Elevated Red Blood Cell Distribution Width Is Associated with Higher Recourse to Coronary Artery Bypass Graft

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Key Words

Coronary bypass • Red blood cell width

Abstract

Background: Red blood cell distribution width (RDW) is a measure of heterogeneity in erythrocyte size used in the differential diagnosis of anemia. High levels are associated with elevated cardiovascular biomarkers and increased mortality. The hypothesis of this study is that high RDW levels on admission are associated with higher recourse to coronary artery bypass graft (CABG) in unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI) patients. **Methods:** An observational, cross-sectional study of all adult patients undergoing coronary angiography admitted to an urban tertiary care center in 2007 with UA or NSTEMI was conducted. Data was gathered by review of inpatient charts. RDW was considered 'high' if it exceeded the 95th percentile (16.3%). **Results:** Among the 503 subjects included in the analysis, high RDW was independently associated with higher recourse to CABG versus a nonsurgical approach [OR = 2.39 (1.04–5.50); $p = 0.041$] but not with conservative management [OR = 0.97 (0.51–1.84); $p = 0.922$] or percutaneous coronary intervention [OR = 0.67 (0.36–1.25); $p = 0.208$]. **Conclusions:** This study of patients with UA or NSTEMI demon-

strated an independent association of elevated RDW with higher recourse to CABG. RDW should be considered in the stratification of patients presenting with UA or NSTEMI.

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Background

Red blood cell distribution width (RDW) is an objective measure of the heterogeneity in red blood cell (RBC) size (coefficient of variability of RBC volume) obtained from the RBC size distribution. Higher values reflect greater heterogeneity in cell sizes. It is automatically calculated by most hemocytometers by dividing the standard deviation of RBC volume by the mean corpuscular volume and multiplying by 100 to express the result as a percentage [1]. A cutoff value of 14% corresponds to the 95th percentile of RDW for the reference population in the Third National Health and Nutrition Examination Surveys (NHANES III) study; however, the normal range can vary based on the type of hemocytometer used [2, 3]. Routinely reported as part of the complete blood count, it is mainly used as an auxiliary index in the differential diagnosis of anemia.

Higher levels of RDW are associated with increased mortality among patients with heart failure, myocardial infarction, coronary artery disease (CAD) or undergoing angiography [4–11]. A high RDW is also associated with elevated cardiovascular biomarkers and cardiac enzymes [12]. The goal of this project was to assess the independent relation between RDW, an inexpensive, readily available measure and the therapeutic decision adopted in unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI) patients. The rationale for selecting this population lies in the difference of treatment algorithms between ST-elevation myocardial infarction (STEMI) that is driven by a time-sensitive emergent revascularization of a likely culprit lesion and UA/NSTEMI which, given the nature of the process at hand, can legitimately lead to any of the three therapeutic strategies [conservative medical management, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)]. The hypothesis of this study is that high RDW levels are associated with higher recourse to CABG in this patient population.

Methods

Study Population

This observational, cross-sectional study was conducted at Beth Israel Medical Center, a tertiary care center in New York City. It included all patients aged 18 years or older, admitted to the telemetry floors between January 1 and December 31, 2007, with a diagnosis of UA or NSTEMI who underwent a coronary angiography during that admission. As the target population consisted of patients presenting with UA or NSTEMI who by hospital policy are sent to monitored beds, the choice of admission to the telemetry floors as an inclusion criterion allowed us to avoid including patients who developed cardiac complaints or complications during their inpatient stay. All patients who needed critical unit level of care, presented with STEMI, admitted to nontelemetry floors or did not require (or did not undergo) coronary angiography were excluded.

