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Prognostic value of RDW at admission in patients with acute myocardial infarction

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Abstract: Objective: The aim of this study is to evaluate the effect of basal RDW value on the in-hospital prognosis (mortality, complications) in patients with acute myocardial infarction, in addition to comparing the prognostic value of RDW in patients with acute myocardial infarction with other laboratory indicators, and the relation between RDW and Global Registry of Acute Coronary Events GRACE score and progression of heart failure and Length of hospitalization

Methods: a study applyed applied at Tishreen University Hospital in Lattakia-Syria during the period between February 2020-February 2021. The study included 145 acute myocardial infarction patients , and determination of the RDW value to study its effect on the prognostic of in-hospital mortality and complications.

Results: A higher RDW value at admission was associated with higher rates of major cardiac complications such as cardiogenic shock (P = 0.007) and, arrhythmias (P = 0.0001) and a higher RDW value was associated with increased length of hospital stay (P = 0.01) and an increased death rate (P = 0.001). The statistically significant variables were entered into the logistic regression equation to identify the independent indicators for the warning of death within the hospital. We found that the high level of RDW is a prognostic biomarker of death in hospital (OR = 4.1, P = 0.0001), in addition to that in the case of previous coronary or peripheral vascular diseases (OR = 3.8, P = 0.006), lower EF (OR = 2.8, P = 0.001) and higher GRACE score (OR = 3.1, P = 0.002).

Conclusion: In patients with acute myocardial infarction, high RDW has an independent predictive value for death, cardiogenic shock, and arrhythmias during hospitalization.

Keywords: Red Blood Cells, myocardial, infarction, Arrhythmia, Heart Failure.

القيمة الإنذارية ل RDW عند القبول لدى مرضى احتشاء العضلة القلبية الحاد

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المستخلص: الهدف: هدفت الدراسة إلى تقييم تأثير قيمة RDW القاعدية على الإنذار ضمن المشفى (وفيات، اختلاطات) عند مرضى احتشاء العضلة القلبية الحاد، بالإضافة إلى مقارنة القيمة الإنذارية ل RDW عند مرضى احتشاء العضلة القلبية الحاد مع المشعرات المخبريَّة الأخرى، وعلاقة RDW بمشعر GRACE وبتطور قصور القلب وطول مدَّة الاستشفاء.

طريقة البحث: دراسة أجريت في مشفى تشرين الجامعي في اللاذقية-سوريا خلال الفترة الممتدة ما بين شباط 2020-شباط 2021. شملت الدراسة 145مريضاً من مرضى احتشاء العضلة القلبية الحاد، وتم تحديد قيمة الـ RDW لدراسة تأثيرها على الإنذار (الوفيات والاختلاطات) ضمن المشفى.

النتائج: ارتبط ارتفاع قيمة RDW عند القبول مع معدلات أعلى لحدوث الاختلاطات القلبية الكبرى كالصدمة القلبية (P=0.007) واضطرابات النظم (P=0.0001)، وكذلك ترافق ارتفاع قيمتها بزيادة مدة البقاء في المشفى (P=0.01) وازدياد معدل الوفاة (P=0.001). تم ادخال المتغيرات الدالة احصائياً إلى معادلة Logistic regressionللتعرف على المشعرات المستقلة للإنذار بالوفاة ضمن المشفى، وجدنا أن المستوى المرتفع لRDW هي مشعر إنذاري للوفاة ضمن المشفى (OR=4.1 ، P=0.0001)، إضافة لذلك في حال وجود سوابق وعائية اكليلية أو محيطية (OR= 3.8، P=0.006)، وانخفاض قيم الوظيفة الانقباضية EF (OR=2.8، P=0.001) وارتفاع درجة المشعر GRACE score (OR=3.1، P=0.002).

الاستنتاج: لدى مرضى احتشاء العضلة القلبية الحاد فإن RDW يملك قيمة تنبؤية مستقلة للوفاة ولحدوث الصدمة القلبية واضطرابات النظم خلال فترة التواجد بالمشفى.

الكلمات المفتاحية: خلايا الدم الحمراء، احتشاء، قلبي، صدمة، اضطراب نظم، قصور القلب.

Introduction.

