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Prognostic Value of Red Cell Distribution Width in Acute Coronary Syndrome

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Abstract

Anisocytosis denotes the presence of unequal sizes of erythrocytes in the circulation and may signify the development of nutritional deficiency anemias, sickle cell anemia, hemolytic anemia, myelodysplastic syndrome, and other hematological disorders. Red cell distribution width (RDW), a quantitative measure of the magnitude of anisocytosis, is routinely reported as a part of complete blood count by automated instruments in hematology laboratories. An elevated RDW is commonly used in the differential diagnoses of nutritional deficiency anemias and thalassemias. Rapidly accruing evidence indicates that RDW may offer prognostic information regarding the clinical outcomes in various cardiovascular scenarios. This article aims to review the current knowledge concerning the predictive value of RDW in patients with acute coronary syndrome. Elevated RDW is a strong predictor for mortality and major adverse cardiac events among patients admitted with acute myocardial infarction. When incorporated into conventional risk assessment models, RDW also enhances the performance in predicting cardiovascular outcome. In light of its wide availability, low cost and common use, future research should consider RDW measurement in the risk stratification schemes for patients with coronary artery disease.

Keywords: Red cell distribution width; Coronary artery disease; Coronary revascularization; Percutaneous coronary intervention; Coronary artery bypass grafting

Abbreviations : ACS: Acute Coronary Syndrome; AF: Atrial Fibrillation; AMI: Acute Myocardial Infarction; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CHF: Chronic Heart Failure; CCU: Coronary Care Unit; DES: Drug-Eluting Stent; FPG: Fasting Plasma Glucose; HF: Heart Failure; ICU: Intensive Care Unit; IHD: Ischemic Heart Disease; LDL-C: Low-Density Lipoprotein Cholesterol; LVEF: Left Ventricular Ejection Fraction; MACE: Major Adverse Cardiac Event; MCV: Mean Corpuscular Volume; NSTE-ACS: Non-ST-Segment Elevation Acute Coronary Syndrome; NSTEMI: Non-ST-Segment Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; RBC: Red Blood Cell; RDW: Red Cell Distribution Width; STEMI: ST-Segment Elevation Myocardial Infarction

Introduction

In humans, the major function of red blood cells (RBCs), also known as erythrocytes, is to deliver oxygen to the peripheral tissues. The normal size of an RBC corpuscle is between 7.2 and 7.9μm in diameter and 2μm in thickness, with a physiologic volume ranging from 80 to 100fL [1]. The plasticity of the plasma membrane allows for considerable enlargement or shrinkage of the RBC in response to pathophysiologic insults, resulting in an increase or decrease in the RBC volume (termed macrocytosis and microcytosis, respectively). The presence of unequal sizes of RBCs in the circulation (anisocytosis) has been considered as a non-specific finding in various conditions such as nutritional deficiency anemias, sickle cell anemia, hemolytic anemia, myelodysplastic syndrome, and other hematological disorders. Red cell distribution width (RDW), a quantitative measure of the magnitude of anisocytosis, is calculated by the standard deviation of corpuscular volume divided by the mean corpuscular volume (MCV) and expressed as a percentage, with an upper limit of normal values of 14.0 to 15.0% [2].This metric is routinely reported as a part of complete blood count by automated instruments in hematology laboratories. An elevated RDW is typically used in differentiating an early stage of nutritional deficiency or megaloblastic anemias from other thalassemias [3]. When used in conjunction with MCV, RDW may also improve the diagnostic accuracy of erythrocyte disorders. In addition to its diagnostic value, rapidly accruing evidence points to the prognostic role of RDW in a wide variety of disorders [4]. This review aims to summarize the current knowledge of RDW for predicting short-, medium-, and long-term clinical outcomes among patients with acute coronary syndrome.

