

## Relation between Red Blood Cell Distribution Width and Left Ventricular Function In Acute Coronary Syndrome Patients

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### ABSTRACT

Red blood cells distribution width (RDW) is a measure of red blood cell width variation, reported as part of a standard complete blood count; although it is usually measured, as a routine test, actually its values have been only used in the differential diagnosis of anemia and high values indicate the presence of anisocytosis. It has been demonstrated that RDW could be considered an independent prognostic marker of cardiovascular events in patients with heart failure and peripheral artery diseases. However the role of RDW in patients with acute coronary syndromes (ACS) is less known.

**Methods:** This study included 40 consecutive patients presented with chest pain suggestive of the acute coronary syndrome. Participating subjects were subjected to a detailed history, complete physical examination 12- lead ECG, and routine laboratory investigations including serum cardiac markers and complete blood count including RDW were performed and echocardiography examination including ejection fraction and tissue Doppler.

**Results:** The study showed statistically significant **positive** correlation with p-value <0.05 between RDW and each of Left atrium, End systolic, and End diastolic dimensions in echo finding which indicates increase in RDW

had positive impact on increase of Left atrium, End systolic, and End diastolic, Resting wall motion abnormalities On the other hand there is **negative** statistically significance correlation with p-value <0.001 between RDW and Ejection fraction which indicates increase in RDW had negative impact on Ejection fraction. Also there was significant correlation between RDW and systolic function (s wave of tissue Doppler) with p value (p value=0.01). Also we found significant correlation between RDW and other parameters age, hypertension, history of ischaemic heart disease. Performing ROC curve analysis between RDW and echocardiography ejection fraction 50% we found that best cut off point to be **16.1** with sensitivity (79.2%) and specificity (62.5%).

**Conclusion:** Finally our study had lent role of RDW prognostication in acute coronary syndrome patients and opened the door for later investigation exploring the specific behavior of RDW in different patient categories.

**KEYWORDS:** Red cell distribution width-Acute coronary syndrome-Tissue Doppler.

## INTRODUCTION

Red blood cells distribution width (RDW) is a measure of red blood cell width variation, reported as part of a standard complete blood count; although it is usually measured, as a routine test, actually its values have been only used in the differential diagnosis of anemia and high values indicate the presence of anisocytosis [Tsuboi S et al, 2013].

RDW is widely available to clinicians because it is routinely reported as part of the complete blood count [Morris M et al, 2001].

Highly significant associations have been described between RDW value and all-cause, noncardiac, and cardiac mortality in patients with coronary artery disease, acute and chronic heart failure, peripheral artery disease, stroke, pulmonary embolism, and pulmonary artery hypertension [Demir A et al, 2002].

It has been demonstrated that RDW could be considered an independent prognostic marker of cardiovascular events in patients with heart failure and peripheral artery diseases [Nishizaki Y et al, 2012].

Some Authors studied the role of RDW as a predictor of mortality in patients with heart failure [Pascual-Figal DA et al, 2009] others analyzed between NT-proBNP and RDW in these patients [Holmström A et al, 2012] however the role of RDW in patients with acute coronary syndromes (ACS) is less known and the mechanism by which RDW is related to a poor prognosis in patients with ACS is still unclear [Wang YL et al, 2011]

### RDW and cardiovascular disease

Classical in vitro studies of the function of the coagulation system are performed in plasma, i.e. without erythrocytes or red blood cells (RBCs) [Dahlbäck et al, 2000]

Few studies have therefore investigated the prothrombotic potential of RBCs. However, RBCs are constituents of clots and thrombi formed in vivo [Wohner et al, 2008]

RBCs may play a prothrombotic role in blood coagulation by increasing blood viscosity and forcing platelets towards the vessel wall [Gersh et al, 2009]

Even small structural differences in RBCs may have a large influence on pathophysiology [Goldsmith et al. 1971]. Moreover, RBCs may actively participate in thrombin generation [Whelihan et al, 2013 ]

### Laboratory measurement of RDW

Modern automated blood cell counters calculate RDW from the RBC volume histogram as an index of heterogeneity [Buttarello et al, 2008]

RDW is often expressed as a percentage coefficient of variation (CV), and is calculated by dividing the standard deviation (SD) of the RBC volume by the MCV [Montagnana et al, 2011] .The result is multiplied by 100 in order to express it as a percentage [Buttarello et al, 2008].

