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PERMANYER

Gac Med Mex. 2016;152:61-7

GACETA MÉDICA DE MÉXICO

ORIGINAL ARTICLE

# The association between red cell distribution width (RDW) and short-term mortality risk in patients with acute coronary syndrome (ACS)

*Alejandro Rosas-Cabral[1]*, Jesús Antonio Viana-Rojas[1], Jorge Prieto-Macías[2], María del Carmen Terrones-Saldívar[1], Rafael Gutiérrez-Campos[1], Silvia Denise Ponce-Campos[1] and José de Jesús de Lara-Castañeda[1]*

*[1]Department of Medicine, Universidad Autónoma de Aguascalientes; [2]Department of Critical Medicine, Hospital General de Zona No. 1, IMSS, Aguascalientes, Ags., Mexico*

## Abstract

**Objective:** *To demonstrate the association between red cell distribution width and short-term mortality risk in patients with acute coronary syndrome.* **Methods***: We prospectively recruited 78 patients with acute coronary syndrome. The study population was classified according to quartiles of the red cell distribution width at hospital admission. A high red cell distribution width was defined as a value in the upper fourth quartile (> 15) and a low red cell distribution width was defined as any value set in the lower three quartiles (≤ 15). After discharge, all patients were followed for three months.* **Results***: The short-term cardiovascular mortality was 47.2% in the high red cell distribution width group vs. 10.2% in the low red cell distribution width group (p < 0.001). In the receiver operating characteristic curve analysis, a red cell distribution width value of more than 15% yielded a sensitivity of 66.7%, a specificity of 83%, and a positive predictive value of 79.7% for cardiac mortality. After multivariate analysis, high levels of red cell distribution width were independent predictors for three-month mortality (p = 0.001).* **Conclusion***: We demonstrated that red cell distribution width is an accessible parameter associated with short-term cardiovascular mortality in patients with acute coronary syndrome.* (Gac Med Mex. 2016;152:61-7)

***Corresponding author:*** *Alejandro Rosas Cabral, drrosascabral@gmail.com*

***KEY WORDS:*** *Red cell distribution width. Acute coronary syndrome. Cardiovascular mortality. Mexico.*

## Introduction

The red blood cell distribution width (RDW) is the variation coefficient of the red blood cell (RBC) mean corpuscular volume (MCV) and, therefore, it is a quantitative measure of anisocytosis[1]. Elevated RDW levels are the reflection of high heterogeneity of the RBC size, which is caused by a disturbance in the degradation or maturation of RBCs[2]. RDW is commonly used in clinical practice to discriminate and differentiate between different types of anemia[3]. However, recent studies have informed that an increased RDW is associated with higher mortality on the long term in patients with heart failure or stable angina and in the general population[4-6].

**Correspondence:**
*Alejandro Rosas Cabral
Departamento de Medicina
Universidad Autónoma de Aguascalientes
Av. Universidad, 940
Ciudad Universitaria
C.P. 20131, Aguascalientes, Ags., México
E-mail: drrosascabral@gmail.com

Date of reception: 15-10-2014
Date of acceptance: 23-01-2015

Large quantities of research have been dedicated for years to the search for prognostic factors with good predictive value for the evolution of patients with acute coronary syndrome (ACS), but these are not available at all hospitals in our country, and their determination adds an extra cost for patients and institutions. This prognostic information could be obtained from routine hematological tests, such as blood count, which has already been documented in other cardiovascular conditions such as heart failure[7].

Since RDW is reported as part of the blood count and is widely available at hospitals, establishing its prognostic magnitude could prove quite valuable for ACS patients risk stratification and to guide decision-making[8]. This study is intended to establish an association of RDW and short-term mortality risk in patients with ACS.