Definitions

Patients in this study presented to the medical center with chief complaints of chest pain, shortness of breath or decreased exercise tolerance for which they were admitted to the telemetry floors and underwent coronary angiography regardless of the presence or absence of electrocardiogram changes. They were divided into 2 groups: UA if they did not have detectable cardiac biomarkers (troponin I <0.03 ng/ml) and NSTEMI if they had a troponin I level $\geq$ 0.03 ng/ml without electrocardiogram changes qualifying for STEMI. End-points were the treatment strategies: medical therapy, PCI or CABG. The revascularization strategy was decided at the discretion of the treating physician. RDW level on admission was considered 'high' if it was greater than the 95th percentile per the normal interval of the institu-

Fig. 1. Study sample selection flow diagram.

tion's laboratory (16.3%), and 'normal' if $\leq$ 16.3%. This grouping was based on the calibration and the reported normal range of the institution's laboratory which uses the COULTER® LH 750 Hematology Analyzer (Beckman Coulter Inc., Brea, Calif., USA).

Data Collection

Information on the subjects' demographics (age, gender and race), angiographic findings, clinical history (heart failure, CAD, hypertension, diabetes, dyslipidemia, smoking, family history of CAD, and previous CABG and stenting), laboratory measurements on admission [white blood cell count, hemoglobin, RDW, platelets, C-reactive protein (CRP), B-type natriuretic peptide (BNP) and creatinine], iron level, ferritin and total iron-binding capacity, maximal troponin I level (Tn Max), diagnosis (UA or NSTEMI) and outcomes (medical therapy, PCI or CABG) was collected by conducting a retrospective chart review of all patients admitted to the hospital from January 1, 2007, until December 31, 2007, using internal electronic databases.

Ethics

The study was approved by the Beth Israel Medical Center Institutional Review Board. The requirement for obtaining informed consent was waived.

Statistical Analysis

Data were analyzed using Stata version 11.2 (StataCorp, College Station, Tex., USA). Categorical data were analyzed using χ^2 or Fisher's exact tests. Continuous variables whose distribution followed the normality assumptions were analyzed using the Student t test and ANOVA. Variables whose distribution did not approximate normality were analyzed using the nonparametric Wilcoxon rank-sum and Kruskal-Wallis tests. Multivariable logistic regression analyses were used to determine the independent

Table 1. Characteristics of the study population overall and by each therapeutic strategy

Characteristics	Overall (n = 503)	Medical therapy (n = 270)	PCI (n = 180)	CABG (n = 53)	p
Demographics					
Age, years	65 ± 13	63 ± 14	68 ± 12	70 ± 12	<0.001
Male	280 (56%)	147 (54%)	101 (56%)	32 (60%)	0.721
Race					0.258
Caucasian	106 (21%)	52 (19%)	40 (22%)	14 (26%)	
Black	63 (13%)	33 (12%)	24 (13%)	6 (11%)	
Hispanic	178 (35%)	105 (39%)	55 (31%)	18 (34%)	
Asian	40 (8%)	27 (10%)	11 (6%)	2 (4%)	
Other	116 (23%)	53 (20%)	50 (28%)	13 (25%)	
Laboratory measurements					
WBC, × 1,000/μl	8 ± 3	8 ± 3	8 ± 2	9 ± 4	0.043
Hemoglobin, g/dl	13 ± 2	13 ± 2	13 ± 2	13 ± 2	0.763
High RDW	101 (20%)	58 (21%)	27 (15%)	16 (30%)	0.037
Platelets, × 1,000/μl	244 ± 87	253 ± 95	235 ± 66	235 ± 103	0.068
Tn Max, ng/ml	0.01 (0.00–0.12)	0.00 (0.00–0.06)	0.01 (0.00–0.42)	0.04 (0.00–0.45)	0.022
Creatinine, mg/dl	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.1 (0.9–1.3)	1.1 (1.0–1.8)	0.025
Anemia	224 (45%)	126 (47%)	75 (42%)	23 (43%)	0.570
Angiographic findings					<0.001
Normal or nonobstructive disease	167 (33%)	162 (60%)	5 (3%)	0 (0%)	
1-vessel disease	109 (22%)	41 (15%)	62 (34%)	6 (11%)	
2-vessel disease	89 (18%)	26 (10%)	52 (29%)	11 (21%)	
≥3-vessel disease	138 (27%)	41 (15%)	61 (34%)	36 (68%)	
Medical history					
Heart failure	173 (34%)	97 (36%)	52 (29%)	24 (45%)	0.064
CAD	287 (57%)	131 (49%)	128 (71%)	28 (53%)	<0.001
HTN	392 (78%)	203 (75%)	144 (80%)	45 (85%)	0.209
Diabetes	218 (43%)	106 (39%)	86 (48%)	26 (49%)	0.137
Dyslipidemia	228 (45%)	114 (42%)	94 (52%)	20 (38%)	0.057
Smoking	155 (31%)	80 (30%)	53 (29%)	22 (42%)	0.204
FHx	106 (21%)	44 (16%)	47 (26%)	15 (28%)	0.017
Prior interventions					
Previous CABG	72 (14%)	27 (10%)	43 (24%)	2 (4%)	<0.001
Previous PCI	139 (28%)	72 (27%)	57 (32%)	10 (19%)	0.163
Diagnosis					0.006
UA	406 (81%)	232 (86%)	134 (74%)	40 (75%)	
NSTEMI	97 (19%)	38 (14%)	46 (26%)	13 (25%)	