RDW may also be expressed as a direct measurement of the width of the distribution, which gives a measure (in fL) that is independent of mean MCV [Van den Bossche et al, 2002].

The lower reference limit for five different instruments varied between 10.7% and 12.9%, and the upper reference limit between 13.8% and 15.3% [Van den Bossche et al, 2002].

At present, any clinical use of RDW must be evaluated by comparison with reference values established for each model of analyser.

### Determinants of RDW

A number of hematological and non-hematological diseases have been associated with increased RDW (Table 1). Increased RDW (i.e. anisocytosis) is common in patients with deficiencies of iron, folate, and vitamin B12 [Briggs et al, 2009].

RDW has been used for differential diagnosis of anemia. RDW is usually normal in

thalassaemia traits and increased in iron deficiency anaemia. Increased RDW is present in megaloblastic anaemia but RDW is usually normal in macrocytosis due to other causes [Briggs et al, 2009].

However, there is a wide distribution of RDW values within a given disease, which has diminished its usefulness in differential diagnosis. [Briggs et al, 2009].

Increased RDW may be seen in other haematological disorders such as haemolytic anaemia, transfusion, sickle cell/beta thalassaemia, anaemia of chronic disorders,

hereditary spherocytosis, and sickle cell anaemia and has also been associated with non-haematological diseases such as chronic hepatobiliary disease, hypothyreosis, hyperthyreosis,

(Dorgalaleh et al, 2013) Behçet's disease, systemic lupus erythematosus and inflammatory bowel disease [Yeşil et al , 2011].

Table 1: Hematological and non-hematological diseases associated with increased red cell distribution width [Bengt Zöller et al, 2014].

Hematologic disorders	Non-hematological disorders
Iron deficiency anemia	Chronic hepatobiliary disease
Megaloblastic anemia (folate and vitamin B12 deficiency)	Hypothyreosis
Haemolytic anemia	Hyperthyreosis
Sickle cell/beta thalassaemia	Behçet's disease
Transfusion	Systemic lupus erythematosus
Anemia of chronic disorders	Inflammatory bowel disease
Hereditary spherocytosis	Peripheral artery disease
Sickle cell anemia	Stroke
	Coronary heart disease
	Heart failure
	Atrial fibrillation
	Pulmonary arterial hypertension
	Venous thromboembolism

Table 2: Laboratory markers and acquired and lifestyle-related factors associated with increased red cell distribution width [Bengt Zöller et al,2014].

Acquired and lifestyle-related factors	Laboratory markers
Age	Inflammatory markers
Obesity	Brain natriuretic peptide
Low cardiorespiratory fitness	Estimated glomerular filtration rate
Smoking	Microalbuminuria
High alcohol consumption	Troponin T
Being unmarried	Unfavourable lipid profile
Obstructive sleep apnoea syndrome	HbA1c
Lung function	Short telomere length
rs1050828 and rs10493739 variants	

RDW was found to be associated with the severity of atherosclerotic disease in patients with PAD [Demirtas et al, 2014] and in a case-control study, increased RDW was associated with ischaemic stroke [Ramírez-Moreno et al, 2013].

In CAD, TDI-derived systolic velocities have been used as an adjunct to WMSI as a predictor of risk [Marwick TH et al, 2004].

The peak systolic velocity by TDI (S') is a sensitive marker of mildly impaired LV systolic function, even in those with a normal LVEF or apparently preserved LV systolic function, such as “diastolic HF” [Sanderson JE. et al,2007], or in diabetic subjects without overt heart disease [Fang ZY et al,2004].

### Aim of the work

To evaluate the prognostic implications of red cell distribution width in acute coronary syndrome patient and its relation to left

ventricular function (ejection fraction and tissue Doppler) in these patient.

## PATIENTS AND METHODS

This study included 40 patients presented with chest pain suggestive of the acute coronary syndrome admitted to coronary care unit at Fayoum university hospital and Fayoum general hospital

### Exclusion criteria

1. Blood products transfusion in the previous week
2. Medical History of hematological disorders.
3. Recent chemotherapy.
4. Hepatic cirrhosis.
5. Use of drugs known to induce changes in the morphology and rheology of RBC (pentoxifyline, erythropoietin, cyclosporine)
6. Anemia with hemoglobin less than 7 g/dl.

