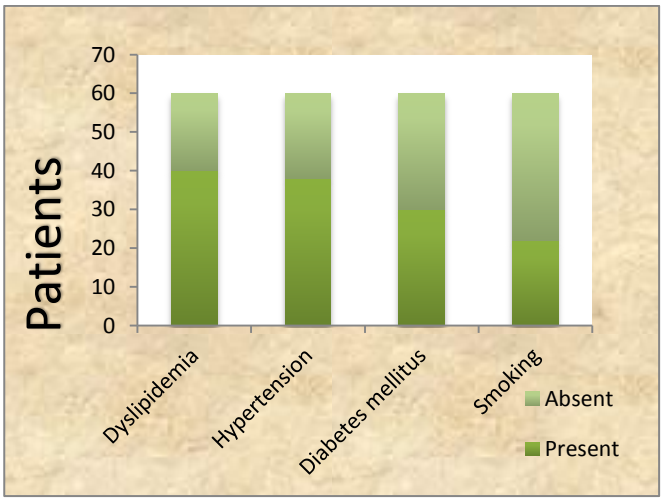

Figure 2: chart showing risk factors distribution among study population.

3-Laboratory data

a- Red cell Distribution Width (RDW)

Red cell distribution width (RDW) is a parameter that measures variation in red blood cell size or red blood cell volume.

RDW has 2 parameters standard deviation(SD) and coefficient of variation (CV).

In our study, the mean RDW(SD) was 42.68FL (±2.67) the minimum was 37.80FL while the maximum was 49.50FL.

While the mean RDW(CV) was 13.43 %, (±1.31) the minimum was 11.30%while the maximum was 17.10%.

b- Other Laboratory Results

Including total serum calcium, ionized calcium, serum creatinine, triglycerides, total cholesterol, low density lipoproteins(LDL), high density lipoproteins(HDL), erythrocyte sedimentation rate(ESR) and hemoglobin.

Table 3: laboratory data results among the study population:

	Mean	Standard Deviation	Minimum	Maximum
Total Serum CA	9.38	0.60	8.30	10.90
Ionized CA	4.70	0.44	4.00	5.90
Serum creatinine	1.09	0.23	.60	1.60
Triglycerides	233.52	85.18	94.80	479.28
Total Cholesterol	205.08	32.82	109.00	267.00
LDL	131.34	33.30	67.00	192.00
HDL	39.98	7.75	26.00	64.00
RDW CV	13.43	1.31	11.30	17.10
RDW SD	42.68	2.67	37.80	49.50
ESR	45.10	23.68	3.00	92.00
HB	12.13	1.23	10.10	15.20

4-Vital Data (blood pressure, pulse)

The mean systolic blood pressure was127.3mmhg (±12.74), the minimum was 100mmhg while the maximum was 150mmhg.

The mean diastolic blood pressure was 83.67mmhg (±12.75), the minimum was 60mmhg, while the maximum 110mmhg. The mean pulse was 58.77 beat per minute (± 4 bpm), the minimum was 52 while the maximum was 67.

5-Multi-Slice CT Coronary Data

We analyzed the CT coronary data according to:

Number of affected vessels (may be 0,1,2 and more than 2), Percentage of lumen stenosis (may be non-significant {less than 50% stenosis}, subtotal {50-99% stenosis} and total {100% stenosis})

Calcium score was classified into 3 categories either 0, from 1 to 400, more than 400.

Table 4: distribution of CT coronary data among the study population

		Count	%
No. of Affected vessels	0	17	28.3%
	1	25	41.7%
	2	16	26.7%
	More Than 2	2	3.3%
Percent of Lumen stenosis	Non-significant (less than 50% stenosis)	33	55.0%
	Subtotal (50-99% stenosis)	21	35.0%
	Total (100% stenosis)	6	10.0%
Calcium score	0	27	45.0%
	1-400	27	45.0%
	>400	6	10.0%

Comparative analysis

The study population was divided into

- Diabetics (30 patients)
- Non-diabetics (30 patients)

A-Risk factors in both study groups were analyzed as follows:

1- **Hypertension(HTN)**

A-HTN in the group of diabetics

Hypertension was found to have statistically significant deference between the diabetic and non-diabetic group regarding RDW(SD) which was higher among diabetics.