## Methods

### *Study population*

A descriptive, longitudinal, prospective study was conducted, which included 78 consecutive patients with ACS who were admitted to the Emergency Department of the Zone no. 1 General Hospital of the Mexican Institute of Social Security of the city of Aguascalientes between November 2011 and February 2013. There were patients with ST segment-elevation myocardial infarction (STEMI) and non-ST segment-elevation myocardial infarction (NSTEMI) and unstable angina (UA). The diagnostic criteria for STEMI were the following: typical chest pain at rest for longer than 30 min, ST-segment elevation > 0.2 mV of the J point in two or more contiguous leads in a 12-lead electrocardiogram (ECG) and increased myocardial damage serum markers, defined as a more than 2-fold increase from normal in the levels of creatine phosphokinase (CPK) and CPK muscle and brain fraction (CPK-MB)[9]. UA/NSTEMI was clinically defined as chest pain with an ECG pattern of ST-segment depression or significant inversion of the T wave and, biochemically, as an elevation of myocardial necrosis serum markers in the absence of ST-segment elevation[10]. Basic drug treatment for ACS included platelet antiaggregants, low molecular-weight heparin, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium antagonists and statins. The patients received thrombolytic therapy or percutaneous coronary intervention (PCI), according with the treating cardiologist for STEMI. Patients with autoimmune conditions, acute or chronic infections, neoplasms with bone marrow metastases, or known hematological, thyroid and hepatic conditions were excluded. The local ethics committee granted approval for the study.

### *Data collection*

Medical history of each patient was assessed at admission and relevant information on lifestyle and risk factors was recorded by means of a questionnaire. Alcohol consumers were defined as those patients who drank at least one cup of wine (or its equivalent) per month. The smoking index (SI) was obtained for each patient. Systemic arterial hypertension (SAH) was defined either by previous diagnosis o prior use of anti-hypertensive drugs or in case of systolic SAH higher than 140 mmHg and/or diastolic SAH higher than 90 mmHg in at least two separate measurements. Diabetes mellitus (DM) was defined by previous diagnosis or prior use of hypoglycemic drugs. Weight and height values were obtained for each patient and body mass index (BMI) was obtained by dividing the weight in kilograms by the square of height in meters. The thrombolysis in myocardial infarction (TIMI) risk scale was calculated based on the initial medical history, the ECG pattern and laboratory values at admission[11]. The left ventricular ejection fraction (LVEF) was measured by Doppler ultrasound during the first five days after admission. Patients were also assessed according to the Killip-Kimball clinical classification[12]. The glomerular filtration rate (GFR) was estimated upon admission using the modification of diet in renal disease simplified equation[13]. Median follow-up was 14 months (12-24).

### *Blood collection and laboratory measurements*

Upon admission, venous blood was obtained from all study patients prior to the start of any medication. Using standardized methods, the laboratory of our institution measured hemoglobin, MCV, RDW, platelet count, lipid profile and blood chemistry 30 min after collection. During three days after admission, CPK and CPK-MB levels were daily measured, and the maximum value was recorded (reference normal range for RDW in our laboratory is 12.0- 14.5).

### *Statistical analysis*

The study population was divided in quartiles based on the RDW values obtained at admission. Elevated

RDW was defined as a value located in the fourth quartile (> 15.0) and low RDW, as a value located within the three lowest quartiles (≤ 15.0). Quantitative variables were expressed as averages and standard deviations (± SD), and categorical variables, as numbers and percentages (%). The parametric values comparison between both groups was made with Student's t-test. Categorical variables were compared using Fisher's exact test. The correlation between the RDW and other parameters was assessed by means of Spearman or Pearson tests, as appropriate. A ROC-curve analysis was performed in order to identify an effective and predictive cutoff point for the RDW value in short-term cardiovascular mortality (3 months). Statistical analysis was performed with the GraphPadInstat and GraphPadPrism pack, version for Windows[14], and with SPSS, version 19. A p-value lower than 0.05 was considered to be statistically significant.

## Results

Baseline characteristics of the study patients are shown in table 1. In comparison with the low RDW group, patients in the elevated RDW group were older and had higher BMI. In addition, patients in the elevated RDW group had a higher Killip-Kimball classification and, by ultrasound, a large number of hypokinesis zones. Other baseline characteristics showed no statistically significant differences between groups (gender, family history of high blood pressure [HBP] or DM, presence of HBP, diagnosis of DM, previous ACS, previous heart failure, tricuspid failure, alcohol consumption, use of antiplatelet agents, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or statins). Patient laboratory values at admission are shown in table 2. Patients with the highest RDW had lower platelet counts than those in the lower RDW group. Differences in other laboratory characteristics were not statistically different.