For each patient, a detailed history, complete physical examination 12-lead ECG, and routine laboratory including serum cardiac markers were performed.

According to clinical presentation, ACS was classified into:

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

### **Transthoracic Echocardiographic**

**Examination:** detailed conventional M-mode and 2-D Transthoracic echocardiographic examination and Doppler study using standard parasternal and apical views following the recommendations by the American Society of Echocardiography (ASE) (Measurements of

1. Left ventricular dimensions (LVED dimension and volume and LVES dimension and volume). Volumes were being estimated using Simpson formula.
2. Left ventricular ejection fraction was estimated by  $EF = (EDV - ESV / EDV) \times 100$
3. Wall motion abnormalities The LV was divided according to the 16-segment model as proposed by ASE For each segments, wall motion was identified. Wall motion abnormality was detected if there was hypokinesis, akinesis or dyskinesis.
4. Diastolic function Mitral inflow was assessed by pulsed Doppler with a sample volume between the tips of the mitral leaflets during diastole. The peak early diastolic velocity (E wave), peak atrial velocity (A wave), the E/A ratio, and IVRT were measure. The IVRT was identified as the interval between the aortic valve closure and the mitral valve opening.

**Pulsed wave TDI Examination :** In each patient, PW-TDI mapping of systolic and diastolic velocities the peak velocities during systole (s wave), and diastole (e and a wave) were measured

**RDW calculation:** RDW is estimated on fully automated fluorescence flow cytometry 5-part differential analyzer (sysmex xs 800i, Japan) using a sample of EDTA blood which uses the following principle: The XS performs hematology analyses using the following methods: Sheath Flow DC Detection Method, Flow Cytometry

Methods using a Semiconductor Laser and SLS-hemoglobin method. Blood cells pass through the aperture of the detector surrounded by a sheath fluid using the sheath flow method. The principle of flow cytometry is also used. A semiconductor laser beam is emitted to the blood cells passing through the flow cell. The forward scattered light is received by the photodiode, and the lateral scattered light and lateral fluorescent light are received by the photo multiplier tube. This light is converted into electrical pulses, thus making it possible to obtain blood cell information. Hemoglobin is measured with the SLS-hemoglobin method using Sodium Lauryl Sulfate, which is an analysis method used in previous Sysmex instrumentation.

### **Statistical Analysis**

- Data was collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows 7.
- Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test:
  - For quantitative parametric data:
    - In-dependent student t-Test used to compare measures of two independent groups of quantitative data
    - Bivariate Pearson correlation test to test association between variables
    - The level  $P \leq 0.05$  was considered the cut-off value for significance.

## RESULTS

### Prognostic yield of red cell distribution width in acute coronary syndrome patients and its correlation with different parameters

Table(1) illustrates that there is statistically significance positive correlation with p-value <0.001 between RDW and age of patients as RDW increase with age. On the other hand RDW shows insignificant correlation with hemoglobin and CK-MB (p value=0.7&p value=0.4 respectively)

Variable	RDW		
	R	p-value	Sig.
Age	0.57	<0.001	HS
HB	-0.06	0.7	NS
CKMB	0.13	0.4	NS

**Table (1): correlation RDW and age, HB and CKMB**

There were significant correlation between RDW and hypertension, ischaemic heart disease and smoking and insignificant correlation between it and dyslipidemia and diabetes mellitus

There were insignificant correlation between RDW and ECG findings (p value=0.2). Also Troponin showed insignificant correlation with RDW (p value=0.3) Also there is statistically significant difference with p-value <0.05 between smoking groups as regards to RDW level with low mean among smokers.