RDW and Short-Term Clinical Outcome in Patients with Acute Coronary Syndrome

The association between red cell distribution width and short-term clinical outcome (≤1 year) in patients with acute coronary syndrome is summarized in Table 1. RDW was positively associated with in-hospital major adverse cardiac event (MACE; the composite of ventricular arrhythmia, acute heart failure, MI, or death) or in-hospital cardiovascular death [5,6]. Patients with a higher RDW tend to have a greater risk of all-cause mortality at 3 months to 1 year [7-12]. Studies from Wang et al. [13] and Ren et al. [14] reported the association between RDW and cardiovascular mortality at 1 month and at 12 months, respectively [13,14]. The risk of reinfarction and other MACE end points was greater in patients with elevated RDW compared to lower RDW [10,11,14,15]. In addition, RDW was also found to be associated with recurrent hospitalization for heart failure or MI [13].

Table 1: Red cell distribution width and short-term clinical outcome (≤1 year) in patients with acute coronary syndrome*.

Author (Year)	N	Design	Median Follow-up	Population	Outcome
Bozorgi (2016) [7]	838	Cohort	6 months	STEMI patients undergoing primary PCI	RDW (categorical): Death at 6 months: 2.485 (1.533–4.027)
Ghaffari (2016) [5]	312	Cohort	7.7 months	STEMI patients indicated for thrombolytic therapy	RDW (categorical): † Death at 1 year: 4.67 (1.51-14.38) In-hospital MACE: 3.169 (1.233 - 8.146)‡
Huang (2016) [8]	3304	Retrospective	12 months	AMI patients admitted to ICU	RDW (continuous): Death at 1 year: 1.21 (1.18-1.25)
Turcato (2016) [10]	979	Retrospective	3 months	ACS patients admitted to the emergency department	RDW (categorical): † MACE at 3 months: 1.36 (1.19 - 1.55)¶ Death at 3 months: 1.34 (1.05 - 1.71)RDW (continuous): MACE at 3 months: 1.52 (1.35 - 1.72)¶
Khaki (2015) [9]	642	Cohort	6 months	AMI patients admitted to CCU	RDW (categorical): Death at 6 months: 1.98 (1.06 - 3.68)
Timóteo (2015) [12]	787	Retrospective	12 months	ACS patients admitted to ICU	RDW (categorical): Death at 1 year: 1.24 (1.12 - 1.37)
Fatemi (2013) [11]	1435	Prospective	12 months	Patients undergoing PCI	RDW (categorical): Death at 1 year: 5.07 (2.07 - 12.40) RDW (continuous): † Death at 1 year: 1.65 (1.22 - 2.23) MI at 1 year: 0.99 (0.76 - 1.29) Unplanned revascularization at 1 year: 1.07 (0.89 - 1.29) MACE at 1 year: 1.03 (0.88 - 1.21)††
Ren (2013) [14]	1416	Cohort	12 months	Patients with stable angina	RDW (categorical): † Cardiovascular death at 1 year: 1.544 (1.058 - 3.216) ACS at 1 year: 1.861 (1.226 - 3.487)
˙Ilhan (2012) [6]	763	Retrospective	NR	AMI patients undergoing primary PCI	RDW (categorical): † In-hospital cardiovascular death: 3.677 (1.228 - 11.008)
Wang (2011) [13]	1654	Cohort	1 month	ACS patients undergoing PCI	RDW (categorical): † Cardiovascular death: 2.116 (1.427 - 3.137) Rehospitalization for HF/MI: 2.134 (1.602 - 2.844)
Nabais (2009) [15]	1796	Cohort	6 months	ACS patients admitted to CCU	RDW (categorical): † Death/MI: 1.43 (1.00 - 2.05) RDW (continuous): † Death/MI: 1.16 (1.03 - 1.30)

*RDW (categorical) indicates comparison between top and bottom categories; RDW (continuous) indicates relative risk of each 1% increase.