B- HTN in the group of non-diabetics:

There was no statistically significant deference between the diabetics and non-diabetics regarding the study variables.

2-Smoking

A-Smoking in the group of diabetics:

Smoking was found to have statistically significant deference between the group of diabetics and non-diabetics regarding total serum calcium, ionized calcium, serum creatinine, triglycerides, RDW (SD) and male gender being higher in diabetics.

B-Smoking in the group of non-diabetics

Smoking was found to have statistically significant deference between the group of diabetics and non-diabetics regarding. RDW(CV) and pulse being higher in the group of non-diabetics.

3-Diabetes Mellitus

About diabetes in relation to other study variables as follow:

In the group of diabetics, diabetes was found to have statistically significant deference between the

group of diabetics and non-diabetics regarding age, total serum calcium, ionized calcium, low density lipoproteins (LDL) and diastolic blood pressure being higher in the group of diabetics.

B-Multi-slice CT coronary data

We analyzed the CT coronary data according to:

Number of affected vessels (may be 0,1,2 and more than 2).

Percentage of lumen stenosis (may be non-significant {less than 50% stenosis}, subtotal {50-99% stenosis} and total {100% stenosis})

Calcium score (witch was classified into 3 categories either 0, from 1 to 400 and more than 400).

Then we did Correlations between RDW(CV) and RDW(SD) and CT coronary data.

1-The number of affected vessels

A-The number of affected vessels in the group of diabetics

The number of affected vessels was found to have statistically significant deference between the group of diabetics and non-diabetics regarding ESR, systolic, diastolic blood pressure, lesion severity, hypertension and smoking being higher in the group of diabetics.

B-The number of affected vessels in the group of non-diabetics:

The number of affected vessels was found to have statistically significant deference between the group of the diabetics and non-diabetics regarding the lesion severity being higher in the group of non-diabetics.

2-The Percent of lumen stenosis

A-Percent of lumen stenosis in the group of diabetics

The percent of lumen stenosis was found to have statistically significant deference between the group of diabetics and non-diabetics regarding total serum calcium, ionized calcium, serum triglycerides, RDW(SD) , diastolic blood pressure, male gender and smoking being higher in the group of diabetics.

B-Percent of lumen stenosis in the group of non-diabetics :

Percentages of lumen stenosis was found to have statistically significant deference between the group of diabetics and non-diabetics regarding male gender being higher in the group of non-diabetics.

1-Calcium score

A- Calcium score in the group of diabetics

Calcium score was found to have statistically significant deference between the group of diabetics and non-diabetics regarding total serum calcium, ionized calciu ,RDW (SD), male gender, hypertension and smoking being higher in the group of diabetics.

B- **Calcium score in the group of non-diabetics**

Calcium score was found to have statistically significant deference between the group of diabetics and non-diabetics regarding age and triglycerides being higher in the non-diabetic group.

4-Correlations between RDW(CV) and RDW(SD) and CT coronary data

RDW (SD) was found to have statistically significant deference regarding calcium score, percent of lumen stenosis and number of affected vessels (the CT data).

Correlations were done using Spearman correlation coefficient.

Table 5: correlations between RDW(CV) and RDW(SD) and CT coronary data

	RDW CV			RDW SD		
	Correlation Coefficient	P value	N	Correlation Coefficient	P value	N
Calcium score	.211	.105	60	.532	<0.001	60
Percent of lumen stenosis	.035	.789	60	.258	.047	60
Number of affected vessels	.068	.606	60	.319	.013	60

C-Red cell distribution width(RDW)

RDW has 2 parameters standard deviation(SD) and coefficient of variation (CV) and has the following relations with other variables in this study as follows:

1-Red cell distribution width(RDW) in the group of diabetics

RDW(CV) was found to have statistically significant deference between the group of diabetics and non-diabetics regarding age, ionized calcium and high density lipoproteins (HDL) being higher in the diabetic group.

While RDW (SD) was found to have statistically significant deference between the group of diabetics and non-diabetics regarding total serum calcium, ionized calcium, low density lipoproteins (LDL), high density lipoproteins (HDL), systolic and diastolic blood pressure being higher in the diabetic group.