On the other hand there is no statistically significant difference with p-value >0.05 in RDW level between groups of diabetes mellitus, and dyslipidemia groups.

there is statistically significant difference with p-value <0.05 between RWMA groups with high mean of RDW (16.1± 2.01) among patients who had RWMA

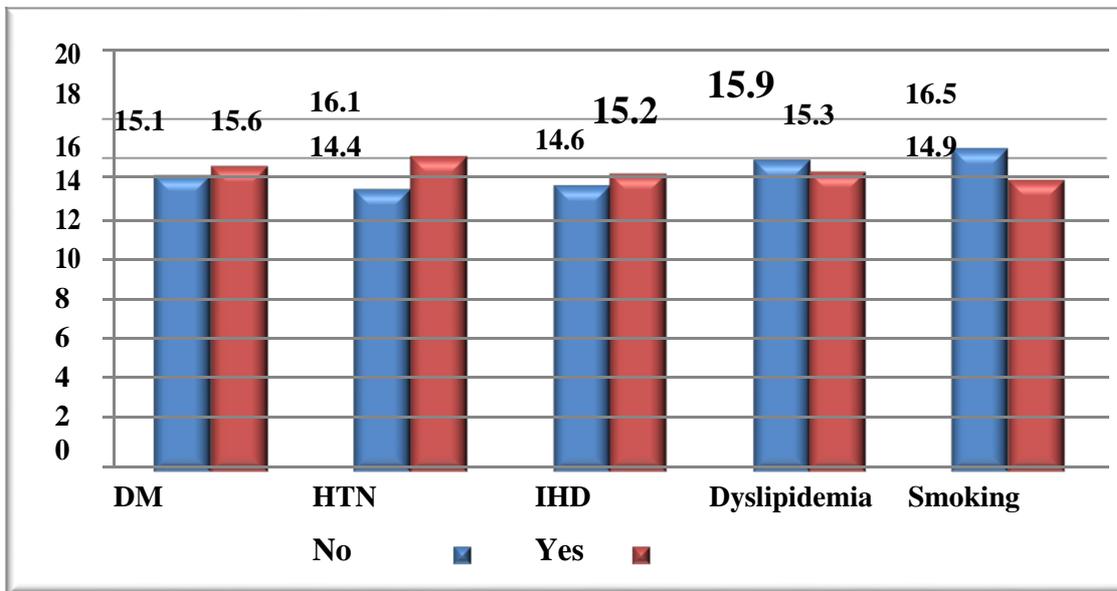
**Table (2): Comparisons of RDW in different history among study group**

Variables	RDW			P-value	Sig.
	No.	Mean	SD		
<b>Diabetes mellitus</b>					
No	13	15.1	2	0.4	NS
Yes	17	15.6	2.4		
<b>Hypertension</b>					
No	15	14.4	2	<b>0.02</b>	<b>S</b>
Yes	25	<b>16.1</b>	2.2		
<b>Ischemic Heart disease (IHD)</b>					
No	18	14.6	2.2	<b>0.03</b>	<b>S</b>
Yes	22	<b>15.2</b>	2.2		
<b>Dyslipidemia</b>					
No	9	15.9	1.9	0.5	NS
Yes	31	15.3	2.4		
<b>Smoking</b>					
No	14	16.5	2.1	<b>0.03</b>	<b>S</b>
Yes	26	<b>14.9</b>	2.2		
<b>Troponin</b>					
Negative	7	16.2	3	0.3	NS
Positive	33	15.3	2.1		

**ECG findings**

Negative	1	12.4	0	0.2	NS
Positive	39	15.5	2.2		
<b>RWMA by echo</b>					
No	16	14.4	2.3	<b>0.02</b>	<b>S</b>
Yes	24	<b>16.1</b>	2.01		

**Figure (1):  
 Mean RDW level in different history**



RDW correlation and echocardiography findings and tissue Doppler findings There were significant correlation between left atrium size (LA), end diastolic volume(ED), end systolic volume (ES) and ejection fraction (EF)

