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Red cell distribution width, C-reactive protein, the complete blood count, and mortality in patients with coronary disease and a normal comparison population ☆

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ABSTRACT

Background: Red cell distribution width (RDW) is associated with morbidity and mortality in coronary artery disease (CAD), but the connection of RDW with chronic inflammation is equivocal.
Methods: In 1,489 patients with CAD and 8.4–15.2 years of follow-up all-cause mortality and RDW were studied using Cox regression. RDW and its associations with inflammation, liver function, renal function, and body mass were assessed. A population of 449 normal (No-CAD) patients also was evaluated.
Results: RDW predicted all-cause mortality in a step-wise manner (HR = 1.37 per quintile; 95% CI = 1.29, 1.46; p-trend < 0.001). A significant but meaningless correlation between RDW and high-sensitivity C-reactive protein (hsCRP) was identified ($r = 0.181$; $p < 0.001$). With full adjustment, RDW remained significant (p-trend < 0.001) and the strongest predictor of mortality among all factors included in the model. RDW also strongly predicted all-cause mortality in the normal control population (HR = 1.33 per quintile, CI = 1.15, 1.55; p-trend < 0.001), but hsCRP did not predict mortality among normal controls.
Conclusions: RDW was associated with mortality in patients with CAD and may provide clinically useful prognostication. Although RDW was correlated with hsCRP, they were independent predictors of mortality. RDW has been incorporated into risk prediction tool using data from basic chemistries available at: http://intermountainhealthcare.org/IMRS.

1. Introduction

The red cell distribution width (RDW) is a readily-available measure of the degree of variation in erythrocyte volume. It is a component of the complete blood count (CBC) and is calculated as a percentage of the standard deviation of the red cell volume divided by the mean corpuscular volume (MCV). Traditionally RDW has been used to differentiate types of anemia; specifically identifying iron-deficiency anemia. However, prior work showed that RDW predicts mortality in patients with coronary artery disease (CAD) [1]. Subsequently it was shown that, independent of hemoglobin or hematocrit, an elevated RDW was associated with increased mortality risk in acute heart failure (HF) patients [2] and in a small population with chronic HF [3]. One study found an elevated RDW to have a stronger association with morbidity and mortality in HF patients than all studied predictors other than age [4]. The RDW associations of Anderson et al. [1] were subsequently confirmed and extended among CAD patients [5] and general medical patients and a general population from NHANES III [6]. Additionally, RDW is associated with elevated troponin levels in patients with acute coronary syndromes and with worse outcomes in patients undergoing percutaneous coronary intervention [7,8]. RDW also predicts left ventricular ejection fraction (LVEF), HF diagnosis, and readmission for HF among CAD patients, and incident HF among HF-free general cardiovascular patients [9].

Despite these associations, the mechanisms underlying elevated RDW remain unknown. The notion that chronic inflammation may cause RDW elevation is supported by a study of unselected patients in which RDW was correlated with both the erythrocyte sedimentation rate and C-reactive protein (CRP) [10]. In contrast, preliminary evidence from a very small population (N = 226) suggests that this

☆ Clinical trial registration: database registry of the Intermountain Heart Collaborative Study: NCT00406185 (ClinicalTrials.gov).

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relationship may not exist in cardiovascular disease [11], but mortality outcomes were not studied therein. Another very small study (N = 195) that focused only on chronic HF patients indicated that RDW and CRP independently predict mortality [3]. The relationships between RDW, CRP, and mortality have not been evaluated in a large, general CAD patient population or among individuals free from HF and CAD.

2. Materials and methods

2.1. Study population

Patients enrolled in the catheterization laboratory registry of the Intermountain Heart Collaborative Study between October, 1993 and August, 2000 were included if they had a baseline CBC, high-sensitivity (hs) CRP, and angiographically-documented CAD (N = 1,489). This study was approved by the Intermountain Healthcare Institutional Review Board.

Coronary angiography was performed for clinical purposes and CAD prospectively assessed as normal (0% to <10% stenosis), mild/moderate (10% to <70% stenosis), or severe (≥70% stenosis). The extent of CAD was categorized as severe 1-, 2-, or 3-vessel disease. Patients were followed for until death or December, 2008. Deaths were determined by telephone survey, hospital records, and death certificates and were verified through US Social Security death records. Patients not listed as deceased were considered to be alive. All-cause mortality was designated as the primary endpoint.

An additional subgroup of patients within the Intermountain Heart Collaborative Study registry was studied in secondary analyses. These patients had structurally normal coronary arteries, were free of clinical HF diagnosis, and had normal systolic function (LVEF>40%, N = 449). They were evaluated for comparison of whether the RDW association with mortality was disease-specific and were not included in the primary analyses.