### *Correlation between RDW and other parameters*

RWD had a significant positive correlation with age, STEMI diagnosis, number of hypokinesis zones, TIMI risk scale score and Killip-Kimball clinical classification. There was a negative correlation between RDW and platelet count at admission. No statistically significant correlation was observed between RDW and other parameters (Table 3).

### *Short-term cardiovascular mortality*

Table 4 shows the short-term adverse results occurred in both groups. Three-month cardiac mortality was 47.3% in the high-RDW and 10.2% in the low-RDW groups (relative risk: 4.6; 95% confidence interval [CI]: 1.78-12.08; $p < 0.001$). Other results measured over the same period were not statistically different between groups.

### *RDW predictive value*

In the ROC curve analysis, a RDW value of 15 was identified as an effective cutoff point to assess short-term cardiovascular mortality in patients with ACS (area under the curve [AUC]: 0.78; 95% CI: 0.64-0.92). An RDW value higher than 15 was associated with a sensitivity of 66.7% (95% CI: 38.3-88.1) and specificity of 83% (95% CI: 70.2-91.9) with a positive predictive value of 79.7% (95% CI: 69.5-87.7) for short-term mortality in patients with ACS (Fig. 1).

### *Multivariate analysis*

Following the performance of the multivariate logistic regression analysis, a RDW value higher than 15 was an independent predictor of 3-month mortality ($p = 0.001$), as was the mean platelet volume (MPV) ($p = 0.001$), the very low-density lipoprotein (VLDL) level ($p = 0.046$), the Killip-Kimball class ($p = 0.001$), the TIMI ($p = 0.001$), the number of hypokinesis zones in the echocardiogram ($p = 0.0001$), the presence of diastolic dysfunction ($p = 0.006$) and the presence of systolic dysfunction ($p = 0.0001$) (Table 5).

## Discussion

The RDW is a quantitative measurement of circulating RBCs size heterogeneity. Typically, an elevated RDW indicates increased RBC destruction or nutritional deficiency, such as iron, folic acid or vitamin $B_{12}$ deficit. In the past few years, studies have been conducted on the relationship of RDW with cardiovascular events in different types of populations, but none in our country. Elevated RDW has been associated with hospital death and long-term mortality increase in primary angioplasty-treated patients with STEMI[15], has been shown to be an independent predictive factor of mortality in patients with UA/NSTEMI[16] and has been associated with a higher incidence of hospital admission

**Table 1. Characteristics of the study patients***

| | Low RDW group (RDW ≤ 15.0; n = 56) | High RDW group (RDW > 15.0; n = 22) | p |
|---|---|---|---|
| Age (years) | 59.4 (10.5) | 66.5 (9.4) | 0.007 |
| Men (%) | 43 (76.7) | 16 (72.7) | 0.77 |
| BMI (kg/m$^2$) | 26.8 (3.4) | 28.6 (2.9) | 0.04 |
| Family history of DM | 36 (65.4) | 9 (40.9) | 0.07 |
| Previous ACS | 15 (27.2) | 4 (20.0) | 0.76 |
| Previous congestive heart failure | 3 (5.8) | 2 (10) | 0.61 |
| SI (packs/year) | 13.1 (15.8) | 18.6 (19.3) | 0.24 |
| STEMI (%) | 40 (7.14) | 20 (90.9) | 0.07 |
| UA/NSTEMI (%) | 16 (28.5) | 2 (9.0) | 0.07 |
| LVEF (%) | 49.1 (10.4) | 48.5 (8.8) | 0.82 |
| Hypokinesis zones (no.) | 2.9 (2.4) | 4.2 (2.3) | 0.03 |
| Killp-Kimball class > 1 | 17 (30.3) | 14 (63.6) | 0.008 |
| TIMI scale | 4.5 (2.5) | 5.1 (2.6) | 0.26 |
| Thrombolysis | 35 (62.5) | 15 (71.4) | 0.59 |
| PCI | 23 (41.0) | 5 (23.8) | 0.19 |

*Continuous and categorical variables are reported as average (± SD) and number (%), respectively.