**Table (3): Correlation between RDW with Echo-finding among study groups.**

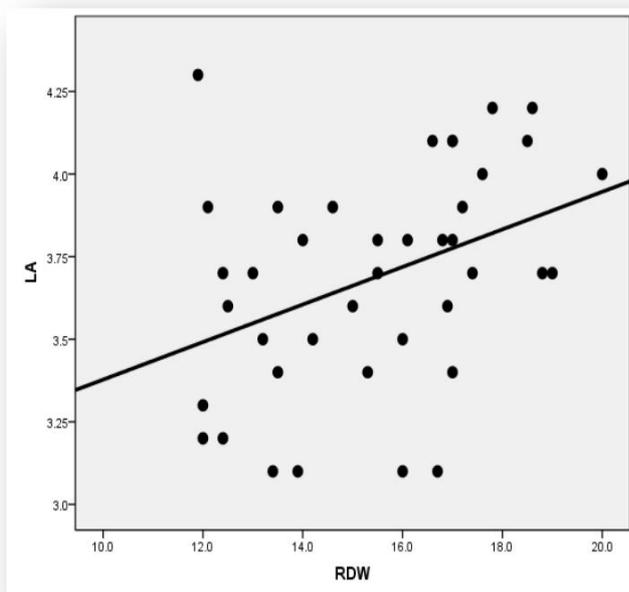
Echo-finding	RDW		
	R	p-value	Sig.
LAD	0.39	0.01	S
EF	-0.56	<0.001	HS
ESD	0.40	0.01	S
EDD	0.31	0.05	S
S-wave	-0.39	0.01	S
E	-0.26	0.1	NS
A	0.05	0.7	NS
E/A ratio	-0.02	0.9	NS

Table illustrates that there is statistically significance **positive** correlation with p-value <0.05 between RDW and each of LAD, ESD, and EDD level in echo finding which indicates increase in RDW had positive impact on increase of LAD, ESD, and EDD On the other hand there is **negative** statistically significance correlation with p-value <0.05 between RDW and EF which indicates increase in RDW had negative impact on EF.

there is statistically significance **negative** correlation with p-value <0.05 between RDW and S-wave in tissue Doppler results which indicates increase in RDW had negative impact on S-wave.

On the other hand there is no statistically significant correlation with p-value >0.05 between RDW and any of other tissue Doppler parameters (E, A, and E/A ratio).