Continuous variables are reported as mean ± standard deviation if normally distributed or median (range) if not. Categorical variables are reported as frequency (percentage). p values <0.05 are in bold. WBC = White blood cell count; High RDW = red blood cell distribution width >16.3%; Tn Max = maximal troponin I; HTN = hypertension; FHx = family history of coronary artery disease.

associations of medical therapy alone, PCI and CABG, respectively. The multivariate models were adjusted for all the variables that were of statistical significance in the univariate and bivariate analyses for each of the endpoints of interest. Assessment for effect modifiers was performed and none were detected. Regression diagnostics and assessment of the fit of the models were conducted via the Hosmer-Lemeshow goodness of fit test which showed that they fit well. p values <0.05 were considered statistically significant.

Results

Among the 1,631 patients who underwent cardiac catheterization in 2007, 536 fulfilled the selection criteria. Thirty-three had incomplete or missing data and were excluded from the analysis (fig. 1). The baseline characteristics and the diagnoses of the remaining 503 subjects are listed in table 1. On average the study popula-

Table 2. Characteristics of the study population by RDW group (n = 503)

Characteristics	Normal RDW (n = 402)	High RDW (n = 101)	p
Demographics			
Age, years	65 ± 13	67 ± 14	0.091
Male	233 (58%)	47 (47%)	0.039
Race			0.772
Caucasian	89 (22%)	17 (17%)	
Black	48 (12%)	15 (15%)	
Hispanic	142 (35%)	36 (35%)	
Asian	31 (8%)	9 (9%)	
Other	92 (23%)	24 (24%)	
Laboratory measurements			
WBC, × 1,000/ μ l	8 ± 3	8 ± 4	0.548
Hemoglobin, g/dl	13 ± 2	11 ± 2	<0.001
Platelets, × 1,000/ μ l	240 ± 71	263 ± 131	0.017
Tn Max, ng/ml	0.01 (0.00–0.10)	0.02 (0.00–0.28)	0.053
Creatinine, mg/dl	1.0 (0.8–1.3)	1.2 (0.8–1.8)	0.002
Anemia	146 (36%)	78 (77%)	<0.001
Angiographic findings			0.066
Normal or nonobstructive disease	130 (32%)	37 (36%)	
1-vessel disease	97 (24%)	12 (12%)	
2-vessel disease	69 (17%)	20 (20%)	
≥3-vessel disease	106 (27%)	32 (32%)	
Medical history			
Heart failure	123 (31%)	50 (50%)	<0.001
CAD	237 (59%)	50 (50%)	0.086
HTN	314 (78%)	78 (77%)	0.849
Diabetes	172 (43%)	46 (46%)	0.617
Dyslipidemia	192 (48%)	36 (36%)	0.029
Smoking	129 (32%)	26 (26%)	0.217
FHx	94 (23%)	12 (12%)	0.011
Prior interventions			
Previous CABG	58 (14%)	14 (14%)	0.884
Previous PCI	113 (28%)	26 (26%)	0.634
Diagnosis			0.320
UA	328 (82%)	78 (77%)	
NSTEMI	74 (18%)	23 (23%)	
Treatment			0.037
Medical therapy only	212 (53%)	58 (57%)	
PCI	153 (38%)	27 (27%)	
CABG	37 (9%)	16 (16%)	

