

# Red blood cell distribution width independently predicts medium-term mortality and major adverse cardiac events after an acute coronary syndrome

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**Background:** The value of red blood cell distribution width (RDW), a simple and inexpensive measure of anisocytosis, has been associated with the outcome of many human chronic disorders. Therefore, this retrospective study was aimed to investigate whether RDW may be associated with medium-term mortality and major adverse cardiac events (MACE) after an acute coronary syndrome (ACS).

**Methods:** A total number of 979 patients diagnosed with ACS were enrolled from June 2014 to November 2014, and followed-up until June 2015.

**Results:** The RDW value in patients with 3-month MACE and in those who died was significantly higher than that of patients without 3-month MACE (13.3% *vs.* 14.0%;  $P < 0.001$ ) and those who were still alive at the end of follow-up (13.4% *vs.* 14.4%;  $P < 0.001$ ). In univariate analysis, RDW was found to be associated with 3-month MACE [odds ratio (OR), 1.70; 95% CI, 1.44–2.00,  $P < 0.001$ ]. In multivariate analysis, RDW remained independently associated with 3-month MACE (adjusted OR, 1.36; 95% CI, 1.19–1.55;  $P < 0.001$ ) and death (adjusted OR, 1.34; 95% CI, 1.05–1.71;  $P = 0.020$ ). The accuracy of RDW for predicting 3-month MACE was 0.67 (95% CI, 0.66–0.72;  $P < 0.001$ ). The most efficient discriminatory RDW value was 14.8%, which was associated with 3.8 (95% CI, 2.6–5.7;  $P < 0.001$ ) higher risk of 3-month MACE. Patients with RDW  $> 14.8\%$  exhibited a significantly short survival than those with RDW  $\leq 14.8\%$  (331 *vs.* 465 days;  $P < 0.001$ ).

**Conclusions:** The results of this study confirm that RDW may be a valuable, easy and inexpensive parameter for stratifying the medium-term risk in patients with ACS.

**Keywords:** Acute coronary syndrome (ACS); myocardial infarction (MI); mortality; major adverse cardiac events (MACE); red blood cell distribution width (RDW)

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## Introduction

According to the recent 2016 Report Update published by the American Heart Association (AHA) (1), as many as 0.21% Americans experiment a new coronary event each

year, and approximately 0.10% will have a recurrent event afterward. It is also estimated that 0.5% Americans will have a silent acute coronary syndrome (ACS) each year, thus raising the cumulative yearly rate of ACS up to 0.35%. Based on mortality data (1), ACS was found to be the

underlying cause of death in approximately 14% of cases in the US, with an overall ACS death rate of 102.6 per 100,000 US residents. Even more importantly, approximately 34% of subjects who experience a new coronary event will die of it. Impressively, the mortality rate at 5 years after a prior ACS is 36% in men and 47% in women at the age of  $\geq 45$  years, but it dramatically increases up to 55% in men and 60% in women after the age of 75 years. Despite the mortality curve rate has considerably bent in the past decades, cardiovascular death remains the leading cause of mortality in the US, as well as in many other Countries worldwide (2). The likelihood of developing chronic complication later after an ACS is also considerably high, wherein heart failure may occur in 16% of men and 22% of women. Overall the estimated direct and indirect cost of ACS exceeds \$200 billion in the US, but this expenditure is predicted to double in the next 15 years (1).

The concerning figures about the overall incidence and the death rate will make ACS the most relevant public health care issue in the forthcoming years, all around the globe. It is hence reasonable that major focus should be placed to identify reliable prediction models, which may help stratify the cardiovascular and overall risk of complications and death after an ACS. The diagnostic approach to patients with ACS encompasses the evaluation of clinical signs and symptoms, electrocardiographic assessment, combined with the measurement of circulating biomarkers which may provide reliable diagnostic and prognostic information (3-5). Despite the introduction of high-sensitivity immunoassays for the measurement of cardiac troponins has virtually revolutionized the diagnostic approach to patients with suspected ACS (6,7) providing also useful valuable information for the prognosis of these patients (8), the prediction of the future risk of major adverse cardiac events (MACE) still engages the minds of many emergency physicians and cardiologists. Many putative biomarkers have been proposed over the past decades, each of them targeting different pathways of ACS such as apoptosis, cardiomyocyte stress, cardiac fibrosis, inflammation and extra-cardiac involvement (9). Among these, interesting data emerged from the assessment of red blood cell distribution width (RDW), a simple measure of anisocytosis that can be routinely obtained from a simple and relatively inexpensive complete blood cell count (CBC) (10). Therefore, we planned a large retrospective analysis to verify whether the value of RDW may provide useful prognostic information on the medium-term risk in patients admitted to our facility for an episode of ACS.