Table 6: relation between RDW (CV), RDW(SD) and other study variables in the group of diabetics

Diabetics		RDW CV	RDW SD
Age	R	.365	.060
	P	.047	.753
	N	30	30
Total Serum CA	R	.342	.581
	P	.064	.001
	N	30	30
Ionized CA	R	.528	.543
	P	.003	.002
	N	30	30
s. creatinine	R	.026	.109
	P	.893	.565
	N	30	30
Triglycerides	R	.038	.256
	P	.842	.172
	N	30	30
Total Cholesterol	R	.086	.182
	P	.652	.335
	N	30	30
LDL	R	.300	.441
	P	.107	.015
	N	30	30
HDL	R	-.381-	-.474-
	P	.038	.008
	N	30	30
ESR	R	.151	.318
	P	.424	.087
	N	30	30
HB	R	.010	-.312-
	P	.959	.093
	N	30	30
SBP	R	-.076-	.385
	P	.691	.036
	N	30	30
DBP	R	.011	.543
	P	.954	.002
	N	30	30
Pulse	R	-.276-	-.080-
	P	.140	.674
	N	30	30

2-Red cell distribution width in the group of non-diabetics: RDW(CV) was found to have statistically significant deference between the group of diabetics and non-diabetics regarding total cholesterol being higher in the group of non-diabetics, while RDW(SD) wasn't found to have statistically significant deference between the group of diabetics and non-diabetics regarding the study variables.

Table7: relation between RDW (CV), RDW(SD) and other study variables in the group of non-diabetics:

Non diabetics		RDW CV	RDW SD
Age	R	-.344-	-.102-
	P	.063	.592
	N	30	30
Total Serum CA	R	.043	.007
	P	.820	.969
	N	30	30
Ionized CA	R	-.213-	.359
	P	.258	.051
	N	30	30
s. creatinine	R	.084	.147
	P	.659	.440
	N	30	30
Triglycerides	R	-.264-	.291
	P	.158	.118
	N	30	30
Total Cholesterol	R	-.547-	.040
	P	.002	.833
	N	30	30
LDL	R	-.316-	.037
	P	.089	.844
	N	30	30
HDL	R	.090	.199
	P	.636	.291
	N	30	30
ESR	R	.099	.291
	P	.603	.119
	N	30	30
HB	R	.073	-.339-
	P	.702	.067
	N	30	30
SBP	R	-.196-	.000
	P	.299	.997
	N	30	30
DBP	R	-.263-	.138
	P	.161	.467
	N	30	30
Pulse	R	.237	-.045-
	P	.208	.815
	N	30	30

D-Independent predictors for high calcium score (more than 100 and more than 400), and for the presence of vessel disease

1-Independent predictors of high calcium score (> 100)

We found that the independent predictors of high ca score more than 100 were total serum calcium and RDW (SD).

Table 8: independent predictors for high calcium score more than 100

		B	S.E.	Wald	df	P value	OR	95% C.I.	
								Lower	Upper
Calcium score>100	Total Serum CA	3.343	1.564	4.570	1	.033	28.309	1.320	606.958
	RDW SD	1.172	.518	5.114	1	.024	3.227	1.169	8.907

2-Independent predictors of high calcium score (> 400)

We found that the independent predictors of high calcium score more than 400 are ionized calcium and systolic blood pressure(SBP).

Table 9: independent predictors for high calcium score more than400

		B	S.E.	Wald	df	P value	OR	95% C.I.	
								Lower	Upper
Calcium score>400	Ionized CA	8.729	2.445	6.419	1	.011	6179.649	7.214	5293288.781
	SBP	.140	.071	3.935	1	.047	1.151	1.002	1.322

3-Independent predictors of presence of vessel disease (1 vessel, 2 vessels & more than 2 vessels)

We found that that the independent predictor of presence of vessel disease was the diabetes mellitus (DM).