**Table 2. Laboratory data of the study patients at admission***

| | Low RDW group (RDW ≤ 15.0; n = 56) | High RDW group (RDW > 15.0; n = 22) | p |
|---|---|---|---|
| Hemoglobin (g/dl) | 14.8 (1.9) | 14.1 (1.8) | 0.11 |
| MCV (fl) | 89.8 (4.4) | 88.7 (3.6) | 0.33 |
| Platelets (x $10^9$/l) | 286.3 (79.0) | 241.4 (59.6) | 0.01 |
| Triglycerides (mg/dl) | 213.3 (117.5) | 213.0 (52.1) | 0.20 |
| Total cholesterol (mg/dl) | 179 (50.5) | 213.2 (63.9) | 0.07 |
| HDL-C (mg/dl) | 35.7 (6.3) | 35.0 (9.6) | 0.81 |
| LDL-C (mg/dl) | 105.8 (48.1) | 122.0 (41.2) | 0.37 |
| Urea (mg/dl) | 38.0 (23.2) | 35.8 (14.0) | 0.90 |
| Creatinine (mg/dl) | 1.0 (0.75) | 0.9 (0.34) | 0.97 |
| GFR | 88.4 (31.9) | 86.5 (30.6) | 0.81 |
| Peak CPK (IU/dl) | 767.6 (950.2) | 679.0 (549.2) | 0.75 |
| Peak CPK-MB (IU/dl) | 126.6 (159.8) | 79.8 (54.3) | 0.73 |
| RDW | 14.0 (0.68) | 15.4 (0.35) | < 0.0001 |

*Continuous and categorical variables are reported as average (SD) and number (%), respectively.
HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

**Table 3. Correlation analysis between RDW and other parameters**

| | r value | p |
|---|---|---|
| Age | 0.249 | 0.02* |
| STEMI | 0.241 | 0.03† |
| Hypokinesis zones | 0.309 | 0.01† |
| Platelets | –0.283 | 0.01* |
| TIMI | 0.294 | 0.01* |
| Killip-Kimball | 0.512 | < 0.0001† |

*Pearson correlation.
†Spearman correlation.

and mortality in patients with acute heart failure[17,18]. Additionally, Wang et al. demonstrated that elevated RDW can predict an increased risk for an adverse outcome, such as cardiac failure or reinfarction at one month after the MI, similar to our findings at 3 months[19]. Furthermore, Akin et al. found a RDW of 15.1 ± 1.7% to be significantly associated with higher severity of the coronary artery disease as measured with the Syntax index, with this RDW value being similar to the cutoff point found by us[20]. Although other authors have also found an association between an elevated RDW and the severity of coronary disease or mortality, their RDW values are different than that found by us (14.1, 12.6 or 12.85)[21-23], which warrants more works to be performed in this sense in order to establish a more significant and consistent cutoff value. Now, although different studies have demonstrated that RDW is an independent predictor of death in coronary disease, the mechanism by means of which an elevated value of RDW is associated with cardiovascular adverse events is not yet fully understood. Inflammatory activity of the disease has been proposed as one of the mechanisms explaining this association[24]. According to this hypothesis, inflammatory activity of the disease would affect bone marrow iron metabolism and suppress RBCs maturation, which would cause for young RBCs to enter the blood stream and, in turn, this would induce an increase in RBCs size heterogeneity; i.e., inflammation could influence on RDW levels by producing an alteration in erythropoiesis, but this hypothesis has yet to be confirmed[25-28]. Emmans et al. found RDW to be negatively-associated with the reticulocyte hemoglobin contents, transferrin saturation and the level of soluble transferrin receptors, and positively-associated with the levels of interleukin 6 in patients with heart failure and cardiorenal syndrome, information that confirms the presence of an inflammatory state that negatively affects erythropoiesis in patients with cardiovascular disease[29]. In addition, elevated RDW has been associated with an increase in the values of pro-inflammatory cytokines, such as tumor necrosis factor alpha and interleukin 6. These cytokines attenuate erythropoietin activity and cause the production of immature RBCs, leading to RDW elevation[30].Other authors have suggested that, in addition to inflammation, oxidative stress plays an important role in RDW in patients with ACS as well, because both factors reduce RBCs life, since RDW has been shown to be elevated with increasing levels of oxidative stress, as in patients with poor renal function or on dialysis[31]. Moreover, in the Women's Health and Aging Study I, reduced levels of antioxidants such as selenium, carotenoids and vitamin E were reported to be associated with elevated values of RDW[32].