Red distribution of width. (RDW) represents the variance in volumes of red blood cells in the blood circulation. High RDW implies a large variation in Red Blood Cells (RBC) sizes, and considered as a non-specific finding in various pathological conditions such as deficiency anemia, sickle cell anemia, hemolytic anemia, and other blood disorders. An elevated RDW is often used to distinguish deficiency anemia from thalassemia [4]. A low RDW implies a more homogeneous populations of RBCs. RDW is calculated as the standard deviation of erythrocyte volume divided by mean corpuscular volume (MCV) × 100 and expressed as a percentage [3]

Cardiovascular diseases are the leading cause of death worldwide. Mortality from ischemic cardiac causes account for about 20% of deaths in Europe; Although this rate has been improved in recent years as a result of advances in thrombolytic therapy and interventional catheterization techniques, the mortality rate is still significantly high, especially in-hospital mortality, which ranged after acute myocardial infarction with ST Segment elevation of more than 4-12%. [1]

Therefore, it is important to distinguish high-risk Myocardial Infarction MI patients who need more emphasis in controlling risk factors, intensive treatment and close medical follow-up, [20]

Acute coronary syndrome (ACS) refers to a spectrum of acute myocardial ischaemia and/or infarction. Classically ACS has been divided into three clinical categories according to the presence or absence of ST-segment elevation on the initial Electrocardiogram (ECG), together with measurement of myocardial biomarkers, such as troponin or creatine kinase.[21]:

- ST-elevation myocardial infarction (STEMI) the ECG shows persistent ST-segment elevation in two or more anatomically contiguous leads with elevated myocardial biomarkers, such as troponin or creatine kinase.
- Unstable angina

- Non-ST segment-Elevation Myocardial Infarction (NSTEMI) which represent with Unstable Angina a continuum of pathology, differing mainly by the presence of markers of myocardial damage in NSTEMI.[22] Therefore some guidelines have grouped unstable angina and NSTEMI as 'non-ST-elevation acute coronary syndromes'.[22]

The primary function of red blood cells is to deliver oxygen to peripheral tissues. The normal size of RBC ranges between 7.2 and 7.9 μm in diameter and 2 μm in thickness, with a physiological volume ranging from 80 to 100 fl [2].The elasticity of the RBC membrane allows erythrocytes to enlarge or shrink in response to pathophysiological injuries, resulting in an increase or decrease in their size. The presence of different volumes of red blood cells in the blood circulation (anisocytosis) is considered as a non-specific finding in various pathological conditions such as deficiency anemia, sickle cell anemia, hemolytic anemia and other blood disorders. An elevated RDW is often used to distinguish iron deficiency anemia from thalassemia[4].

The first studies that studied the prognostic value of RDW in cardiovascular diseases was by Felker et al 2007 who showed that high RDW is a strong predictor of adverse outcomes in patients with heart failure.. Then many researches studied the relationship between high RDW and each of Stable Coronary Arterial Disease (SCAD) and acute myocardial infarction[5].

According to Meta-analysis (Abrahan 2018), which aimed to study the relation between RDW value and risk for mortality and Major Adverse Cardiac Events

(MACEs) in patients diagnosed with Acute Coronary Syndrome (ACS), low RDW was associated with lower rates of death and major cardiac events in the short and long term after acute coronary syndrome[6].

MATERIALS and Methods.

The present analysis was a prospective observational study conducted at Tishreen University Hospital (Latakia - Syria between February 2020 and February 2021)

Patients with Acute Myocardial Infarction (AMI) (both ST Elevation Myocardial Infarction and Non-ST segment-Elevation Myocardial Infarction STEMI and NSTEMI) admitted to the cardiac care unit, Tishreen University Hospital, Latakia, were studied. Exclusion criteria were:

- Anemia (hemoglobin less than 13 g/dl for men and less than 12g/dl for women according to WHO standards).
- A history of blood transfusions during the past three months.
- Patients with chronic kidney disease and malignancy.

The RDW value was taken from the complete blood count which is routinely performed for all patients admitted with acute myocardial infarction within the first 18 hours of symptoms in addition to

the rest of the routine emergency blood test upon admission. The complete blood count was performed on the URIT-3000 Plus device.

A detailed history was taken, the associated risk factors were known, the GRACE score was calculated, a full clinical examination with infarction pattern was determined from initiation, and the patients were managed and followed up accordingly.

All subjects underwent two-dimensional echocardiography to determine left ventricular ejection fraction (LVEF) before discharge (unless needed earlier). All required investigative and therapeutic procedures were done as available.

The study population was divided into 2 groups based on admission RDW values. The high RDW group (n=48) was defined as having values (RDW >14.6), and the normal RDW group (n=97) with RDW ≤14.6%.