**Figure (2): correlation between RDW and left atrium**



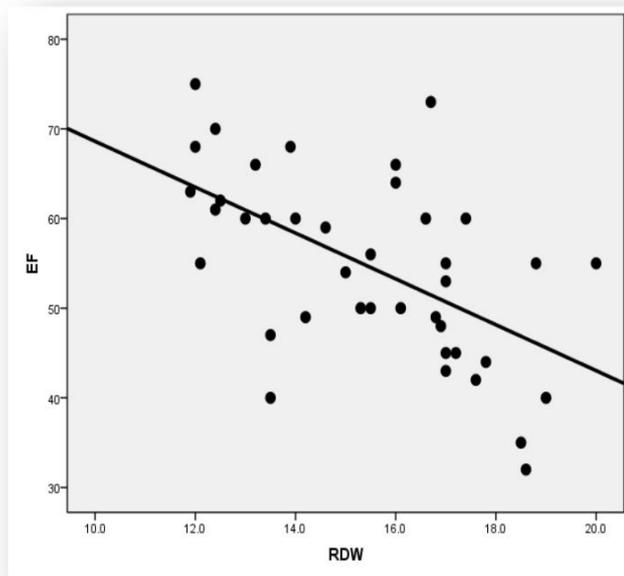


Figure (3): correlation between RDW and ejection fraction

Mean RDW among different RWMA categories

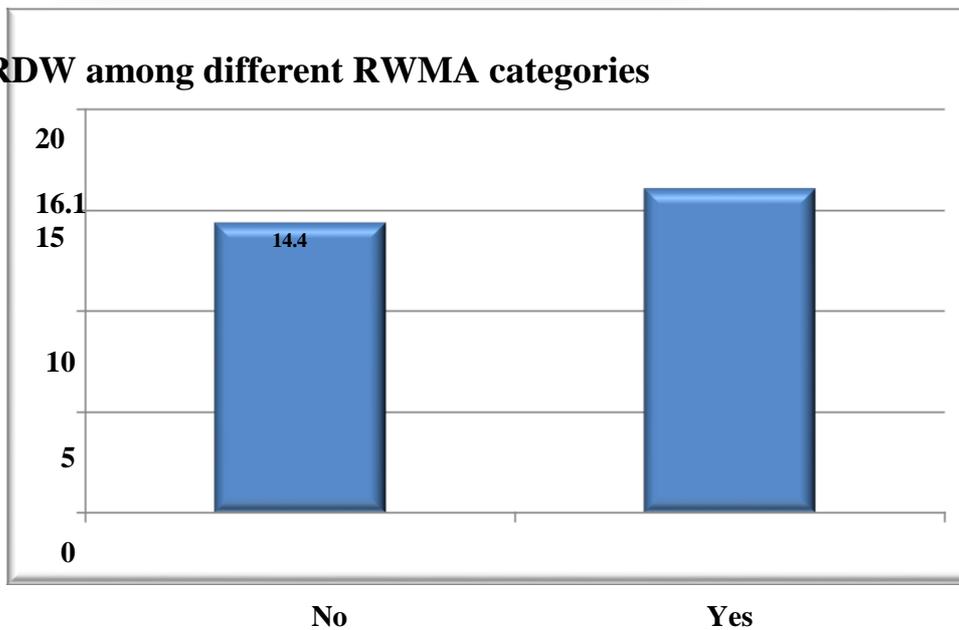
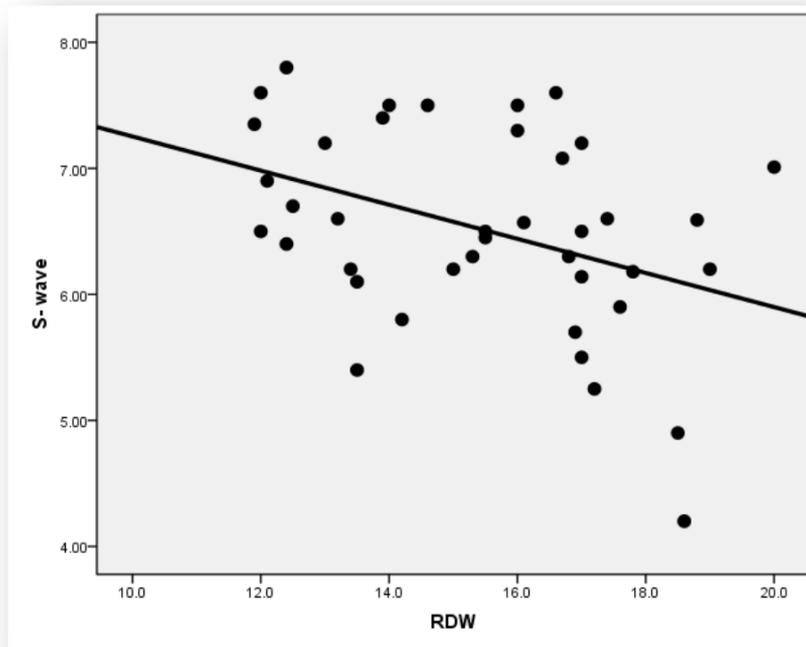


Figure (4): correlation between RWMA and RDW Correlation between RDW and systolic and diastolic function by echocardiography

There was significant correlation between systolic function (s wave of tissue Doppler) with p value (p value<0.01) and there were no significant correlation between RDW and E, A and E\A ratio



**Figure (5): correlation between RDW and s wave tissue doppler**

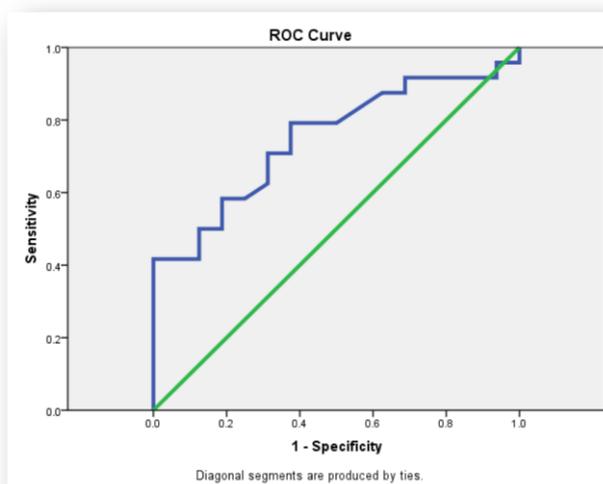
**ROC curve for RDW:**

Performing ROC curve analysis between RDW & echocardiography ejection fraction 50% we found that best cut off point to be **16.1** with Sensitivity and specificity test for RDW with illustrates probability of being true positive is (74.9%) more than being false positive when repeat test 100 times with sensitivity (79.2%) and specificity (62.5%)