## Methods

### *Study population*

This study was designed to retrospectively evaluate all patients admitted to Emergency Department of University Hospital of Verona from June 2014 to November 2014 for chest pain of proven cardiac origin. The baseline demographic and clinical characteristics, previous medical history regarding cardiovascular risk factors, past and concomitant medications and clinical characteristics of chest pain were collected. Patients with incomplete medical history were not originally included in the dataset. Obesity was defined as a body mass index (BMI)  $> 25$ .

The primary endpoint in this study was the occurrence of MACE within 3-month of initial presentation. The definition of MACE (11) consisted in the development of acute myocardial infarction (AMI), need of percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and coronary angiography, revealing procedurally correctable stenosis managed conservatively.

The diagnosis of ACS was made in accord with the ESC guidelines, as a rise and fall of cardiac troponin I values (Siemens Dimension Vista, Siemens Healthcare Diagnostics, Tarrytown, NY, USA) with at least one value above the 99<sup>th</sup> percentile of the upper reference limit (i.e., 45 ng/L) (12) along with evidence of myocardial ischemia. Within the diagnosis of AMI, distinction was made between either ST-elevation myocardial infarction (STEMI) or non ST-elevation myocardial infarction (NSTEMI) (13). PCI was defined as any therapeutic catheter intervention in the coronary arteries, whereas CABG was defined as any cardiac surgery in which coronary arteries were operated. Coronary angiography revealing critical coronary stenosis, not treated with coronary revascularization but only with conservative medical therapy for reasons of comorbidity, was also considered a MACE. The secondary endpoint of the study was death occurred at the end of follow-up, which lasted until June 2015 (i.e., approximately 1-year). Data were retrieved from digital and written patient records, including discharge letters, revascularization reports and any other relevant documentation. In a few cases where follow-up data were not available from hospital records, the patients or their general practitioner were contacted to obtain information on their condition, hospital admissions, ACS and revascularization.

The CBC, thus including the measurement of RDW and hemoglobin, was performed in all patients using Sysmex

analyzer (Sysmex XE-2100, Sysmex Inc., Kobe, Japan). The quality of data was validated throughout the study period by regular internal quality control (IQC) procedures and participation to an External Quality Assessment (EQA) scheme.

### Statistical analysis

Continuous variables were reported as median value and interquartile range. The difference between groups was evaluated using Kruskal-Wallis Test. Discrete variables were described as percentage and overall number of events, and were then analyzed by Chi-square test (or Fisher's exact test). RDW was compared with clinical outcomes after ACS (MACE at 3 months from initial presentation or death at the end of follow-up) as continuous and categorical variable (quartiles). Logistic binomial regression was used to evaluate independent effects of RDW on clinical outcomes. All variables that were found to be significant associated with RDW were entered into a multivariate model. The predictive accuracy of RDW for MACE at 3 months after ACS and the most informative cut-off value were identified by receiver operating characteristics (ROC) curve analysis. A Kaplan Meier curve was also constructed to evaluate the survival difference at the end of follow-up according to the RDW cut-off value previously identified. Statistical analysis was performed using SPSS 22.0. The level of statistical significance was set at  $P < 0.05$ . This retrospective observational study was carried in accordance with the Declaration of Helsinki and under the terms of relevant local legislation.

### Results

A total number of 979 patients were included from Jun 2014 to Nov 2014. The median and interquartile ranges of RDW were 13.4% and 12.8–14.1%, respectively. The baseline characteristics of patients stratified according to quartiles of RDW are shown in *Table 1*. Patients in the highest quartile of RDW displayed a higher frequency of cardiovascular risk factors, an older age and more concomitant medical treatments. The median value of the HEART (history, electrocardiogram, age, risk factors and troponin) score also increased in parallel with RDW values.

As regards the follow-up, the median RDW value in patients with 3-month MACE and in those who died was significantly higher than that of patients without 3-month MACE (14.0% *vs.* 13.3%;  $P < 0.001$ ) and in those who

were still alive at the end of follow-up (14.4% *vs.* 13.4%;  $P < 0.001$ ). After stratifying the entire study population in quartiles of RDW, the incidence of death and 3-month MACE increased in parallel with RDW quartiles ( $P = 0.001$  for both) (*Table 2*).

