Gender Differences in the Association of Red Cell Distribution Width and Coronary Artery Disease

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Abstract

Objective: Red cell distribution width (RDW) is independently associated with morbidity and mortality in cardiovascular diseases. The aim of the present study was to explore the gender difference of RDW in patients with coronary artery disease (CAD).

Methods: A total of 674 consecutively hospitalized individuals who received coronary angiography (CAG) were enrolled and divided into two groups: a CAD group (n = 499) and a control group (n = 175). Their baseline clinical characteristics were collected, and the gender differences of RDW in predicting the presence of CAD were assessed.

Results: RDW in female patients with CAD was significantly higher than in those without CAD. In contrast, no significant difference in RDW between male individuals with and without CAD was found. Multivariate logistic regression analysis showed that age and RDW were independent predictors for CAD in females. Receiver operating characteristic (ROC) curve analysis indicated that a RDW value of 12.75% was an effective cut-off point in the segregation of the presence or absence of CAD with a sensitivity of 57.1% and a specificity of 66.3%.

Conclusion: The present study shows a significant association between RDW levels and female CAD across gender strata, suggesting that elevated RDW may be an independent predictor of CAD in women.

Keywords: Red blood cell distribution width, coronary heart disease, gender difference, risk factors

Introduction

Red blood cell distribution width (RDW) is an objective measure of the heterogeneity in red blood cell size (coefficient of variability of red blood cell volume) obtained from red blood cell size distribution curves and is routinely reported as part of a standard complete blood count used in the diagnosis or differential diagnosis of anemia. Recently, RDW has emerged as a predictor of morbidity and mortality in a variety of cardiovascular issues, including heart failure (1, 2), stable coronary artery disease (CAD) (3), and acute myocardial infarction (4). However, few studies have addressed the possible association between gender difference and RDW in predicting CAD.

The purpose of the present study was, therefore, to evaluate the potential role of RDW in predicting the presence of CAD in both male and female patients with angiography-proven CAD in a consecutive Chinese cohort from a single center.

Methods

Study population

This was an observational study derived from a cohort of patients in our division of the Fu Wai Hospital who were prospectively entered into a database to assess the prognostic significance of various plasma biomarkers in patients with known or suspected coronary artery disease. The study population included 674 consecutive non-anemic patients who were referred to elective coronary angiography due to angina-like chest pain between May 2011 and April 2012. The study protocol was reviewed and approved by the Ethics Committee of Fu Wai Hospital and Cardiovascular Institute, Beijing, China, and informed consent was obtained from all patients.

All patients then received coronary
Table 1. Baseline characteristics of the study population across genders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=441)</th>
<th>Women (n=233)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.7 ± 9.8</td>
<td>60.9 ± 9.4</td>
<td>0.000</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 3.1</td>
<td>25.3 ± 3.4</td>
<td>0.445</td>
</tr>
<tr>
<td>Smoking history [n, (%)]</td>
<td>329 (74.6)</td>
<td>18 (7.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>Family history of CAD [n, (%)]</td>
<td>228 (51.7)</td>
<td>96 (41.2)</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes [n, (%)]</td>
<td>149 (33.8)</td>
<td>70 (30.0)</td>
<td>0.342</td>
</tr>
<tr>
<td>Hypertension [n, (%)]</td>
<td>292 (66.2)</td>
<td>167 (71.7)</td>
<td>0.165</td>
</tr>
<tr>
<td>Dyslipidemia [n, (%)]</td>
<td>320 (72.6)</td>
<td>171 (73.4)</td>
<td>0.840</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>146.1 ± 11.6</td>
<td>128.7 ± 10.1</td>
<td>0.000</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>13.0 ± 0.8</td>
<td>12.8 ± 0.7</td>
<td>0.106</td>
</tr>
</tbody>
</table>

Data shown as mean ± standard deviation and percentage (%).

BMI: Body mass index; CAD: coronary artery disease; RDW: Red cell distribution width.

Angiographic Examination

The selective coronary angiography for all enrolled individuals was performed using the standard Judkin’s techniques, and the results were analyzed by at least two interventional physicians according to our previous study (5).

Statistical Analysis

Statistical analyses were carried out using SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA) software. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. Comparison of continuous variables between the two groups was performed using a Student’s t-test and/or Mann-Whitney U test. Receiver operating characteristic curves for RDW values were plotted to determine the optimal cutoff values for individual parameters in order to predict angiographic CHD and establish the optimal cutoff points for usefulness in clinical decision-making. Multivariate logistic regression analysis was used to identify the independent predictors of angiographic CHD. All variables showing significance values of less than 0.1 in an univariate analysis were included in the model. In a receiver operating characteristic (ROC) curve analysis, an RDW value of 12.75% was identified as an effective cut-off point in determining the presence or absence of CAD. A p value < 0.05 was considered statistically significant.