Table 10: independent predictors for presence of vessel disease

		B	S.E.	Wald	Df	P value	OR	95% C.I.	
								Lower	Upper
Presence of vessel disease	Diabetes mellitus	1.835	.739	6.168	1	.013	6.264	1.472	26.648

E-Cut off value of RDW to predict high calcium score (more than 100) and (more than 400)

Table 11: detecting positive and negative predictive value, sensitivity, specificity, area under the curve and diagnostic accuracy for the rock curve of high calcium score (> 100)

high calcium score (> 100)	Area under curve	P value	95% Confidence Interval		Cut off value	Sensitivity (%)	Specificity (%)	PPV	NPV	Diagnostic accuracy
			Lower Bound	Upper Bound						
RDW CV	.683	.031	.530	.836	13.45	81.3	70.5	50.00	91.18	73.33
RDW SD	.908	<0.001	.823	.992	44.45	81.3	95.5	86.67	93.33	91.67

Table 12: detecting positive and negative predictive value, sensitivity, specificity, area under the curve and diagnostic accuracy for the rock curve of high calcium score (>400)

High calcium score (> 400)	Area Under curve	P value	95% Confidence Interval		Cut off value	Sensitivity (%)	Specificity (%)	PPV	NPV	Diagnostic accuracy
			Lower Bound	Upper Bound						
RDW SD	.943	<0.001	.884	1.000	45.1	100	90.7	54.55	100.00	91.67

DISCUSSION

This study was done to assess the relation between red cell distribution width (RDW) and coronary artery calcium sco".re (CACS) in the diabetic patients undergoing coronary CT angiography.

Other studies were done to study the association between RDW and heart diseases like the study done by **Welmin *et al.*** [12]; **Turgay *et al.*** [13] and **Ozgul *et al.*** [14].

In this study, the CT data was found to have statistically significant difference with RDW(SD) this was concordant with results found by WEIMIN **Welmin *et al***. [12] who found significant relation between RDW and CAD group of patients compared to control group(0.001).

RDW(SD) was found to have statistically significant difference with hypertensives in the group of diabetics while RDW (SD)& RDW(CV) was found to have non-significant relation with diabetics and with hypertensives in the group of diabetics and this was concordant with results found by **Welmin *et al***. [12], in their study ; they found non-significant relation with diabetes and/or hypertension(0.763).

In our study, RDW(SD) & RDW(CV) were found to have no statistically significant relation in both groups (diabetics &non-diabetics) regarding HB & TG, this was discordant with results found by **Welmin *et al***. [12] in their study since they found significant relation with HB(0.001) &TG(<0.001).

In our study, in the group of diabetics RDW(CV) was found to have statistically significant difference with age& HDL-C while RDW(SD) was found to have statistically significant difference with HDL-C &LDL-C , and in the group of non-diabetics RDW(CV) was found to have statistically significant difference with total cholesterol, this was discordant with results found by **Welmin *et al***. [12] in their study; they found non-significant relation with age(0.212),serum creatinine (0.703),total cholesterol(0.775), HDL-C(0608)& LDL-C(0.290).

Turgay *et al*. **[13]** studied the relation of red cell distribution width with the presence, severity and complexity of coronary artery disease witch was done on 193 non-anemic patients who had undergone coronary angiography for stable angina pectoris showed that CAD had significantly elevated RDW levels compared with the patients without CAD (14.4±1.3 vs. 12.5±0.9, P<0.001) , this was concordant with our study witch showed that RDW (SD) was found to have statistically significant deference regarding calcium score(<0.001), percent of lumen stenosis(.047) and number of affected vessels(.013) (the CT data reflecting the presence of CAD).

Ozgul *et al*. [14] in their study used the ROC curve analysis, an RDW value of 13.05% was identified as an effective cut-off point for predicting the severity of the CACS (>100), with a sensitivity of 58.9% and a specificity of 72.0%, and the area under the curve (AUC) was 0.70".

Turgay *et al.* [13 showed in a receiver operating characteristic (ROC) curve analysis, an RDW value of 13.25 was identified as an effective cut-point in the segregation of the presence or absence of CAD [area under curve=0.87, 95% confidence interval (CI) 0.81–0.92], An RDW value of more than 13.25 yielded a sensitivity of 84%, a specificity of 79%, a positive predictive value of 89%, and a negative predictive value of 71%.

In our study, we studied cut off value of RDW(SD)&RDW(CV) to predict high calcium score more than 100 & cut off value of RDW(SD) to predict high calcium score more than 400 and found that Cut off value of RDW(CV) to predict high calcium score more than 100 was 13.45, (Area under curve was .683, and the confidence interval (CI) Lower Bound was .530 while upper bound was .836) , An RDW (CV) value of more than 13.45 yielded a sensitivity of 81.3%, a specificity of 70.5%, a positive predictive value of 50.00%, and a negative predictive value of 91.18%, with Diagnostic accuracy 73.33% .