Acute coronary syndrome was defined as presentation with symptoms of ischemia in association with electrocardiographic changes or positive cardiac enzymes [1]. Arterial hypertension was considered in patients with repeated blood pressure measurements >140/90 mm Hg or active use of antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose levels more than 126 mg/dL in multiple measurements or active use of antidiabetic medications. Smoking was defined as current smoking. RDW, a measure of variance in cell volums, is calculated as the standard deviation of erythrocyte volume divided by mean corpuscular volume (MCV) × 100 and expressed as a percentage [3]. We defined adverse cardiovascular events during in-hospital period as cardiogenic shock, arrhythmia (ventricular fibrillation and ventricular tachycardia after 24h of symptoms), acute heart failure (with reduced ejection fraction), and stroke.

Statistical analysis:

The analysis was performed using the Statistical Package for Social Sciences (SPSS) (version 20) (IBM Corporation, Armonk, New York, USA) and Excel 2010 program. A predictive value less than 0.05 was considered statistically significant. Basic Descriptive statistics included means, standard deviations (SD), Frequency and percentages. Statistical analyses were performed using the chi- square test, Student's t-test, Spearman and Pearson correlation and Fischer's exact test. Multivariate logistic regression was used to assess the association of explanatory variables with mortality in the presence of other potential confounders/risk factors.

Results.

Table (1) shows that 86.2% of the patients with myocardial infarction had STEMI

Table (1) Distribution of a sample of 145 patients according to the type of infarction from acute myocardial infarction patients

Infarction Pattern	The number	percentage
STEMI	126	86.2%
NSTEMI	19	13.8%
The total	99	100%

Table (2) shows that there are no statistically significant differences with regard to demographic distribution according to the value of the RDW.

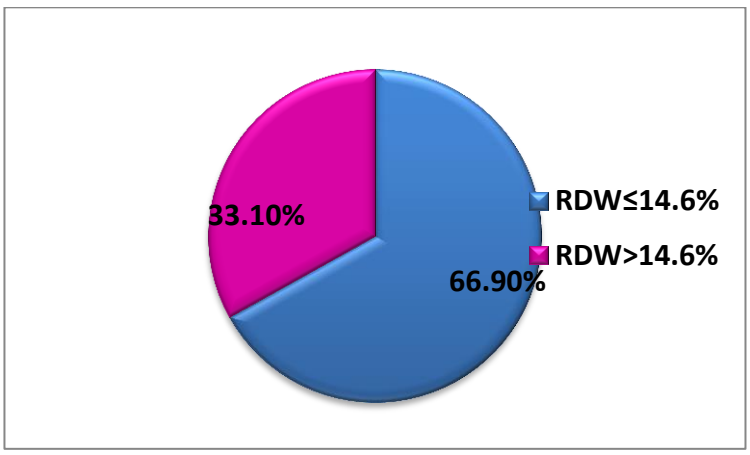
Table (2) Differences of demographic distribution upon admission among groups of acute myocardial infarction patients according to the value of the RDW.

Differences of demographic distribution	RDW>14.6%	RDW≤14.6%	p-value
Gender			
Male	36(75%)	74(76.3%)	0.8
Female	12(25%)	23(23.7%)	
Age			
≥60	27(56.3%)	41(42.3%)	0.1
<60	21(43.8%)	56(57.7%)	

Table (3) shows distribution of a sample of 145 patients according to the RDW value, 97 patients with normal RDW value, 48 patients with high RDW value

Table (3) Distribution of a sample of 145 patients according to the RDW value

Research sample	number	percentage
RDW≤14.6%	97	66.9%
RDW>14.6%	48	33.1%
Total	145	100%



Distribution of a sample of 145 patients according to the RDW value

Table (4) shows that there are statistically significant differences with regard to the presence of dyslipidemia and cerebrovascular accidents, as well as in the case of a family history of cardiovascular disease, as with the value of RDW > 14.6 there were 27.1% had dyslipidemia, 12.5% had cerebrovascular accidents, and 29.2 % Coronary or peripheral artery disease.

Table (4) Distribution differences according to risk factors in the patients according to the value of the RDW

Risk factors	RDW>14.6%	RDW≤14.6%	p-value
Diabetes mellitus	9(18.8%)	33(34%)	0.05
Hypertension	18(37.5%)	37(38.1%)	0.9
dyslipidemia	13(27.1%)	10(10.3%)	0.009
obesity	1(2.1%)	10(10.3%)	0.07
smoking	41(85.4%)	77(79.4%)	0.3
Cerebrovascular Accident CVA	6(12.5%)	4(4.1%)	0.04
Coronary or peripheral artery disease	14(29.2%)	14(14.4%)	0.03
Family history of cardiovascular disease	26(54.2%)	55(56.7%)	0.7

Table (5) shows there are statistically significant differences with regard to the ratio of neutrophils to lymphocytes (P=0.001).