Continuous variables are reported as mean ± standard deviation if normally distributed or median (range) if not. Categorical variables are reported as frequency (percentage). p values <0.05 are in bold. WBC = White blood cell count; Tn Max = maximal troponin I; HTN = hypertension; FHx = family history of coronary artery disease.

tion was 65 years of age and had a high prevalence of comorbidities. Fifty-six percent (n = 280) were male, 28% (n = 139) had a prior stent placed and 14% (n = 72) had prior CABG. Baseline laboratory analysis showed normal white blood cell count ($8 \pm 3 \times 10^3/\mu\text{l}$), hemoglobin (13 ± 2 g/dl), RDW [14.3 (2.2) %] and platelet ($244 \pm 87 \times 10^3/\mu\text{l}$) levels. The study population showed racial diversity with relative (35%) Hispanic preponderance.

After the diagnostic coronary angiography, 270 patients (53%) were treated with medical therapy alone whereas the remaining 233 underwent either PCI (n = 180; 36%) or CABG (n = 53; 11%). Compared to the subjects undergoing medical therapy and PCI, respectively, patients requiring CABG were on average older (70 years vs. 63 and 68; $p < 0.001$), less likely to have prior CABG (4 vs. 10 and 24%; $p < 0.001$) and had a higher prevalence of elevated RDW (30 vs. 21 and 15%; $p = 0.037$). Patients with CABG had a more extensive atherosclerotic burden (in terms of number of diseased vessels by catheterization findings). A higher prevalence of heart failure was noted in the CABG group compared to the other two (45 vs. 36 and 29%, respectively) with borderline statistical significance ($p = 0.064$). High RDW ($>16.3\%$) was associated with anemia (77 vs. 36%; $p < 0.001$) and heart failure (50 vs. 31%; $p < 0.001$; table 2). The prevalence of a higher atherosclerotic burden was noted in the high RDW group compared to the normal one (32 and 20% vs. 27 and 17%, respectively) but it reached only borderline statistical significance ($p = 0.066$). Race did not show any statistically significant difference across the RDW or the outcome divides ($p = 0.772$ and $p = 0.258$, respectively).

In multivariable logistic regression analyses and after adjusting for age, gender, race, hemoglobin, atherosclerotic burden, heart failure, smoking, family history of coronary artery disease and previous CABG, a high RDW was not found to be statistically significantly associated with either conservative management (noninvasive, i.e. medical treatment only) versus recourse to any form of revascularization [PCI or CABG; OR = 0.97 (0.51–1.84); $p = 0.922$] nor with discrimination between PCI and non-PCI approaches [OR = 0.67 (0.36–1.25); $p = 0.208$]. It was, however, found to be independently associated with recourse to CABG versus nonsurgical strategy [OR = 2.39 (1.04–5.50); $p = 0.041$]. This finding was similar after excluding all patients who had undergone previous CABG (table 3). This association had a sensitivity of 30%, a specificity of 81% and a negative predictive value of 91%. Few patients had CRP, BNP, iron, ferritin, total iron-binding capacity and ejection fraction measurements performed for these variables to be properly tested in the regression analyses.