Results

Comparison of baseline characteristics in total population

Table 1 presented the distribution of overall baseline characteristics across gender strata. There were significant differences in traditional risk factors of CAD between the stratified groups, including age, smoking history, family history, and levels of hemoglobin (p < 0.05). The hemoglobin concentration was lower in women than in men. In addition, the women were older, smoked less, and less family history of CAD compared with men. However, the levels of RDW were similar in both groups (p > 0.05), indicating that sex itself has little effect on the variation of RDW (Table 1, Figure 1a).

Difference of RDW in male and female patients with CAD
Table 2 listed the baseline data of the CAD group and control group across gender strata. As shown in Table 2, there were significant differences regarding the traditional risk factors of CAD between the CAD and control groups in both men and women, such as age and the incidence of diabetes, hypertension, and dyslipidemia \((p < 0.05)\). Although there was no difference in RDW levels between men and women in both patients with CAD and controls the levels of RDW were higher in female patients with CAD than in women in the control group \((12.9 \pm 0.7 \text{ vs. } 12.6 \pm 0.6, p = 0.001)\). In contrast, the levels of RDW were similar between male patients with CAD and male controls \((13.0 \pm 0.8 \text{ vs. } 12.8 \pm 1.0, p = 0.144, \text{ Table 2, Figure 1b})\).

**Univariate and multivariate analysis**

In the present study, univariate logistic regression analysis indicated that age, diabetes, hypertension, dyslipidemia, family history, and RDW were risk factors for predicting CAD in females. We put those six variables into the multivariate logistic regression analysis and found that age and RDW were independent predictors in female patients with CAD \((\text{OR} = 1.07, 95\% \text{ CI: } 1.03 \sim 1.10, p < 0.001; \text{ OR} = 2.03, 95\% \text{ CI: } 1.28 \sim 3.23, p < 0.01, \text{ Table 3})\).

**ROC curve analysis**

In a ROC curve analysis with area under curve \((\text{AUC}) = 0.63, 95\% \text{ CI: } 0.56 \sim 0.70\) in female patients, we found that an RDW value of 12.75% was an effective cut-off point in determining the presence or absence of CAD, and a sensitivity of 57.1% and a specificity of 66.3% were obtained (Figure 2), suggesting that independently, the prognostic ability of RDW was mild to modest.

**Discussion**

It has been recognized that the incidence of CAD is strongly associated with gender difference—that is, the male is predominant. Several studies indicate that RDW is a reliable marker for the development, severity, and clinical outcomes of CAD. Because there is usually a sex difference in the available clinical markers for predicting CAD, we decided to evaluate the sex difference in the role of RDW in predicting CAD. The main findings of the present study are: (1) that RDW values were significantly higher in female CAD patients compared to the female controls, while no such changes were found in male individuals; (2) that RDW was an independent risk factor for female patients with CAD.
as analyzed by a multivariate logistic regression evaluation; and (3) that the RDW boundary value was 12.75% by AUC examination and could predict female CHD with a sensitivity of 57.1% and a specificity of 66.3%. Although the independent prognostic ability of RDW was rather mild to modest, our findings might provide additional information regarding the relation of RDW to CAD.

In fact, numerous studies have suggested a marked gender difference in the clinical characteristics of CAD (6, 7). For example, women typically develop CAD approximately ten years later than men—typically after menopause (8). Female patients with CAD had a higher mortality rate and poorer prognosis than male patients. Women are less likely to be referred for coronary angiography and revascularization procedures than men, and referral tends to occur at a later stage in the disease process (9, 10). Recently, Kim et al. investigated whether multiple biomarkers contribute to improved CAD risk prediction in post-menopausal women compared to assessment using traditional risk factors, and they found a modest improvement in CAD risk prediction when 18 biomarkers (which reflect inflammation, endothelial function, fibrin formation and fibrinolysis, oxidative stress, renal function, ventricular function, and even myocardial cell damage) were evaluated individually and in multi-marker predictive models along with traditional cardiovascular risk factors (11). Therefore, the determination of novel biomarkers for predicting CAD in women may be of great interest clinically.

In recent years, RDW was found to be a marker indicating the presence and prognosis in a variety of cardiovascular diseases. However, limited information is available about gender differences in RDW in patients with CAD. A newly published study investigated the gender and ethnic differences in RDW and its association with mortality among low-risk, healthy adults in the United States (12). They found that African Americans and men had significantly higher RDW compared to Caucasians and women. A higher RDW was associated with a greater risk of mortality in men than in women, but no effect modification was observed by ethnicity. However, the population in their study was from the Third National Health and Nutritional Examination Survey (1988 to 1994) data, and individuals were healthy, low-risk American adults ≥20 years old who were free of cardiovascular disease and diabetes. In a prospective study of 162 consecutive patients with pulmonary hypertension (PH), RDW was recorded and followed for 2.1 ± 0.8 years to determine vital status (13). Of the 162 study patients, 78% were women. They found that RDW was independently associated with death in patients with PH. Another study performed by Lippi G. et al. assessed whether RDW was associated with decreased kidney function for 8,585 adult outpatients over a three-year period. They found that in a logistic regression analysis, a lower estimated Glomerular filtration rate (GFR) strongly predicted higher RDW levels (p < 0.0001) independent of age, gender, MCV, and hemoglobin values (14).