In univariate analysis, RDW was found to be a risk factor for 3-month MACE calculated both as continue [odds ratio (OR), 1.52; 95% CI, 1.35–1.72;  $P < 0.001$ ] and as a categorical variable (OR, 1.70; 95% CI, 1.44–2.00;  $P < 0.001$ ). This association was then confirmed in multivariate analysis (*Table 3*), which showed that RDW remained independently associated with 3-month MACE (adjusted OR, 1.36; 95% CI, 1.19–1.55;  $P < 0.001$ ) and death at the end of follow-up (adjusted OR, 1.34; 95% CI, 1.05–1.71;  $P = 0.020$ ).

Dyslipidemia, hypertension, smoking status and obesity were found to be additional independent predictors of MACE at 3 months, whereas no significant association was noticed between 3-month MACE and diabetes mellitus, previous history of myocardial infarction (MI) and the presence of chronic kidney disease (*Table 2*). The accuracy of RDW for predicting 3-month MACE was characterized by an area under the curve (AUC) of 0.67 (95% CI, 0.66–0.72;  $P < 0.001$ ). The most efficient discriminatory RDW value was 14.8%, which was associated with a relative risk (RR) of 3.82 (2.55–5.70;  $P < 0.001$ ) for 3-month MACE. The median survival at the end of follow-up of patients stratified according to this cut-off of RDW is shown in *Figure 1*. Patients with RDW value  $> 14.8\%$  exhibited a significantly short survival period at the end of follow-up than those with RDW values  $\leq 14.8\%$  (331 *vs.* 465 days;  $P < 0.001$ ).

### Discussion

Despite the establishment of many preventive strategies and the development of effective treatments have significantly contributed to reduce the frequency and complication of ACS, heart disease remains the leading cause of mortality and morbidity around the globe (1). Therefore, the assessment of reliable, rapid, easy and relatively inexpensive biomarkers for predicting clinical outcomes in these patients should be regarded as a highly valuable perspective for stratifying the future risk of MACE and death, so establishing the most appropriate therapeutic management in the individual patient (14). Anisocytosis is conventionally referred as the heterogeneity of erythrocyte volumes, which may be dependent upon many demographic and clinical variables. Briefly, the release of erythrocytes of different shape and volume from the bone marrow is not

**Table 1** Demographic and clinical characteristics of the study population stratified according to quartiles of red blood cell distribution width (RDW)

Characteristics	RDW (%)				P
	<12.8	12.8–13.3	13.4–14.1	>14.1	
N	205	317	213	244	–
Male gender, n (%) <sup>*</sup>	145 (25.0)	187 (32.2)	117 (20.2)	131 (22.6)	<0.001
Age, years [range]	48 [37–60]	56 [42–70]	66 [50–76]	72 [51–82]	<0.001
Medical history, n (%) <sup>*</sup>					
Hypertension	67 (13.8)	139 (28.6)	122 (25.1)	158 (32.5)	<0.001
Diabetes mellitus	17 (14.3)	27 (22.7)	29 (24.4)	46 (38.7)	<0.001
Dyslipidemia	50 (15.6)	86 (26.9)	75 (23.4)	109 (34.1)	<0.001
Obesity	15 (10.4)	45 (31.3)	39 (27.1)	45 (31.3)	0.003
Smoking	43 (16.7)	69 (26.7)	58 (22.5)	88 (34.1)	<0.001
Family history of MI	28 (19.2)	53 (36.3)	27 (18.5)	38 (26.0)	0.577
Previous history of MI	23 (11.7)	48 (24.4)	46 (23.4)	80 (40.6)	<0.001
CKD	2 (3.2)	8 (12.7)	15 (23.8)	38 (60.3)	<0.001
Previous history of stroke	0 (0.0)	4 (26.7)	2 (13.3)	9 (60.0)	<0.010
Clinical findings					
HEART score [range]	2 [1–3]	3 [1–4]	4 [2–5]	5 [3–6]	<0.001
CPS [range]	4 [1–6]	5 [1–6]	5 [2–7]	5 [2–7]	0.017
Hemoglobin (g/L) [range]	141 [135–153]	142 [134–152]	139 [129–147]	131 [118–140]	<0.001
Medical treatment, n (%) <sup>*</sup>					
Aspirin	33 (12.0)	73 (26.4)	72 (26.1)	98 (35.5)	<0.001
Double anti-aggregation	10 (15.2)	15 (22.7)	16 (24.2)	25 (37.9)	<0.001
Warfarin	1 (2.7)	5 (13.5)	8 (21.6)	23 (62.2)	<0.001
Beta-blockers	27 (11.6)	56 (24.0)	56 (24.0)	94 (40.3)	<0.001
ACEI/ARB	46 (14.4)	97 (30.4)	73 (22.9)	103 (32.3)	<0.001
Diuretics	15 (8.4)	42 (23.5)	41 (22.9)	81 (45.3)	<0.001
Statins	40 (14.9)	69 (25.7)	65 (24.2)	95 (35.3)	<0.001

