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Original Article

Association between red cell distribution width and thromboembolic events in patients with atrial fibrillation

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ABSTRACT

Background: We investigated whether an increase in the value of red cell distribution width (RDW) was associated with thromboembolic outcomes in patients with atrial fibrillation (AF).
Methods: We performed a retrospective analysis of 5082 consecutive patients with non-valvular AF. Thromboembolic events ($N = 723$, 14.2%) were recorded and analysed according to RDW value.
Results: The peak RDW value during follow-up was higher in patients with thromboembolic events than in those without thromboembolic events (15.1% vs. 14.2%, $p < 0.001$). The RDW value showed similar power in predicting thromboembolic outcomes compared with the factor of age. The risk of thromboembolic events was higher in patients with a peak RDW ≥ 13.9% than in patients with a peak RDW < 13.9% (hazard ratio 1.63, $p < 0.001$), and increased with each quartile increase of RDW. In a subgroup of 739 patients with congestive heart failure (CHF), there were 112 (15.2%) thromboembolic events. The peak RDW value of patients with CHF with thromboembolic events was also significantly higher (16.4% vs. 15.6%, $p = 0.019$) compared to that of those without thromboembolic events.
Conclusion: An increased RDW value during follow-up could be associated with thromboembolic events in patients with non-valvular AF. The suggested cut-off values for RDW used to predict an increased thromboembolic risk in were ≥13.9% in patients with AF in general, ≥15% in patients with co-existing AF and CHF.

1. Introduction

The traditional stroke risk stratification system for atrial fibrillation (AF) contains various clinical risk factors. However, the current suggested schemes only demonstrate a modest predictive value (C-statistics 0.55–0.64) for thromboembolic events [1]. Furthermore, the usefulness of these schemes can only be validated by using the patient's clinical status during follow-up. Recent studies regarding AF have further complicated these stratification systems, adding more and more clinical factors associated with risk [2,3]. This has resulted in a cumbersome, and oftentimes, confusing system with too many risk factors, which has hindered the selection of an optimal stroke prevention strategy [4]. Recently, research on AF has focused on biomarkers, trying to identify markers related to a mechanism in the AF pathway or indicators that could predict thromboembolic events [5–7]. Several studies have indicated that certain biomarkers can substantially improve the current risk stratification system and improve the understanding of AF pathophysiology [5,8].

The red cell distribution width (RDW) concept stems from the variation of the size of red blood cells present in the bloodstream, and it can reflect the general health condition of a patient. An increased RDW value can be associated with inflammation [9], nutritional deficiencies [10], impaired bone marrow function [11], or increased red blood cell destruction [12]. In cardiovascular medicine, RDW has been shown to have prognostic power comparable to N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with congestive heart failure (CHF) [13]. An elevated RDW is also associated with stroke and strongly predicts both cardiovascular and all-cause death in patients with a stroke history [14–16]. In this study, we sought to evaluate the association of RDW and clinical outcomes in a population of patients with AF.

2. Methods

Our study protocol was approved by the Institutional Review Board of Seoul National University Hospital, and was conducted in accordance with the Declaration of Helsinki. Patient consent was waived because it

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was impractical to obtain written consents from a large number of patients for a retrospective review. Data was analysed anonymously.

2.1. Study population

From 2000 to 2013, 5082 consecutive patients with electrocardiogram-documented, non-valvular AF and with available RDW values were enrolled in the retrospective study. Patients with any malignancies, cytopenia of any aetiology, end-stage renal disease, any diagnosed rheumatic disease, or those under the age of 18 years old were excluded at screening.

2.2. Red cell distribution width (RDW)

The RDW is a measure of the variation of red blood cell volume that is reported as a part of the standard complete blood count (CBC) test. The formula for calculating RDW is as follows: [Standard deviation (SD) of mean corpuscular volume (MCV)/mean MCV] × 100. The reference range of RDW for normal adults is 11.5% to 14.5%.

For this study, a CBC sample was obtained at the initial visit, and was routinely checked every year at subsequent visits. If needed, additional samples were obtained at the order of the responsible physician. A professional nurse dedicated to acquiring blood samples collected the sample through venepuncture, drawing the blood into a test tube containing an anticoagulant (ethylenediaminetetraacetic acid [EDTA] or citrate). The mean number of CBC tests for each patient was 8.6 ± 15.7 during follow-up (mean 5.2 ± 3.7 years). The nadir, peak, and mean RDW were defined as the lowest, highest, and mean values, respectively, acquired during the follow-up period.