A study performed by Fukuta et al. hypothesized that higher RDW might reflect neurohumoral activation and a chronic inflammatory state that each contribute to adverse clinical outcomes in patients with CAD (15). They measured RDW and plasma levels of B-type natriuretic peptide (BNP) and hs-CRP in 226 consecutive patients undergoing cardiac catheterization for CAD. They found that plasma BNP (r = 0.21, p < 0.01) but not hs-CRP (r = 0.04, p > 0.01) levels correlated with RDW. After adjustment for potential confounders including age, gender, body mass index,
GFR, hemoglobin, and known hemodynamic determinants of BNP (including elevated left ventricular end-diastolic pressure and volume and slow left ventricular relaxation), RDW was independently predicted by BNP ($r (2) = 0.058$, $p < 0.001$). They concluded that elevated BNP levels are independently associated with higher RDW in patients with CAD. Neurohumoral activation may be a mechanistic link between increased RDW and adverse clinical outcomes in this population. In the present study, we further demonstrated that RDW in female patients with CAD was significantly higher than in those without CAD ($p = 0.001$). In contrast, RDW in males with CAD had no statistical significance compared to those without CAD ($p = 0.144$). In a multivariate logistic regression analysis, RDW was found to be an independent predictor of angiography-proven CAD in females (OR = 2.03, 95% CI: 1.28 ~ 3.23, $p < 0.01$). In a receiver operating characteristic (ROC) curve analysis, an RDW value of 12.75% was identified as an effective cut-off point to ascertain the presence or absence of CAD with a sensitivity of 57.1% and a specificity of 66.3%, suggesting that the independent prognostic ability of RDW was, at most, modest. Therefore, our study confirmed and provided additional information regarding the role of RDW in cardiovascular diseases. Gender difference may be a factor that could affect the levels of RDW in CAD patients.

The mechanisms explaining the gender differences associating RDW with CAD remain largely unknown. Previous studies hypothesized that inflammation might be one of the most likely causes of this unclear association. In fact, the association between increased RDW and active inflammatory bowel disease (IBD) was evident in IBD patients with and without anemia (15). RDW levels were also significantly increased in patients with Alzheimer’s-an inflammation-related disease (16). In addition, a strong association between RDW and inflammatory markers was found in a large cohort of unselected adult outpatients (17). Additionally, it has been hypothesized that inflammatory cytokines inhibit the maturation of red blood cells, and immature erythrocytes infiltrate blood circulation, which increases cell size heterogeneity, resulting in an elevated RDW in low-grade, chronic inflammatory status (1, 18). Indeed, it has widely been accepted that atherosclerosis is an inflammatory disease (19). Interestingly, women with CAD showed more serious inflammation. For example, plasma hs-CRP levels in women with CAD were higher than in men (20). Lippi G. et al. reported that RDW was strongly associated with plasma markers of inflammation, including CRP and the erythrocyte sedimentation rate (ESR) for cardiovascular risk prediction (21). Theoretically, chronic subclinical inflammation is a well-established entity preceding de novo cardiovascular events and could adversely influence erythropoiesis through 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 cells, and promoting cell apoptosis (22, 23). Thus, inflammation could lead to anisocytosis as a result of the release of immature red blood cells into peripheral circulation. In accordance with those findings, greater RDW values have been independently associated with greater CRP levels-a well-established surrogate marker of inflammation-as well as numerous other inflammatory markers such as interleukin-6 and soluble tumor necrosis factor receptors 1 and 2 (1, 21). Therefore, we speculated that inflammation was a primary influence on the gender difference in RDW between women with CAD and men. We also measured high-sensitivity hs-CRP in this cohort of patients; while no gender difference was found (hs-CRP: 1.52 vs. 1.58, $p > 0.05$), the CRP level was higher in females than in male patients with CAD, which may be due to the limited sample size. Therefore, the exact mechanisms-including the inflammatory hypothesis explaining gender differences associated RDW with CAD-need further investigation.

There were several limitations in the present study. First, the cardiovascular events were not analyzed due to a cross-sectional feature of the study. Second, relying on data from a single center may also limit the study. Moreover, other factors such as iron, vitamin B12, and folate were not measured in this study. Finally, although we demonstrated significant gender differences associated with elevated RDW in women with CAD, we could not determine the exact mechanism of this association. Further investigation is needed.

In conclusion, in the present study, the data demonstrated that RDW was associated with CAD across gender strata, and high RDW was an independent predictor of CHD in women. Although the independent prognostic ability of RDW was rather mild to modest, our findings might provide additional information regarding the relation of RDW to CAD.

Conflict of interest

All authors declare that there is no conflict of interest.

References