†Multivariable adjustment

‡The composite of: 1) ventricular (wide QRS complex) dysrhythmias beyond 24 hours after STEMI; 2) acute heart failure presenting with either cardiogenic shock or pulmonary edema; 3) repeat MI; or 4) death

¶The composite of: 1) AMI requiring coronary revascularization; or 2) critical coronary stenosis on angiography

††The composite of: 1) all-cause mortality; 2) MI; or 3) unplanned revascularization

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RDW and Medium-Term Clinical Outcome in Patients with Acute Coronary Syndrome

The association between red cell distribution width and medium-term clinical outcome (>1 to ≤3 years) in patients with acute coronary syndrome is summarized in Table 2. Numerous studies identified the link between RDW (analyzed as a categorical or continuous variable) and all-cause death [16-20]. In contrast, Sahin et al. [21] found that there was no association between RDW and death among NSTEMI patients. Elevated RDW was associated with a higher rate of cardiovascular death in both STEMI and NSTEMI patients [22-24]. There is an association of increased RDW with MACE end points such as recurrent MI, stroke, stent thrombosis, and target vessel revascularization [15,25-27]. It is noteworthy that the risk of new-onset atrial fibrillation increased with RDW among STEMI patients undergoing primary PCI [28].

Table 2: Red cell distribution width and medium-term clinical outcome (>1 to ≤3 years) in patients with acute coronary syndrome*.

Author (Year)	N	Design	Median Follow-up	Population	Outcome
Tunçez (2017) [27]	321	Retrospective	16.9 months	STEMI patients undergoing PCI	RDW (categorical): † Stent thrombosis: 1.397 (1.177 - 1.657)
Karataş (2016) [28]	621	Retrospective	22 months	STEMI patients undergoing primary PCI	RDW (categorical): † New-onset AF: 1.43 (1.19 - 1.71)
Bekler (2015) [22]	202	Retrospective	18 months	NSTE-ACS patients admitted to CCU	RDW (categorical): Cardiovascular death: 3.6 (1.2 - 10.5)
Liu (2015) [16]	1891	Retrospective	17.6 months	Elderly patients undergoing elective PCI	RDW (categorical): Death: 2.052 (1.182 - 3.561)
Sahin (2015) [21]	335	Cohort	18 months	NSTEMI patients admitted to the emergency department	RDW (categorical): Death: not significant (p=0.621)
Arbel (2014) [25]	3222	Prospective	13.8 months	CAD patients undergoing angiography	RDW (categorical):MACE at 3 years: 1.12 (1.07 - 1.18)#
Yao (2014) [18]	2169	Prospective	29.1 months	Non-anemic CAD patients undergoing PCI with DES	RDW (continuous): Death: 1.4 (1.23 - 1.59)MACE: 1.27 (1.13 - 1.42)**
Osadnik (2013) [17]	2550	Retrospective	30.5 months	Patients with stable CAD undergoing PCI	RDW (continuous): † Death: 1.23 (1.13 - 1.35)
Gul (2012) [23]	310	Prospective	36 months	NSTE-ACS patients admitted to the emergency department	RDW (categorical): † Cardiovascular death: 3.2 (1.3 - 7.78)
Vaya (2012) [26]	119	Cohort	21 months	AMI patients admitted to ICU	RDW (categorical): MACE: 6.19 (2.1 - 18.5)§§
Uyarel (2011) [24]	2506	Retrospective	21 months	STEMI patients undergoing PCI	RDW (categorical): † Cardiovascular death: 1.831 (1.034 - 3.24) Cardiovascular death (non-anemic): 2.703 (1.208 - 6.048)
Cavusoglu (2010) [19]	193	Cohort	24 months	Male patients with ACS referred for coronary angiography	RDW (categorical): † Death at 2 years: 2.90 (1.32 - 6.38)
Dabbah (2010) [20]	1709	Cohort	27 months	ACS patients admitted to CCU	RDW (categorical): Death: 4.8 (3.8 - 8.1)

*RDW (categorical) indicates comparison between top and bottom categories; RDW (continuous) indicates relative risk of each 1% increase.