In our study, the cut off value of RDW(SD) to predict high calcium score more than 100 was 44.45, (Area under curve was .908, and the confidence interval (CI) Lower Bound was.823, while upper bound was .992) ,An RDW (SD) value of more than 44.45 yielded a sensitivity of 81.3%, a specificity of 95.5%, a positive predictive value of 86.67%, and a negative predictive value of 93.33% , with Diagnostic accuracy 91.67%.

Also in our study, cut off value of RDW (SD) to predict high calcium score more than 400 was 45.1, (Area under curve was .943 , and the confidence interval (CI) Lower Bound was .884, while upper bound was 1.000), An RDW (SD) value of more than 45.1 yielded a sensitivity of 100%, a specificity of 90.7% , a positive predictive value of 54.55%, and a negative predictive value of 100.00%, with Diagnostic accuracy 91.67%.

Turgay *et al*.[13 showed that RDW was observed to be an independent predictor for angiographic CAD (odds ratio=4.80, 95% CI

2.41–9.57, P<0.001) ,while in our study independent predictors for high calcium score more than 100 were Total Serum CA (odds ratio=28.309, 95% CI Lower=1.320 & upper= 606.958 , P<0.033) & RDW SD (odds ratio=3.227, 95% CI lower=1.169 and upper=8.907, P<0.024).

In our study independent predictors for high calcium score more than 400 were ionized calcium(odds ratio=6179.649, 95% CI Lower=7.214 and upper=5293288.781, P<0.011) &SBP (odds ratio=1.151, 95% CI lower=1.002& upper=1.322, P<0.047), and independent predictors for presence of vessel disease (1 vessel, 2 vessels and more than 2 vessels) was Diabetes mellitus (odds ratio=6.264, 95% CI lower=1.472& upper=26.648, P<0.013).

Turgay *et al.* [13] showed that DM (OR= 2.42, 95% CI 1.14–5.13, P=0.02), HTN (OR=2.44, 95% CI 1.19–5.02, P=0.01), and male sex (OR=2.12, 95% CI 1.03–4.34, P=0.03) were identified as independent correlates of an elevated RDW value, this was concordant with our study which showed statistically significant deference between hypertension and RDW(SD) in the group of diabetics (p < 0.001), however there was no statistically significant deference between hypertension and RDW(SD) (p=0.140)in the group of non-diabetics, while there were no statistically significant deference between hypertension and RDW(SD)(P=0.070)& RDW(CV)(p= 0.573).

Turgay *et al.* [13] found that higher baseline RDW values were independently associated with more severe and complex CAD "this was concordant with our study which found that RDW(SD) was associated with worse CT coronary data(calcium score, number of affected vessels and percent of lumen stenosis).

Our study proposed some possible mechanistic explanations for the relationship between RDW and complexity of CAD. One of the possible mechanisms is inflammation (that's why systemic inflammatory disease was considered as one of the exclusion criteria) ,which plays an important role in the entire setting of the atherosclerotic process: from the very beginning of leukocyte migration until eventual plaque rupture[15] .

It is known that elevated inflammatory markers such as ESR (so we used ESR as one of the study variables), CRP and BNP, are associated with the extent and severity of CAD.

In our study, we did not measure CRP and BNP; however, elevated RDW values were readily been shown to be associated with markers such as BNP[16,17]and CRP[18,19] in the previous studies.

Atherosclerotic risk factors such as DM, HTN, smoking, obesity, sex, and advanced age were found to be independent determinants of the presence of CAD as well as extent and severity [20,21]. In our study, the presence of HTN was found to be independently associated with elevated RDW(SD) levels in diabetics and RDW(CV) was found to have statistically significant deference with age in the diabetic group.

Nabai*s et al.* [22] in a study based mainly on patients with acute coronary syndrome found that elevated RDW was associated with older age, HTN, previous history of myocardial infarction, coronary artery bypass grafting, peripheral artery disease, and renal dysfunction, this was concordant with our study which found higher levels of RDW(CV) associated with higher age of diabetic patients and higher RDW(SD) associated with hypertension in the group of diabetics.

