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Original article

Impact of red blood cell distribution width on non-cardiac mortality in patients with acute decompensated heart failure with preserved ejection fraction

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ABSTRACT

Background: The prognostic impact of red blood cell distribution width (RDW) on adverse outcomes in patients with heart failure with preserved ejection fraction (HFpEF) is unclear. We investigated the association between RDW values at admission and long-term prognosis in patients with acute decompensated HFpEF.

Methods: The present study enrolled 278 consecutive patients with acute decompensated HFpEF, whose RDW levels were measured at admission. We divided enrolled patients into 2 groups according to RDW value and investigated the association between RDW and patients' mortality.

Results: A Kaplan–Meier analysis demonstrated that patients with higher RDW levels had significantly higher all-cause and non-cardiac mortality, but not cardiac-based mortality, than did patients with lower RDW levels. A multivariate Cox regression analysis revealed that RDW levels were independently correlated with all-cause and non-cardiac mortality after adjusting for other risk factors, including age, brain natriuretic peptide, hemoglobin, and Charlson comorbidity index score. In a receiver-operating curve analysis, the cut-off value to maximize the prognostic impact of RDW on mortality was 15.2%. The evaluation of RDW and other prognostic factors improved their predictive value for both all-cause and non-cardiac mortality.

Conclusions: The current study demonstrated that RDW levels at admission independently predict poor outcomes because of non-cardiac events in patients with acute decompensated HFpEF. Evaluation of RDW could provide useful information for the long-term prognosis of HFpEF.

Introduction

Heart failure is a prevalent disorder that leads to high mortality and morbidity worldwide [1,2]. In particular, heart failure with preserved ejection fraction (HFpEF) is rapidly becoming widespread in industrialized countries with an aging population [3]. Approximately half of the people with heart failure have HFpEF, which has a similar prognosis to that of heart failure with reduced ejection fraction (HFrEF) [4,5]. However, the pathophysiology and patient characteristics of HFpEF are different from those of HFrEF [6,7]. Therefore, it is clinically valuable to stratify the risk for prognosis separately in these types of heart failure.

Red blood cell distribution width (RDW) is automatically measured in a complete blood count. RDW represents a variability of sizes of circulating erythrocytes and is combined with the mean corpuscular volume for the differential diagnosis of microcytosis such as thalassemia, iron deficiency, and chronic disease-related anemia [8,9]. Recently, RDW has been extensively investigated as a significant predictor of clinical outcomes for various disorders, such as acute coronary syndrome, malignancy, and infectious diseases [10–12].

Recent studies have reported that RDW levels are associated with adverse outcomes in patients with heart failure in various

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clinical settings [13–16]. However, the prognostic impact of RDW in patients with HFpEF has not been fully elucidated. In the present study, we investigated the association between RDW levels and long-term prognosis in patients with acute decompensated HFpEF.

Methods

Study population

We assessed consecutive HFpEF patients who were admitted to Anjo Kosei Hospital between April 2010 and March 2013. We excluded patients who were on hemodialysis. Informed consent was obtained from each patient, and the study was approved by the hospital's ethics committee.

All patients were diagnosed with heart failure based on the Framingham criteria [17]. Preserved ejection fraction was defined as left ventricular ejection fraction (LVEF) $\geq$ 50%. Hypertension was defined as a systolic blood pressure (BP) of $\geq$ 140 mmHg or a diastolic BP of $\geq$ 90 mmHg after repeated measurements, or patients who received antihypertensive treatment. Diabetes mellitus was diagnosed according to the World Health Organization's criteria [18]. Dyslipidemia was defined as a total cholesterol level of $\geq$220 mg/dL, triglyceride levels of $\geq$150 mg/dL, high-density lipoprotein cholesterol levels $<$ 40 mg/dL, or patients who received lipid-lowering therapy.

At the time of admission, information on any previous diagnosis of chronic illness was obtained from the patients, and the Charlson comorbidity index score was calculated to evaluate the severity of co-morbidities [19].