With regard to the finding of a significant association between elevated RDW and the presence of thrombocytopenia, this could be indicating bone marrow inability to adapt to ACS-induced hypoxia and, with platelet turnover being faster than that of RBCs, by the time RDW is increased, thrombopoiesis is already altered, which entails a platelet count reduction[33]. This is also significantly associated with the fact that, on average, patients with higher RDW are older and, thus, have a

**Table 4. Short-term mortality***

| | Low RDW group (RDW ≤ 15.0; n = 56) | High RDW group (RDW > 15.0; n = 22) | p |
|---|---|---|---|
| Cardiovascular mortality | 5 (10.2) | 9 (47.3) | 0.001 |
| Reinfarction | 3 (6.1) | 1 (5.2) | 1.00 |
| Hospitalization due to heart failure | 1 (2.0) | 1 (5.2) | 0.48 |

*Continuous and categorical variables are reported as the average (SD) and number (%), respectively.

**Table 5. Short-term mortality multivariate regression logistic analysis**

| | p |
|---|---|
| RDW | 0.001 |
| MCV | 0.001 |
| VLDL | 0.046 |
| Killip-Kimball class | 0.001 |
| TIMI | 0.001 |
| Number of hypokinesis zones in echocardiogram | 0.0001 |
| Diastolic dysfunction | 0.006 |
| Systolic dysfunction | 0.0001 |

bone marrow decreased capability to adequately respond to the flow decrease caused by ACS.

### *Limitations*

An undeniable weakness of this study is the sample size, which is modest for the prevalence of ACS, although it represents the totality of patients admitted in our center due to the diagnoses motivating this study.

On the other hand, we did not have information available on iron, folate and vitamin $B_{12}$ levels of our patients but, as the results clearly indicate, no one displayed hemoglobin levels lower than 12 g/dl or 13.5 g/dl or MCV alterations, which rules out the possibility of anemia or megaloblastosis.

## Conclusions

RDW has been shown to be a prognostic factor of short-term cardiovascular mortality in ACS patients of our population, but the conduction of prospective studies with larger numbers of patients in different centers of our country is clearly required in order to corroborate if the findings here referred are valid for the rest of the Mexican population.

## Conflict of interests

The authors declare not having any conflicts of interest.

## Acknowledgements

The present work was carried out with the support of the Post-degree Head Office of the Universidad Autónoma de Aguascalientes, under the PIEC-2013 project.

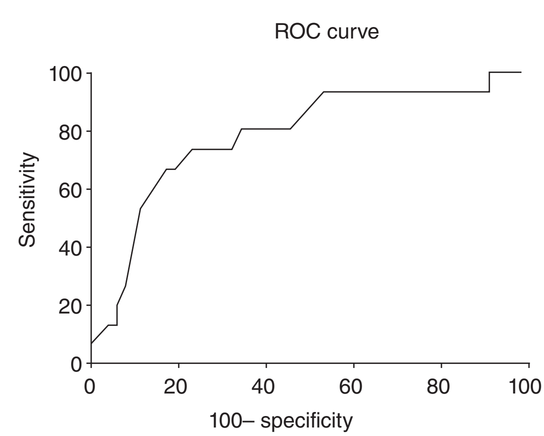


**Figure 1.** *RDW ROC curve analysis to predict cardiovascular mortality (area under the curve: 0.78; 95% CI: 0.64-0.92; p = 0.0008).*

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