<sup>\*</sup>, percentage among quartiles. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CPS, Chest Pain Score; MI, myocardial infarction. HEART, history, electrocardiogram, age, risk factors and troponin.

**Table 2** Incidence of death and major adverse cardiac events (MACE) at 3 months in patients with an acute coronary syndrome (ACS), stratified according to quartiles of red blood cell distribution width (RDW)

Outcome	RDW (%)				P
	<12.8	12.9–13.3	13.4–14.1	>14.1	
Death, n (%)	0 (0.0)	6 (1.9)	5 (2.3)	20 (8.2)	<0.001
MACE, n (%)	17 (8.3)	40 (12.6)	33 (15.6)	74 (30.3)	<0.001

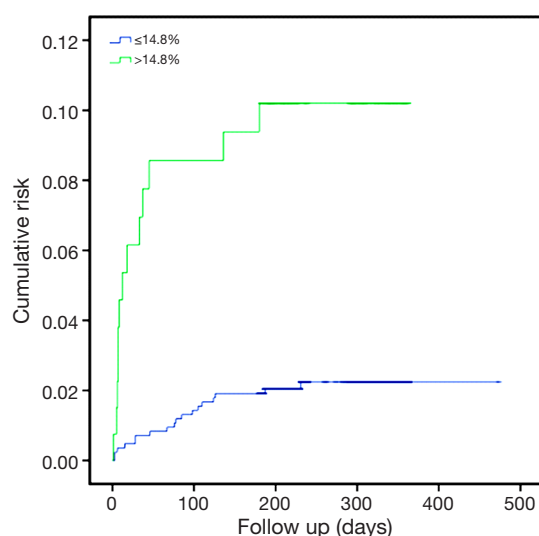
only influenced by the birth season (15), ageing (16) and eventually physical exercise (17), but also by a number of red blood cells disorders such as iron, vitamin B or folate deficiencies, genetic diseases (e.g., thalassemia, sickle cell anemia, hereditary spherocytosis), hemolytic anemia

and transfusions. Several lines of evidence also attest that oxidative stress, inflammation, dyslipidemia, hypertension, poor nutritional status, impairment of erythropoietin synthesis and erythropoietin hyporesponsiveness may be concomitant causes of anisocytosis (18). Many of these

**Table 3** Multivariate analysis for predicting major adverse cardiac events (MACE) at 3 months in patients with an acute coronary syndrome (ACS)

Parameter	OR	95% CI	P
RDW	1.36	1.19–1.55	<0.001
Diabetes mellitus	1.45	0.86–2.42	0.159
Dyslipidemia	1.66	1.10–2.72	0.046
Hypertension	1.83	1.14–2.96	0.013
Smoking	3.93	2.69–5.75	0.001
Previous history of MI	1.31	0.79–2.17	0.296
CKD	1.67	0.89–3.13	0.111
Obesity	1.64	1.03–2.60	0.035

CKD, chronic kidney disease; MI, myocardial infarction; OR, odds ratio; RDW, red blood cell distribution width.

**Figure 1** One-year survival curve (Kaplan-Meier) of patients who suffered from an acute coronary syndrome (ACS), stratified according to red blood cell distribution width (RDW) values  $\leq 14.8\%$  or  $> 14.8\%$  ( $P < 0.001$ ).

metabolic abnormalities are commonly encountered in patients with heart disease, and may contribute to development of acute events such as an ACS. Therefore, the potential association between anisocytosis and ACS is supported by reliable biological mechanisms (19).