2.3. Outcome analysis

The primary outcome was defined as thromboembolic events, including ischemic stroke and systemic embolism. As this study was designed as a retrospective study, outcomes were established based on the judgment made by the physician at the time of the event. Ischemic stroke included strokes due to both thrombotic and embolic causes. Each outcome was additionally reviewed by three separate cardiologists after study enrolment. For validation, our event rate was compared with other previous studies, and was comparable to existing studies [17]. When data was divided according to the **C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75 years [2 points], **D**iabetes mellitus, **S**troke [2 points], **V**ascular disease, **A**ge 65–74 years, **S**ex **c**ategory (CHA_2DS_2-VASc) score, there was a positive correlation between the score and the event rate (Table A.1.). The association between RDW values and these outcomes were studied, and the cut-off value was determined by receiver operator characteristic (ROC) curve analysis. The study population was divided into four quartile groups according to the peak RDW value. We also performed subgroup analysis by assessing patients with AF who also had CHF.

2.4. Variables

Hypertension (HTN) was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a current prescription of medication for HTN treatment. Diabetes mellitus (DM) was defined as a fasting blood sugar level ≥ 126 mg/dL, a 2-h blood sugar level ≥ 200 mg/dL, or the use of medications to control blood sugar. CHF was defined as a left ventricular ejection fraction of 35% or less with a clinical diagnosis. Vascular disease included myocardial infarction, complex aortic plaque, and peripheral artery disease. Chronic kidney disease (CKD) was defined based on the presence of kidney damage or pathologically reduced glomerular filtration rate (GFR) (i.e., Modification of Diet in Renal Disease [MDRD]-estimated GFR <60 mL/min/1.73 m^2) for over 3 months, irrespective of the cause.

2.5. Statistical analysis

Baseline characteristics were compared between groups with and without thromboembolic events. Continuous variables were presented as mean ± SD, and compared using Student's *t*-test. Categorical variables were compared by Fisher's exact test or the χ [2] test. The significance of the *p*-value was two-sided. A 95% confidence interval (CI) was reported with the sensitivity, specificity, and predictive values. The relationship between RDW and other factors was assessed by linear regression analysis. The predictive power of RDW was analysed by Cox regression analysis. Previously known prognostic factors of thromboembolism included in the CHA_2DS_2-VASc system were adjusted for in the statistical analyses. ROC curve analysis was used to examine the ability of RDW to detect future thromboembolic events. The area under the curve (AUC) was derived from the ROC curve. For each RDW quartile group, the rate of thromboembolic events or mortality was calculated by dividing the number of cases with the total person-years of that category. We used four Cox proportional hazards models to assess the associations between RDW quartiles and event risk. The lowest quartile was used as the reference group. Model 1 estimated the crude association with RDW quartiles. Model 2 adjusted for haemoglobin level. Model 3 included the factors in the CHA_2DS_2-VASc scoring system, and model 4 included the type of antithrombotic medication used. Model 5 included all factors in models 2–4 as covariates.

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 21.0 software package (IBM SPSS, New York, USA). The category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices were calculated with R: A Language and Environment for Statistical Computing (Version 3.0.2) (R Foundation for Statistical Computing, Vienna, Austria, 2013).

3. Results

The baseline characteristics according to thromboembolic events are shown in Table 1. The correlation matrices for RDW and other related variables are described in Table A.2. RDW had no correlation with either previously reported clinical predictors or biomarkers for thromboembolic events. The distributions of these values in Table 1 are shown in Fig. A.2.

3.1. Outcome analysis

Patients with thromboembolic events were older and had more clinical risk factors, which correlated with having a higher CHA_2DS_2-VASc score. The peak and mean values of RDW were also higher in patients with thromboembolic events. There were no differences in gender or the percentage of patients with CHF between the groups. In addition, the rate at which medications for rate or rhythm control were used were not different between the two groups.

In logistic regression analysis, peak and mean RDW values were significantly higher in patients with thromboembolic events, regardless of other clinical factors. ROC curves displayed similar power for peak RDW and age in predicting thromboembolic outcomes (Fig. A.1). The AUCs were 0.59 (95% CI 0.57–0.61, $p < 0.001$), 0.63 (95% CI 0.61–0.65, $p < 0.001$), and 0.62 (95% CI 0.60–0.64, $p < 0.001$), for age, peak, and mean RDW, respectively. The combined predictive power of peak RDW and age showed the greatest AUC at 0.65 (95% CI 0.62–0.67, $p < 0.001$), but integration did not improve predictive power as measured by the category-free NRI and IDI.

3.2. Predictors of thromboembolic events

During the follow-up period, 723 (14.2%) patients suffered thromboembolic events. ROC curve analysis for peak RDW produced a best cut-off value of 13.9%, with a sensitivity of 62% and a specificity of 59%. A cut-

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