Table (5) Differences of mean values of laboratory parameters among the patients according to the value of the RDW

Laboratory parameters	RDW>14.6%	RDW≤14.6%	p-value
Urea	36.5±12.8	34.7±13.4	0.4
C-Reactive Protein CRP	9.5±14.1	10.6±20.9	0.7
Glucose GLU	169.5±78.6	182.1±91.2	0.4
Neutrophil Lymphocyte Ratio NLR	5.07±2.09	3.54±1.6	0.001
Mean Platelet Volume MPV	9.19±1.5	8.97±1.3	0.3

Table (6) shows that there were statistically significant differences with regard to ejection fraction (EF), which decreased with higher RDW values (P=0.005).

Table (6) Distribution differences according to the type of infarction and echogenic findings among groups of infarct patients according to the value of the RDW

	RDW>14.6%	RDW≤14.6%	p-value
Infarction type	45(93.8%)	80(82.5%)	0.06
STEMI	3(6.3%)	17(17.5%)	

	RDW>14.6%	RDW≤14.6%	p-value
NSTEMI			
EF	41.29±9.01	45.77±7.9	0.005

Table (7) shows that there are statistically significant differences with regard to the mean values of blood pressure and pulse upon admission, as well as the GRACE score, as with the increase in the values of the RDW, there was a rise in the mean values of each.

Table (7) Differences according to clinical status and GRACE score among infarction patient groups according to RDW

Variables	RDW>14.6%	RDW≤14.6%	p-value
Blood pressure			
Systolic	141.5±32.7	132.8±19.8	0.04
Diastolic	85.4±15.2	80.1±11.9	0.03
Pulse	88.4±18.9	80.06±16.7	0.008
Cardiac arrest	2(4.2%)	2(2.1%)	0.4
GRACE score	123.1±31.1	110.2±24.3	0.007

Table(8) shows that there are statistically significant differences with regard to complications occurring within the hospital (cardiogenic shock[P=0. 007] and arrhythmias[P=0.0001), as well as in-hospital mortality [P=0. 01], which were higher with the high RDW values.

Table (8) Differences according to length of stay in hospital, complications and deaths among groups of patients with infarction according to the value of the RDW

Variables	RDW>14.6%	RDW≤14.6%	p-value
Length of stay in hospital	6.35±11.4	3.37±1.5	0.01
complication			
cardiogenic shock	11(22.9%)	7(7.2%)	0.007
arrhythmia	20(41.7%)	7(7.2%)	0.0001
CVA	2(4.2%)	0(0%)	0.04
mortality	11(22.9%)	5(5.2%)	0.001

From the previous table, there are statistically significant differences with regard to complications occurring within the hospital (cardiogenic shock [P=0. 007] and arrhythmias[P=0.0001), as well as in-hospital mortality [P=0. 01], which were higher with the high RDW values.

Figure (1) shows a positive correlation between RDW and the value of GRACE score, in the presence of statistically significant differences.

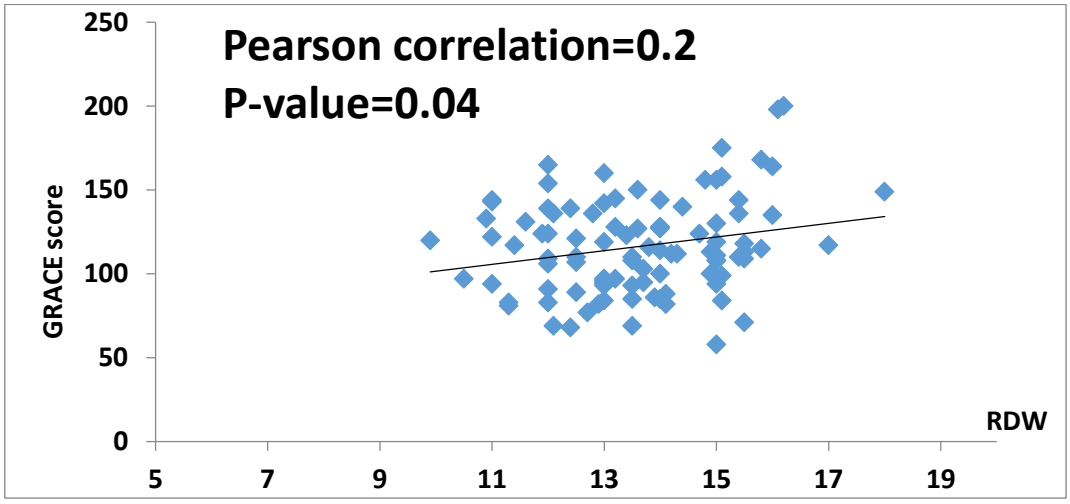


Figure (1) The relationship between the RDW and the GRACE score in patients with myocardial infarction

The statistically significant variables were entered into the logistic regression equation to identify the independent indicators of in-hospital mortality. We found that the high level of the RDW is an independent indicator of in-hospital mortality in association with Coronary or peripheral artery disease, Low EF and GRACE score (Table.9).