HTN, DM, obesity and chronic renal disease are also known to be associated with more severe and complex CAD[23,24],On the basis of these facts, we propose that the link between elevated RDW and atherosclerotic risk factors might be closely associated with the complexity of CAD.

In concordance with the literature, we found that elevation in the RDW (SD) values were associated with both the presence and the complexity of the CAD. The pathophysiological mechanistic link driving this association remains obscure at present and requires a more thorough understanding of the physiological mechanism. However, theoretically we considered that inflammatory activation and the presence of atherosclerotic factors that are considered as risk factors for severe, diffuse and complex CAD affect the erythropoiesis and thereby lead to elevated RDW values.

Ozgu *et al.* [14] showed that group II(n.106 patients) with high calcium score more than 100 found significant relation with age(<0.001), this was concordant with our study which showed significant relation between calcium score and age in the group of non-diabetics(0.003).

Ozgu *et al.* [14] showed significant relation between hypertension and calcium score (0.006), this was concordant with our study which showed significant relation between hypertension and calcium score in the group of diabetics(0.045).

Ozgu *et al.* [14] showed significant relation between hemoglobin and calcium score(0.030), this was discordant with our study which showed non-significant relation between hemoglobin and calcium score in the group of diabetics (0.354)&in the non-diabetic group(0.557).

Ozgu *et al*. [14] showed significant relation between RDW and calcium score(0.010), this was concordant with our study which showed significant relation between RDW(SD) and calcium score in the group of diabetics(0.002), while RDW(CV) showed non-significant relation with calcium score in the group of diabetics(0.175).

Ozgu *et al*. [14] showed non-significant relation between total serum calcium and calcium score(0.638),this was discordant with our study which showed significant relation between calcium score & total serum calcium(0.009)& ionized calcium(< 0.001).

Ozgu *et al*. [14] showed non-significant relation between calcium score and Total cholesterol(0.930), LDL(0.859), HDL(0.605) & triglycerides(0.644) this was concordant with our study which showed non-significant relation between calcium score and Total cholesterol (0.208), LDL(0.089), HDL(0.163) & triglycerides (0.127) in the group of diabetics.

Ozgu *et al*. [14] showed significant relation between calcium score and RDW, this was concordant to our study which showed significant relation between calcium score and RDW(SD)(<0.001), while Chaikriangkrai[25] ***et al*.** found no association between the complete blood cell count, including the RDW, and the CACS in 868 patients without known CHD.

previous studies have linked an increased RDW with inflammatory markers such as high-sensitivity C-reactive protein, soluble tumor necrosis factor receptors, and IL-6 in the setting of atherosclerosis[26].

LIMITATIONS

First, elevated RDW levels were observed in many clinical settings such as hemolysis, increased red cell destruction after blood transfusion, and in the setting of ineffective red cell production such as that of iron, vitamin B12, or folate deficiency. RDW is also increased in clinical states such as pregnancy, thrombotic thrombocytopenic purpura, and inflammatory bowel diseases.(That's why systemic inflammatory disease, Any Hematological disorder, Pregnancy and Poor general condition were considered as exclusion criteria).

Only Hb levels and ESR were measured in this study, and other factors including iron, vitamin B12, and folate were not measured. There were no pregnant, no inflammatory bowel diseases, no thrombotic thrombocytopenic purpura, and no malnourished patients.

Second: single center study.

Third: small sample size.

Fourth, in our study we found only 2 patients with more than 2 coronary arteries affected and this was one of the biggest limitations in our study affecting the results.

RECOMMENDATIONS

Multi-center study with large number of patients is needed for better assessment of the relation between RDW and CACS in patients undergoing MSCT coronary angiography.

CONCLUSION

A greater baseline RDW(SD) value was independently associated with the presence of and a greater coronary complexity of CAD and higher calcium score.

In our study

1- We found that the independent predictors of high ca score more than 100 were total serum calcium and RDW (SD).

2- We found that the independent predictors of high calcium score more than 400 were ionized calcium and systolic blood pressure(SBP).

3- We found that the independent predictor of presence of vessel disease is diabetes mellitus(DM).

4- Cut off value of RDW to predict high calcium score (more than 100) was RDW(CV) more than 13.45 & RDW(SD) more than44.45.