†Multivariable adjustment

#The composite of: 1) all-cause mortality; 2) MI; or 3) stroke

**The composite of: 1) all-cause mortality; 2) MI; 3) stent thrombosis; or 4) target vessel revascularization

§§The composite of: 1) unstable angina; 2) new AMI episode; 3) cerebrovascular accident; or 4) cardiovascular mortality

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RDW and Long-Term Clinical Outcome in Patients with Acute Coronary Syndrome

The association between red cell distribution width and long-term clinical outcome (>3 years) in patients with acute coronary syndrome is summarized in Table 3. In consistent with aforementioned studies, RDW is reported to be associated with all-cause mortality [29-39] and cardiovascular mortality [35,40] in patients with STEMI, NSTEMI, or stable CAD. The study from Tsuboi et al. focused on patients with CAD and concurrent diabetes, and reported an extraordinary greater risk of cardiovascular death in high RDW group [35]. Thus far it is unknown whether or not diabetes would potentiate the prognostic value of RDW. This finding should be validated in further large-scale studies, given the wide variation of confidence interval of effect size. Tonelli et al. [41] studied patients with recent ACS free of heart failure who were randomized to receive pravastatin 40mg daily or placebo [41]. In addition to the relatively large sample size and long follow-up duration, RDW measurement was performed in a central laboratory and outcomes were ascertained based upon prespecified criteria by individuals blinded to RDW levels. After adjustment for hematocrit and traditional cardiovascular risk factors, there was a graded independent relation between higher levels of RDW and the risk of mortality and cardiovascular events such as reinfarction, stroke, or symptomatic heart failure.

Table 3: Red cell distribution width and long-term clinical outcome (>3 years) in patients with acute coronary syndrome*

Author (Year)	N	Design	Median Follow-up	Population	Outcome
Guimarães (2016) [29]	6447	Cohort	50.4 months	Patients undergoing coronary angiography for evaluation of IHD	RDW (continuous): Death: 1.13 (1.09 - 1.17) Death/MI: 1.12 (1.08 - 1.16)
Isik (2016) [40]	96	Prospective	48 months	STEMI patients undergoing primary PCI	RDW (categorical): † MACE at 4 years: 1.84 (1.50 - 2.26)§
Oleksiak (2016) [30]	269	Retrospective	43.2 months	Stable, symptomatic patients with significant CAD	RDW (categorical): † Death/non-fatal MI: 2.80 (1.23 - 6.36)
Zhao (2015) [32]	480	Cohort	37.2 months	ACS patients undergoing PCI with stenting for the first time	RDW (continuous): Death/non-fatal MI: 2.092 (1.654 - 2.646)
Arbel (2014) [31]	535	Prospective	33.8 months	STEMI patients undergoing primary PCI	RDW (categorical): Death at 5 years: 6.4 (2.7 - 15.5)RDW (continuous): Death at 5 years: 1.17 (1.025 - 1.34)
Sun (2014) [34]	691	Retrospective	41.8 months	STEMI patients without heart failure	RDW (categorical): Death: 4.03 (1.25 - 7.54)
Lee (2013) [33]	1596	Prospective	54.5 months	AMI patients	RDW (categorical): Death/nonfatal MI at 1 year: 5.22 (3.24 - 8.41) RDW (continuous): † Death/nonfatal MI at 1 year: 1.19 (1.03 - 1.37)
Tsuboi (2013) [35]	560	Retrospective	46.8 months	Diabetic patients with stable CAD undergoing PCI	RDW (categorical): Cardiovascular death: 16.2 (2.09 - 124.7) † Death: 3.52 (1.60 - 8.53)
Warwick (2013) [39]	8615	Retrospective	69.6 months	Patients undergoing isolated CABG	RDW (continuous): † In-hospital death: 1.23 (1.17 - 1.32) Death: 1.05 (1.02 - 1.07)
Azab (2011) [36]	619	Cohort	48 months	NSTEMI patients	RDW (categorical): Death at 30 days: 1.296 (1.145 - 1.468) Death at 4 years: 1.281 (1.200 - 1.369)
Lappé (2011) [37]	1489	Prospective	100.8–182.4 months	Patients with angiographically-documented CAD	RDW (categorical): Death: 1.37 (1.29 - 1.46)
Poludasu (2009) [38]	859	Cohort	48 months	ACS patients underwent PCI and a glycoprotein IIb/IIIa bolus-only regimen	RDW (categorical): Death at 4 years: 6.06 (3.56 - 10.31)
Tonelli (2008) [41]	4111	RCT	60 months	Patients with ACS in 3–20 months, LDL-C 115–174 mg/dL, FPG≤220 mg/dL, LVEF ≥25%, and no symptomatic CHF	RDW (categorical):† Death: 1.78 (1.28 - 2.47) Fatal CAD or nonfatal MI: 1.56 (1.17 - 2.08) Stroke: 2.58 (1.47 - 4.55) MI: 1.43 (1.03 - 1.99) HF: 1.80 (1.25 - 2.60)