Table 9 shows that high RDW value upon admission is associated with a risk of in-hospital mortality 4.1 times, as well as Coronary or peripheral artery disease 3.8 times and a high GRACE score 3.1 times and with a decrease in the value of EF where is a risk of death 2.8 times.

Table (9) Risk factors associated with in-hospital death for a group of myocardial infarction patients

Variables	OR a	Confidence interval (95%)	p-value
Coronary or peripheral artery disease	3.8	[1.2 – 8.1]	0.006
RDW	4.1	[1.3 – 10.6]	0.0001
EF↓	2.8	[0.2 – 7.9]	0.001
GRACE score	3.1	[2.4 – 3.9]	0.002

Table 10 shows high RDW upon admission is a risk factor for the occurrence of arrhythmias, as it is associated with a 3.6-fold risk, as well as a 2.9-fold risk of cardiogenic shock

Table (10) platelets to lymphocytes ratio and in-hospital complications occurring for myocardial infarction patients

Variables	OR a	Confidence interval (95%)	p-value
Arrhythmia	3.6	[1.9 – 7.5]	0.002
Cardiogenic shock	2.9	[1.2 – 9.3]	0.001

The high RDW upon admission is a risk factor for the occurrence of arrhythmias, as it is associated with a 3.6-fold risk, as well as a 2.9-fold risk of cardiogenic shock.

DISCUSSION.

This study showed that high RDW values in patients with myocardial infarction at admission give an independent prognostic value for in-hospital mortality and major cardiac complications.

While many studies have shown the relationships between RDW and Cardiovascular Diseases CVDs, the pathophysiological mechanisms remain unclear. Does elevated RDW level have a direct impact on CVDs, or is it merely a marker, reflecting something else going on in the body?

RDW is an indicator of inflammation related to early inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [7,8]. Accordingly, systemic chronic inflammation leads to dysfunctional bone marrow with unsuccessful production of red blood cells [9]. As a result, it determines the migration of reticulocytes into the peripheral circulation, followed by an increase in circulating levels of immature Red Blood Cells (RBCs), as well as in higher RDW levels [8]. Thus, inflammation is the principal pathophysiological inducer in the development of atherosclerosis, but also of other CVDs [10-11]. In addition, an increase in RDW levels also is related to augmented oxidative damage in blood circulation [12], which associates with exacerbation of pathophysiological conditions linked to the worsening of atherosclerosis [13]. This leads to hypothesize, that interplay between RDW and atherosclerosis might to be related to the inflammatory state, which can inhibit erythropoiesis both directly through the action of cytokines able to increase resistance to the effect of erythropoietin, and indirectly by the reduction of iron levels [14]. Inflammatory state determines a reduction of iron levels, which reduces the capacity of the bone marrow to generate new erythrocytes. This is due to lower absorption of iron [15]. In addition to inflammation, the cholesterol content in the erythrocyte membrane has been suggested to be the link between RDW and the poor prognosis in Myocardial Infarction MI. Pathological elevations of cholesterolemia lead to an excessive increase in membrane cholesterol content [16,17] and decreased erythrocyte stability and deformability. This may increase blood viscosity, disturb blood flow through the microcirculation, and promote the adverse consequences of the arterial occlusion [18]

And what explains the poor prognosis in the case of low deformability is the damage caused by oxidative stress, as the lack of elasticity of the cell membrane exposes it to rupture and releases hemoglobin. Free hemoglobin has a great potential to generate reactive oxygen species (ROS) due to the presence of iron [19].

Conclusion.

This study showed that high RDW is an independent predictor of in-hospital cardiovascular mortality in patients with MI. Complete blood count analysis is a routine and inexpensive method that may be useful for the identification of high-risk patients.

List of abbreviations:

AMI: Acute Myocardial Infarction.

RDW: Red Distribution of Width.

LVEF: Left Ventricular Ejection Fraction.

MACE: Major Adverse Cardiovascular Events.

GRACE: Global Registry of Acute Coronary Events

MI: Myocardial Infarction

STEMI: ST segment Elevation Myocardial Infarction

N STEMI: Non- ST Elevation Myocardial Infarction

CVD: Cardiovascular Diseases

CRP: C-Reactive Protein

GLU: Glucose

MI: Myocardial Infarction

NLR: Neutrophil Lymphocyte Ratio

MPV: Mean Platelet Volume

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