2.2. Laboratory testing

CBC testing was performed for clinical purposes during the baseline hospitalization (Coulter Gen·S Hematology Analyzer, Beckman Coulter Corp., Hialeah, FL). CBC metrics included: hematocrit, hemoglobin, RDW (normal range: 11.3%–15.6%), MCV, red blood cell count (RBC), platelet count, mean platelet volume (MPV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and total white blood cell (WBC) count. For all multivariable analyses using all CBC components, the hemoglobin, RBC, and MCH variables were excluded as redundant due to multicollinearity. The testing of hsCRP used a particle-enhanced immunoturbidimetric assay (Tina-Quant, Roche, Indianapolis, IN). RDW thresholds were: <12.5%, 12.5–12.8%, 12.9–13.3%, 13.4–14.2%, and >14.2% for quintiles 1–5, respectively. The thresholds for hsCRP quintiles were: <0.85, 0.85–1.79, 1.80–3.49, 3.50–8.80, and >8.80 mg/l for quintiles 1–5, respectively. Other CBC components' quintile thresholds are available in previous work [6].

2.3. Statistical analysis

Independent variables included age, gender, diabetes, hypertension, dyslipidemia, smoking, family history of early CAD, and other risk factors. Diabetes was defined as a fasting blood sugar >125 mg/dl or use of antidiabetic medication. Hypertension was reported if the systolic blood pressure was ≥140 mm Hg, the diastolic blood pressure ≥90 mm Hg, or for use of antihypertensive drugs. Hyperlipidemia was defined as a total cholesterol level ≥200 mg/dl, a low-density lipoprotein level ≥130 mg/dl, or use of cholesterol-lowering medication. Family history was self-reported when a first-degree relative had cardiovascular death, myocardial infarction, or coronary revascularization at ≤65 years. Smoking included active or previous (>10 pack-years) tobacco use.

Body mass index (BMI) was measured at the time of angiography. Renal insufficiency (RI) was physician-reported and defined as a creatinine >2.0 mg/dl or prior clinical RI diagnosis. Estimated glomerular filtration rate (GFR) used the MDRD formula. LVEF was determined by ventriculography performed at the time of angiography or by echocardiography performed around the time of enrollment and HF was defined as LVEF≤40% or normal LVEF with clinical diagnosis. Additional variables included history of myocardial infarction (MI) and stroke history – both defined by ICD-9 codes from the electronic medical records, the patient's presentation at the index admission (stable angina, unstable angina, acute MI), the number of severely diseased coronary arteries (1, 2, or 3 for patients with CAD), the type of baseline intervention (medical only, percutaneous revascularization, or bypass surgery), and discharge medications (statin, beta-blocker, angiotensin-converting enzyme inhibitor, diuretic).

The primary analysis of RDW association with mortality used Cox regression, with multivariable analyses adjusting for hsCRP and adding other independent variables for subsequent models. Since the association of RDW with mortality was first reported as a component of the CBC risk score [1], modeling added the other CBC risk score variables.

Secondary analyses explored hypotheses regarding the mechanisms underlying RDW elevation and the association with mortality. Comparisons were made of RDW to surrogates for liver function, renal function, and nutrition, including for albumin, creatinine, blood urea nitrogen (BUN), and a low or high BMI (i.e., <20 and >30 kg/m^2, respectively).

For baseline characteristics, variables are summarized as means ± standard deviations for continuous variables (median with standard error for non-normally distributed variables) and percentages for discrete variables. Intergroup comparisons between RDW quintiles used analysis of variance or the chi-square test. RDW, hsCRP, and other CBC variables were divided into quintiles prior to analysis, with trend statistics utilized as the primary analytical strategy. The secondary strategy comprised comparisons of each quintile to the first quintile as referent. Correlations among RDW, hsCRP, and other biomarkers were calculated using Pearson's correlation coefficient with non-normally-distributed variables (i.e., hsCRP, creatinine, BUN, and WBC) being transformed first using the natural logarithm. A P≤0.05 was accepted as statistically significant. All statistical calculations were made using SPSS v15.0 (SPSS, Chicago, IL).

3. Results

Baseline characteristics for CAD patients are provided in Table 1, stratified by median RDW of 13.0%. Patients with an elevated RDW were slightly older on average and more likely to have hypertension, diabetes, a prior cardiovascular event, and worse renal function. As has been reported previously, patients with an impaired LVEF had a higher RDW. Corresponding with the higher burden of comorbidities, patients with an elevated RDW were more often medically managed for their CAD then patients with a lower RDW. Finally, patients with an elevated RDW were more likely to be discharged on a statin, beta-blocker, and a diuretic.

Average RDW was 13.2 ± 1.3% and ranged from 11.2% to 24.2%. A steady but small rise in RDW level was observed according to hsCRP level, with mean RDW of 13.0 ± 0.9%, 13.2 ± 1.2%, 13.3 ± 1.3%, 13.4 ± 1.2%, and 13.7 ± 1.6% for hsCRP quintiles 1, 2, 3, 4, and 5, respectively (p-trend<0.001). Although this minor effect was statistically significant, RDW did not have a meaningful correlation with hsCRP (r = 0.181). Mean RDW among patients who died was 13.6 ± 1.6% compared to 13.1 ± 1.1% among those who survived (p<0.001), while