Biomarker analysis

Blood samples were obtained at the time of hospital admission. Complete blood counts were performed utilizing a Sysmex XE-5000 analyzer (Sysmex, Kobe, Japan). The normal range of RDW in this system is 11.5–14.5%. Plasma B-type natriuretic peptide (BNP) was measured with the AIA-2000 enzymatic immunoassay analyzer (TOSOH, Tokyo, Japan). Other biomarkers were measured using a LABOSPECT 008 autoanalyzer (Hitachi Co., Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the Japanese equation that is based on serum creatinine level, age, and sex [20].

Echocardiography

An experienced sonographer performed an echocardiographic examination using Vivid E9 with XD clear (GE Healthcare, Tokyo, Japan). The images were recorded in a console and analyzed offline. LVEF was calculated using a modified Simpson's rule [21].

Follow-up and assessment of clinical outcomes

All patients regularly visited the hospital (typically once every month), and they were followed for up to 3 years. Cardiologists at the Anjo Kosei Hospital determined the causes of death. Cardiac-based death was defined as heart failure, myocardial infarction, or sudden death clinically suspected of coronary heart disease due to the situation and examination of the patient. Non-cardiac death included non-cardiovascular causes of death such as stroke, infection, cancer, and gastrointestinal diseases.

Statistical analysis

All analyses were performed using PASW Statistics 18 software (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as means $\pm$ standard deviation or medians with interquartile range (IQR), as appropriate. Categorical variables are presented as counts and/or percentages. Univariate correlations between RDW at admission and other variables were investigated using the Spearman's rank correlation test. We then developed the multivariate linear regression analysis incorporating the factors with p-value less than 0.05. The mortality rate was determined by a Kaplan–Meier analysis with the log-rank test. Cox proportional hazard models were applied to determine independent predictors of mortality. Hazard ratios with 95% confidence intervals were determined. Variables with $p < 0.05$ in the univariate analysis were entered into multivariate model. Receiver operator characteristic curve analyses were performed to identify the potential cut-off value of RDW for predicting the incidence of all-cause death and non-cardiac death. To assess the incremental value of RDW on mortality, we calculated the continuous net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). In all analyses, $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 278 patients with acute decompensated HFpEF were enrolled in this study. Table 1 shows their baseline characteristics. The median (IQR) value was 14.7% (range, 13.8–15.9%). Patients were divided into two groups according to RDW levels: the low RDW group ($<$14.7%, n = 134) and the high RDW group ($\geq$14.7%, n = 144). In the high RDW group, the patients were older and more of them had history of heart failure. Furthermore, the hemoglobin levels were lower and the levels of C-reactive protein (CRP) and BNP were higher in the high RDW group than those in the low RDW group. Incidences of cerebrovascular disease (except hemiplegia) and connective disease were significantly different between the 2 groups. However, Charlson comorbidity index score was comparable (Table 1 and Supplementary Table 1). Age, hemoglobin, CRP, albumin, BNP, and Charlson index score were found to be correlated with RDW at admission in the univariate analysis, and only hemoglobin was found to be significant in the multivariate analysis (Table 2).

Correlation between RDW levels and clinical outcomes

We examined the association between RDW levels and mortality. In this study, 17 patients were lost to follow-up. During the 3-year observation period, 88 (31.7%) patients died. The Kaplan–Meier survival analysis demonstrated that patients in the high RDW group had significantly higher all-cause mortality compared with those in the low RDW group (log-rank $p < 0.001$) (Fig. 1). To determine the clinical parameters that were associated with all-cause mortality in patients with acute decompensated HFpEF, we performed Cox regression analyses. The multivariate Cox regression analysis revealed that RDW, age, BNP, and Charlson comorbidity index score were independent predictors of all-cause mortality (Table 3).

Of the 88 all-cause deaths, the causes of death included cardiac-based and non-cardiac deaths in 47 (53.4%) and 41 (46.7%) patients, respectively. The non-cardiovascular causes of death include 12 patients with cancer, 10 with stroke, 9 with infection, 4 who died of old age, and 6 with other causes of death. Kaplan–Meier analyses revealed that non-cardiac mortality, but not cardiac-based mortality, was significantly higher in the high RDW group than in the low RDW group (log-rank $p = 0.004$) (Fig. 2A and B). In the univariate and multivariate Cox regression analyses, RDW was found to be a significant independent predictor of non-cardiac mortality, but not cardiac mortality (Table 4 and Supplementary Table 2).

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