**Table (4): Sensitivity and specificity of RDW in diagnosis of EF % level among study group.**

Variable	Sensitivity	Specificity	Accuracy	Cut off point
RDW	79.2%	62.5%	74.9%	16.1

**Figure (6): ROC curve for RDW**



From all the above we found that RDW has strong correlation with ejection fraction and systolic function by tissue Doppler

## DISCUSSION

Many researchers have demonstrated the role of RDW in patients with heart failure. According to [Al-Najjar et al, 2009] RDW has an independent prognostic power in these patients. They analyzed a cohort of patients with heart failure, comparing RDW with NT proBNP, and they suggested that the two factors can be considered similar in predicting cardiovascular events.

Moreover, the role of RDW as a predictor of mortality in patients with heart failure was investigated. [Pascual-Figal et al, 2009] in patients with acute heart failure higher RDW levels at discharge were associated with worse long-term outcome regardless of hemoglobin levels and anemia status. A role in the prognosis was established also for patients with diastolic heart failure in a study on the relationship between RDW and NT-proBNP [Celik A et al, 2012].

The role of RDW in patients with acute coronary syndrome has not been investigated as well as its role in patients with heart failure.

In this study we evaluated the value of monitoring RDW and its prognostic value and correlation with ejection fraction and pulsed tissue Doppler.

Our study had been conducted over 40 patient diagnosed as acute coronary syndrome.

patients had been enrolled in our study within 24 hours of acute coronary syndrome diagnosis and managed according to standard guidelines of acute coronary syndrome and correlation between RDW and ejection fraction and tissue Doppler was done.

Our patients had mean age  $56.4 \pm 9.5$  years, thirty patients (75%) were males and 10 patients (25%) females our patients had the following presentations:

ST segment elevated myocardial infarction (STEMI) 15 patients (37.5%), Non ST segment elevation myocardial infarction (Non

STEMI) 14 patients (35%), and unstable angina 11 patients (27.5%).

We investigated the prognostic impact of RDW in acute coronary syndrome and correlate it with echocardiographic findings especially ejection fraction.

Our study revealed a significant negative correlation between RDW and ejection fraction ( $p$  value  $< 0.001$  and  $r$  value  $= -0.56$ ). this come in context with [yan ling wang et al, 2011] who studied patients with acute coronary syndrome for cardiac mortality and events (heart failure and recurrent infarction within one month) and found that in patients with higher levels of RDW there is lower levels of left ventricular ejection fraction ( $p$  value  $< 0.001$ ).

Also we agreed with [Tadeusz Osadnik et al, 2013] who studied patients with stable coronary disease who underwent PCI and found that with higher RDW values there is lower ejection fraction ( $p$  value  $< 0.0001$ ). Also this come in context with [Michael Felker et al, 2007] who studied patients from the North American CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program with symptomatic heart failure there were strong correlation between ejection fraction and RDW ( $p$  value  $< 0.0001$ ).

Also our study agreed with [Ali Zorlu et al, 2015] who found that ejection fraction correlated significantly with RDW ( $p$  value  $< 0.017$ ).

But our study disagreed with [Domingo a. pascual-figal et al, 2009] who correlate between RDW and left ventricular ejection fraction (LVEF) and left ventricular diastolic function in acute heart failure patients and found no significant correlation but this difference may be due to different type of patients.

The strong correlation between RDW and ejection fraction suggest RDW as a cheap

rapid noninvasive prognostic marker that affect patient outcome.

Also our study showed positive correlation between left atrial diameter and RDW (r value=0.39 and p value <0.01) this agreed with [**Domingo a. pascual-figal et al, 2009**] who found that there is positive correlation between left atrial diameter and RDW (r value=0.163 and p value<0.006).

Also there was strong significant correlation between age and RDW (r value=0.57) with p value <0.001 this come in context with [**Mustafa Çetin et al, 2012**] who studied patients with chest pain who underwent coronary angiography and found a positive relationship between and RDW.