*RDW (categorical) indicates comparison between top and bottom categories; RDW (continuous) indicates relative risk of each 1% increase.

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†Multivariable adjustment

§The composite of: 1) cardiovascular mortality; 2) repeat target vessel revascularization; or 3) reinfarction

Discussion

The association between RDW and cardiovascular disease was first reported by a study from Felker et al. [42], in which elevated RDW was a strong independent predictor of morbidity and mortality in 2,679 patients with symptomatic chronic heart failure after controlling for clinical variables and other laboratory parameters. The etiopathogenesis between RDW and adverse cardiovascular event among ACS patients remains unclear. Chronic inflammation may impact RDW values by affecting the membrane stability and shortening the life span of erythrocytes [43].This mechanism is supported by the correlation between RDW and inflammatory markers such as erythrocyte sedimentation rate and high-sensitivity C-reactive protein [44]. Elevation of RDW may therefore be viewed as an extension of the inflammatory hypothesis for atherothrombosis [45]. Other pathways such as increased oxidative stress and activated neurohumoral system have also been implicated in the association of higher RDW with thrombosis [27]. Alternatively, RDW may represent an integrative measure of pathologic processes in atherosclerotic patients. Its association with adverse clinical outcome could be explained by the link to malnutrition, hepatic dysfunction, or renal insufficiency [46-48]. Stated differently, RDW may represent a universal marker of disease progression in the ACS setting.

The usefulness of a biomarker may reside in not only its capacity to independently predict disease outcome, but also its ability to improve the performance of risk assessment models comprised of clinical variables [49]. In the context of acute myocardial infarction, several studies have examined the incremental prognostic value of RDW. Incorporating RDW into the Global Registry of Acute Coronary Events (GRACE) risk score was demonstrated to enhance the accuracy for cardiovascular risk prediction, as reflected by improvement in discrimination and reclassification [12,32,50]. In addition, the pivotal role of RDW was further reinforced by its relationship with various parameters of CAD severity. Tanboga et al. [51] reported RDW as an independent predictor for angiographic thrombus burden among STEMI patients [51]. Acikgoz et al. [52] demonstrated that RDW was independently associated with functional stenosis of angiographically intermediate coronary artery lesions [52]. Gürel et al. indicated that RDW might be a useful marker for predicting CAD based on the correlation with coronary artery calcification. Regardless of whether elevated RDW is related to a direct mechanistic pathway of thrombogenesis or a marker of disease burden, a wealth of clinical evidence suggests that ACS patients with a higher RDW are more likely to have unfavorable cardiovascular prognosis compared with those with lower RDW.

Conclusion

Red cell distribution width (RDW) is routinely reported as a part of complete blood count by automated instruments in hematology laboratories. RDW is typically elevated in conditions of ineffective erythropoiesis, increased erythrocyte destruction, or after blood transfusion. An accruing body of evidence suggests that RDW is an independent predictor for mortality and major adverse cardiac events among patients with acute coronary syndrome. When incorporated into conventional risk assessment models, RDW also enhances the performance in predicting cardiovascular outcome. Future research should focus on utilizing the prognostic value of RDW to better characterize the cardiovascular risk profile of patients with coronary artery disease.

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