Table 3. Multivariable logistic regression models for high RDW

Outcome	OR (95% CI)	P
Medical Management		
Unadjusted	1.21 (0.78–1.88)	0.399
Adjusted ¹	0.97 (0.52–1.81)	0.916
Adjusted ²	0.97 (0.51–1.84)	0.922
PCI		
Unadjusted	0.59 (0.37–0.96)	0.035
Adjusted ¹	0.69 (0.38–1.25)	0.222
Adjusted ²	0.67 (0.36–1.25)	0.208
Adjusted ³	0.60 (0.34–1.06)	0.078
CABG		
Unadjusted	1.86 (0.99–3.49)	0.055
Adjusted ¹	2.33 (1.02–5.32)	0.044
Adjusted ²	2.39 (1.04–5.50)	0.041
Adjusted ⁴	2.43 (1.02–5.82)	0.045

p values <0.05 are in bold.

¹ Adjusted for age, gender, race, atherosclerotic burden, anemia, heart failure, smoking, family history of coronary artery disease and previous CABG.

² Adjusted for age, gender, race, hemoglobin, atherosclerotic burden, heart failure, smoking, family history of coronary artery disease and previous CABG.

³ Adjusted for age, gender, atherosclerotic burden, coronary artery disease, dyslipidemia, family history of coronary artery disease, previous CABG and diagnosis.

⁴ n = 431 after excluding patients with previous CABG. Adjusted for age, gender, race, hemoglobin, atherosclerotic burden, heart failure, smoking and family history of coronary artery disease.

Discussion

RDW reflects variability in the size of circulating red cells (anisocytosis) and is routinely reported by automated laboratory equipment for complete blood counts. Although its use had been limited to the narrowing of the differential diagnosis of anemia, mounting evidence suggests additional roles for this measurement. The present study demonstrated an independent association between high RDW on admission and recourse to CABG in patients presenting with UA or NSTEMI. We found this association to be independent of multiple potential confounding factors, such as anemia, heart failure, age, race and smoking. RDW did not demonstrate any statistically significant association with medical therapy alone or PCI. No deaths were reported in this study. The likely reason for this finding is the lower acuity of the selected patient population, which excluded STEMI and intensive care patients.

This study extends previous work on the role and impact of RDW. In an analysis of 15,852 adult participants in

NHANES III, Perlstein et al. [4] determined that higher RDW (with a median of 14.35 in the highest quintile) was associated with increased risk of all-cause mortality independently of CVD risk. Patel et al. [5] found similar results in a meta-analysis on older populations (aged 73.6–79.1 years). They noted a graded increased risk of death associated with higher RDW values. The RDW-mortality association occurred in all major demographic, disease and nutritional risk factor subgroups examined. Tonelli et al. [6] had similar conclusions regarding all-cause mortality but also with increased risk of coronary death/nonfatal myocardial infarction, new symptomatic heart failure and stroke. The relation of high RDW and greater CHD risk was also the main theme of the study conducted by Zala-wadiya et al. [7]. An RDW level greater than the seventy-fifth percentile in both anemic and nonanemic participants was a significant predictor of greater CHD risk. As for cardiovascular disease, a high RDW has been reported to be associated with worse prognosis in patients with heart failure, acute myocardial infarction and those referred for percutaneous coronary interventions [8–11]. The study by Lippi et al. [12] analyzed the RDW values on admission of patients presenting to the local emergency department for chest pain suggestive of acute coronary syndrome (ACS). They found that RDW levels were highly correlated with troponin T levels and an RDW greater than 14% had a clinical sensitivity and specificity for diagnosing ACS of 79 and 50%, respectively. When combined, troponin T and RDW levels had a diagnostic sensitivity of 99%. They concluded that RDW might be considered alongside other conventional cardiac markers for the risk stratification of ACS patients admitted to emergency departments.

Despite cumulative reports associating RDW and prognosis, the underlying biological mechanism for this relation remains unknown. Chronic subclinical inflammation is the most frequently hypothesized pathway as it is a well-established entity preceding de novo cardiovascular events and could adversely influence erythropoiesis by a variety of mechanisms, including direct myelosuppression of erythroid precursors, reducing renal erythropoietin production and the bioavailability of iron, increasing erythropoietin resistance in erythroid precursor cell lines, promoting cell apoptosis and RBC membrane deformability, factors that might increase anisocytosis [13]. It is less likely to be the case though as RDW was not found to be correlated with inflammatory markers such as CRP [14]. However, in patients with conditions characterized by increased levels of oxidative stress, such as Down syndrome, poor pulmonary function and dialysis, RDW values are elevated [15–17].