Also our study agreed with [**feng-lian et al, 2013**] who studied patients who underwent coronary angiography due to presence of chest pain and positive treadmill exercise test and RDW is correlated with age.

In our study there was strong positive correlation between s wave which is systolic wave of lateral annulus of mitral valve tissue Doppler and RDW (p value<0.01)

In our study there was no significant correlation between RDW and creatinine kinase-MB fraction with (p value=0.4) and This agreed with [**Mustafa Duran et al, 2013**] who found no correlation between RDW and creatinine kinase-MB fraction insignificant (p value=0.1) and this comes in context with [**yan ling wang et al, 2011**]who found that no correlation between RDW and creatinine phosphokinase.

In our study we found no significant correlation between troponin level and RDW (p value=0.3) and This agreed with [**Erdal Cavusoglu et al, 2009**] who studied RDW as predictor of adverse outcome in congestive heart failure with previous history of myocardial infarction and found that correlation between RDW and troponin and found that it was insignificant (P value=0.65) and also run parallel to [**Mustafa Duran et al, 2013**] who found no significant correlation between troponin and RDW.

Both creatinine kinase-MB fraction and troponin are diagnostic markers it is not necessary that they correlate with RDW as it is prognostic.

But in this point our study disagreed with [**Ramazan can oncel et al, 2013**] Who investigated global registry of acute coronary events (GRACE score) and RDW in ST elevation myocardial infarction patients and found that there is significant correlation between RDW and troponin (p value<0.001) a finding that was not clear in our study as we did not limit patients to ST segment elevation myocardial infarction.

In our study RDW shows insignificant correlation with hemoglobin level (r value=-0.06 and p value=0.7).

This comes in context with [**Onur Kadir Uysal et al, 2012**]who investigated the relation between RDW and STEMI in young patients and found no significant correlation between RDW &hemoglobin ( p value=0.5) and with [**Savas Sarıkaya et al, 2014**] who studied the relation between atrial fibrillation incidence in hypertensive patient and RDW and found that correlation RDW and hemoglobin (p value<0.3).

And also agreed with [**Feng-lian, et al, 2013**] who also found no correlation between RDW and hemoglobin.

Our study discordant with [**Michael Felker et al, 2007**] who found that correlation between RDW &hemoglobin significant (p value<0.001) this may be due to different type of patients as we excluded anemic patients in our study but they did not.

Our study shows insignificant correlation between RDW and diabetes (p value=0.4). This agreed with [**Tadeusz Osadnik et al, 2013**] who found RDW and diabetes correlation to be insignificant (p value=0.2).

Our study shows insignificant correlation between RDW and dyslipidemia (p value=0.5). This agreed with [**Onur Kadir Uysal et al, 2012**] showed insignificant correlation between hyperlipidemia (p value=0.5).

Our study shows significant correlation between RDW and hypertension (p value<0.02). This agreed with [yan ling wang et al, 2011] who found that there is significant correlation between RDW and hypertension (p value <0.001).

Our study shows significant correlation between RDW and history of ischaemic heart disease (p value 0.03). This agreed with [Mustafa Çetin et al, 2012] who found during his study for RDW and its association with coronary atherosclerosis in patient with stable angina that there is significant correlation between RDW and history of ischaemic heart disease (p value<0.005).

## CONCLUSION

- RDW is promising prognostic tool for acute coronary syndrome patients assessment
- RDW on admission can be able to correlate with left ventricular function

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Upon attempting to find the best cutoff value of RDW for prediction of left ventricular ejection fraction less than 50% in acute coronary syndrome patients we found that best cut off point to be 16.1 with sensitivity 79.2% and specificity 62.5%.

Also this come in cotext with [Ali Zorlu et al, 2015] who found that best cutoff point for diagnosing of severity of ejection fraction less than 45% is 14 with sensitivity 70% and specificity 62.5%.

Finally our study suggest a prognostic role of RDW in acute coronary syndrome patients and opened the door for later investigation exploring the specific behavior of RDW in different patient categories.

- (ejection fraction and s wave tissue Doppler) in acute coronary syndrome
- More evaluation of RDW in acute coronary syndrome patients is required

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