5- Cut off value of RDW to predict high calcium score (more than 400) was RDW(SD) more than 45.1.

REFERENCES

1-**Reddy KS (2004):** Cardiovascular disease in non-Western countries. N. Engl. J Med., 350(24):2438-2440.

2-**Meijboom WB** (2008): Diagnostic accuracy of 64-slice computed tomography coronary angiography. J.Am. Coll. Cardiol., 52:2135-2144.

3-**Miller JM (2008):** Diagnostic performance of coronary angiography by 64-row CT. N. Engl. J. Med., 359: 2324-2336 .

4-**Demir A(2002):** Most reliable indices in differentiation between thalassemia trait and iron deficiency anemia. Pediatr. Int., 44:612-616.

5-**Lappé JM (2011)*:*** The complete blood count, and mortality in patients with coronary disease and a normal comparison population. Clin. Chem. Acta, 412:2094-209.

6-**Felker GM(2007)***:*Red cell distribution width as a novel prognostic marker in heart failure. J. Am. Coll. Cardiol.,50:40-47.

7-**Ye Z (2011):**Usefulness of red cell distribution width to predict mortality in patients with peripheral artery disease. J. Am. Coll. Cardiol.,107:1241-1245.

8- **Karabulut A (2012):** Elevated red cell distribution width level predicts worse post interventional thrombolysis in myocardial infarction flow reflecting abnormal reperfusion in acute myocardial infarction treated with a primary coronary intervention. Coron. Artery Dis.,23:68-72.

9- **Rumberger JA(1995):**Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. Circulation, 92:2157–2162.

10- **Detrano R (2008):** Coronary calcium as a predictor of coronary events in four racial or ethnic groups. New Engl. J.Med., 358:1336–1345.

11- **Polonsky TS (2010):** Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA., 303:1610–1616.

12- **Bulugahapitiya U (2009):** Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet. Med., 26:142–148.

13- **Welmin li (2015)**: Association between red cell distribution width and the risk of heart events in patients with coronary artery disease . Experimental and Therapeutic Medicine,9:1508-1514.

14- **Turgay Isik (2012)**: Relation of red cell distribution width with the presence, severity, and complexity of coronary artery disease, Coronary Artery Disease, 23:51–56.

15- **Ozgul Malcok Gürel(2015)**:Association between red blood cell distribution width and coronary artery calcification in patients undergoing 64-multidetector computed tomography. Korean Circ. J .,45(5):372-377.

16- **Drakopoulou M (2009):** Association of inflammatory markers with angiographic severity and extent of coronary artery disease. Atherosclerosis, 206:335–339.

17- **Fukuta H(2009):**Elevated plasma levels of B-type natriuretic peptide but not C-reactive protein are associated with higher red cell distribution width in patients with coronary artery disease. Int. Heart J., 50:301–312.

18- **Jackson CE (2009):**Red cell distribution width has incremental prognostic value to B-type natriuretic peptide in acute heart failure. Eur. J .Heart Fail., 11:1152–1154.

19- **Lappe JM(**2011):Red cell distribution width, C-reactive protein, the complete blood count, and mortality in patients with coronary disease and a normal comparison population. Clin Chim Acta.,412:2094–2099.

20- **Lippi G(**2009):Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med.,133:628–632.

21- **Jousilahti P(**1999):Sex, age, cardiovascular risk factors, and coronary heart disease. Circulation, 99:1165–1172.

22- **Dent TH(**2010):Predicting the risk of coronary heart disease. The use of conventional risk markers. Atherosclerosis ,213:345–351.

23- **Nabais S(2009):**Association between red blood cell distribution width and outcomes at six months in patients with acute coronary syndromes. Rev Port Cardiol.,28:905–924.

24- **Yan LQ(**2011):The relationship between kidney function and angiographically-derived SYNTAX score. Can J Cardiol doi:10.1016/j.cjca.2011.04.004.

25- **Rubinshtein R(**2006):Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. Am J Cardiol., 97:1277–1280.

26- **Chaikriangkrai K(**2014):Association between hematological indices and coronary calcification in symptomatic patients without history of coronary artery disease. N Am J Med Sci6:433-9.

Weiss G(2005):Anemia of chronic disease. N Engl J Med.,352:1011-23.