A number of studies previously investigated the role of RDW in predicting adverse outcomes after an ACS. Arbel *et al.* studied 3,222 patients undergoing coronary angiography and explored the association between RDW and 3-year outcome using Cox's proportional hazards analysis (20). The

overall MACE rate was found to be consistently higher for patients in the highest RDW quartile compared to those in the lowest quartile (18.2% *vs.* 7.7%;  $P < 0.001$ ). In the fully adjusted model, the RDW value remained independently associated with worse outcome [hazard ratio (HR) for 1% increase, 1.12; 95% CI, 1.07–1.18;  $P < 0.001$ ]. In a subsequent study, Bekler *et al.* retrospectively studied 202 patients with ACS, who were followed up for a median period of 3 months (21). The rate of both cardiovascular death and MACE was found to be higher in patients with increased RDW values than in those with normal values. In multiple regression analysis, a RDW value  $> 14.0\%$  was found to be an independent predictor of cardiovascular mortality (OR: 3.0; 95% CI, 1.0–8.9;  $P = 0.039$ ). In another large population study, including as many as 1,760 coronary angiography patients, Gijsberts *et al.* (22) reported that each one standard deviation (SD) increase of RDW was associated with a 19% higher risk of MACE in multivariable, fully adjusted analysis (HR, 1.19; 95% CI, 1.08–1.32;  $P < 0.001$ ). The relationship between RDW and 4-year cardiovascular events after PCI was also investigated in 96 consecutive patients with ACS by Isik *et al.* (23), who finally reported that an increased RDW value was an independent predictor of long-term MACE (HR 5.26; 95% CI, 1.71–16.10;  $P = 0.004$ ). More recently, Ghaffari *et al.* studied 312 patients undergoing thrombolysis for ACS (24), and reported that RDW was an independent predictor of in-hospital occurrence of MACE (RR, 3.17; 95% CI, 1.23–8.46;  $P = 0.017$ ). Important evidence also emerged from the recent study of Huang and Hu, who analyzed 3,304 subjects admitted to the intensive care unit after an ACS (25). Interestingly, in univariate analysis the RDW was found to be significantly associated with both in-hospital mortality (OR for 1% increase, 1.21; 95% CI, 1.15–1.28;  $P < 0.001$ ) and 1-year mortality (OR per 1% increase, 1.21; 95% CI, 1.18–1.25;  $P < 0.001$ ). The association between RDW and 1-year mortality remained significant also in multivariate analysis (HR for 1% increase, 1.06; 95% CI, 1.02–1.11;  $P = 0.005$ ).

Taken together, the results of our study corroborate and extend previous findings relative to short-term (i.e., in-hospital) and long-term (i.e.,  $> 1$ -year) mortality in patients with increased RDW values, by confirming that anisocytosis should be regarded as a significant predictor of medium-term outcomes (i.e., 3-month MACE and 1-year mortality). More specifically, a RDW higher than 14.8% was found to be associated with a more than 3-fold enhanced risk of 3-month MACE after an ACS, and



patients with increased RDW values also exhibited a 29% reduced survival compared to those with RDW within the normal range (*Figure 1*). Notably, the association between RDW, 3-month MACE and mortality was confirmed to be independent from other known risk factors of adverse outcome after cardiac ischemia, thus highlighting the valuable role of measuring RDW in this clinical setting.

The intriguing association between RDW and outcomes of ACS adds further evidence about the clinical usefulness of investigating anisocytosis in health and disease. Enhanced RDW values have been found to be associated with death and complications in many other chronic and highly prevalent conditions such as cancer (26), diabetes (27), venous thromboembolism (28) and severe allergic reactions (29). Indeed, major derangements of many common biological pathways are known to occur in these conditions, which are mostly characterized by apoptosis, malnutrition, chronic inflammatory response and fibrosis.

## Conclusions

It presently remains to be definitely evaluated whether anisocytosis and MACE are both due to common metabolic abnormalities, and therefore increased RDW values should only be considered an epiphenomenon, or rather the heterogeneity of erythrocyte volumes directly interplays with the pathogenesis of ACS and its complications. Nevertheless, the results of this large retrospective study confirm that RDW may be regarded as a valuable, easy and inexpensive parameter for stratifying the medium-term risk of MACE and death in patients with ACS. We hence suggest that its measurement should be routinely implemented in current models for stratifying the risk of adverse events after an episode of myocardial ischemia.

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## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** This retrospective observational study was carried in accordance with the Declaration of Helsinki and under the terms of relevant local legislation.

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