Decreased serum antioxidant levels, including carotenoids, selenium and vitamin E, were also associated with increased RDW [18]. An elevated RDW can also be a sign of 'reticuloendothelial block' or impaired iron metabolism that may directly contribute to disease progression [19]. It is conceivable that there are subclinical disease processes that cause a subtle dysregulation of erythrocyte homeostasis that is expressed in RDW.

Several limitations should be considered in the interpretation of the results. This study is a retrospective non-randomized analysis and has inherent limitations of a retrospective design. Data on medication, previous admissions, as well as factors required for disease burden scoring (whether as separate variables or as a score) was not present in the medical records collected and information on ejection fraction, iron profile, CRP and BNP was not consistent enough to allow for a proper analysis of these factors. This was a single-center study of UA and NSTEMI patients only, a potential hindrance to external validity. Since the study population was fairly diverse from clinical and racial perspectives this study should have reasonable generalizability within the target population. Baseline characteristics between the RDW and outcome groups were reasonably similar, but certain differences, especially high-RDW patients having, for example, a higher prevalence of anemia and heart failure, had to be adjusted for. Despite adjustment for multiple variables and assessment of potential confounding factors and effect modifiers, residual unrecognized confounding variables could influence the observed differences in outcomes between the groups. As with all analyses of observational data, this study cannot distinguish causality from association. However, the hypothesis that elevated RDW measurements is associated with higher recourse to CABG (based on a review of the available literature in this regard) had been formulated before performing analyses on the database. This approach reduced the risk of spurious conclusions. Nevertheless, RDW was assessed on a single occasion (admission) that might be influenced by biologic variability or measurement error, although such errors are likely to attenuate the observed association between RDW and outcome. The cutoff value for high RDW differed from that of larger studies such as NHANES III, but it was consistent with the laboratory's range. The actual angiograms were not reviewed to verify the reported findings, especially among those with no (or nonobstructive) CAD. There was no standardized evaluation of atherosclerotic burden such as the SYNTAX score [20] as the required data was not available in the medical records at hand. The revascularization strategy (especially CABG) was at the

discretion of the treating physician and depended on the patients' consent. The treating physician was also aware of the actual RDW value, introducing a potential bias to the results. However, in view of the retrospective nature of this investigation it is less likely to be the case. We also could not account for patients who were considered high risk for surgery as we did not have reliable means to assess nonatherosclerotic disease burden. These factors were a likely source of bias and may be the reason behind this relatively low frequency of CABG (11%) for a tertiary care center. However, findings such as the marked prevalence of higher atherosclerotic burden and of heart failure in subjects undergoing CABG are consistent with the current recommendations [21] and therefore indicate a trend towards adherence to the established guidelines rather than personal or group practice behavior. Finally, this study does not provide a mechanism for the association between RDW and the observed outcome, but to date no biological pathway for RDW's role has been clearly established.

In conclusion this study has demonstrated an independent association of elevated RDW with recourse to CABG. These findings are concordant with, and extend, previous reports about the potential roles of RDW in patients with cardiovascular disease. Despite its low sensitivity but considering its high negative predictive value, its availability to clinicians as part of the complete blood count and lack of additional costs, RDW should be considered as a potential additional tool for stratification of patients presenting to emergency departments with UA or NSTEMI. A potential benefit from such early classification may be the successful avoidance of thienopyridine loading in patients who are more likely to be CABG candidates as this may incur a 5- to 7-day delay in surgery. In view of the retrospective, observational and chart abstraction design of this investigation further prospective studies are recommended to confirm the association between RDW and clinical outcomes and explain its underlying mechanism.

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