Original Article

Relation of red cell distribution width with HAS-BLED score in patients with non-valvular atrial fibrillation

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Background: Numerous researchers have shown that there is a close correlation between red cell distribution width (RDW) and cardiovascular disease such as heart failure, coronary heart disease, and atrial fibrillation. This study was designated to investigate the correlation between RDW and the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol (HAS-BLED) score.

Methods: The HAS-BLED scores of 251 hospitalized patients with non-valvular atrial fibrillation were calculated and the receiver operating characteristics were used to evaluate the predictive value of RDW on high HAS-BLED score (≥3 scores). Multiple logistic regression analysis was used to analyze the independent predictor of high HAS-BLED scores.

Results: Correlation analysis between RDW and HAS-BLED scores showed the RDW was positively correlated with HAS-BLED score, with r=0.393 (P<0.0001). The RDW of the high HAS-BLED score group was higher than that of the no-high HAS-BLED score group. The area under the receiver operating characteristic curve of RDW was 0.796 (0.740–0.844, P<0.0001) to predict a high HAS-BLED score, and multiple logistic regression analysis showed that a high RDW value could be used as an independent predictor of high HAS-BLED.

Conclusions: RDW value is associated with HAS-BLED value, and can be used as the independent predictive factor of high HAS-BLED scores.

Keywords: Red cell distribution width (RDW); atrial fibrillation; HAS-BLED score

Submitted Mar 01, 2021. Accepted for publication Apr 29, 2021.
doi: 10.21037/jtd-21-567
View this article at: http://dx.doi.org/10.21037/jtd-21-567

Introduction

Atrial fibrillation is an independent risk factor of cerebral ischemic stroke and anticoagulant therapy is particularly important for the prevention of cerebral arterial thrombosis (1,2). Strategies for antithrombotic therapy are made according to the thromboembolism and bleeding risk evaluation of atrial fibrillation patients, with the CHA2DS2-VASc score the most common scoring system evaluating thromboembolism risk in patients with atrial fibrillation (3). In 2010, the anticoagulation bleeding risk scoring system (HAS-BLED) was firstly proposed in ESC guidelines for the management of atrial fibrillation (4). The red cell distribution width (RDW) mainly reflects the nonuniformity of red blood cell volume in peripheral blood and in the past, has mainly been used in the clinical evaluation of hematological system diseases (5). Research

Table 1 HAS-BLED score

Risk factors	Score
H (hypertension)	1
A (abnormal renal/liver function)	1 or 2
S (stroke)	1
B (bleeding history or predisposition)	1
L (labile international normalized ratio)	1
E (elderly, N>65)	1
D (drugs/alcohol concomitantly)	1 or 2

has shown that RDW was associated with the prognosis of cardiovascular disease such as heart failure, coronary heart, disease and atrial fibrillation (6-9) and with some components of major scoring systems such as those used in stroke and hypertension (10,11). In the absence of clinical information to calculate embolism or bleeding scores, a convenient index with a high predictive value for CHA2DS2-VASc or HAS-BLED scores, stroke, and bleeding risk would hold high clinical utility. While Kurt *et al.* (12) showed that the RDW value could be used as an independent predictive factor for high CHA2DS2-VASc scores (≥2), to date, there has been no research reporting the relationship between RDW and HAS-BLED, which is the objective of this study.

We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/jtd-21-567).

Methods

Study population:

We selected 251 non-valvular atrial fibrillation patients hospitalized between January 2014 and January 2015 in the cardiovascular department of the Second Affiliated Hospital of Nantong University, of which there were 129 males and 122 females with an average age of 67.15±7.55 years. Other factors recorded at admission included blood pressure, history of past or concomitant disease such as hypertension, diabetes, cerebral ischemic or stroke, bleeding history, past drinking history, international normalized ratio (INR) labile history, and non-steroid anti-inflammatory and antiplatelet drug use. Blood samples were collected on an empty stomach in the morning the day after hospitalization to test the following: RDW, hematocrit value, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume, hemoglobin, platelet count, mean platelet volume, platelet distribution width, and alanine aminotransferase, total bilirubin, serum creatinine, cystatin, and N-terminal pro brain natriuretic peptide (NT-proBNP) levels. The exclusion criteria for this study were the presence or history of valvular atrial fibrillation, serious hepatic and renal dysfunction, blood disease, malignancy, active bleeding, thyroid dysfunction, chronic rheumatic immune disease, recent infection, surgical operation, and blood transfusion.

Atrial fibrillation was defined as absolutely irregular RR intervals and no discernible, distinct P waves (1). We evaluated the risk of bleeding with HAS-BLED score using specific scoring rules which included (4) hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (N>65), and drugs/alcohol concomitantly (*Table 1*), with a score of "≥3" recognized as a high bleeding risk. We also employed a HAS-BLED score that is used to estimate the risk of long-term bleeding events associated with atrial fibrillation in which patients scoring "≥3" were allocated into a high-risk group and those with a score of "<3" were allocated to a no-high risk group.

The mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, RDW, hemoglobin, platelet count, mean platelet volume, and platelet distribution width were determined by the automated hematology analyzer XE-2100 (Sysmex, Kobe, Japan), while the serum creatinine, alanine aminotransferase, cystatin, and total bilirubin levels were determined using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). The NT-proBNP level was measured by electrochemiluminescence immunoassay on the Dimension Vista 500 Intelligent Laboratory System (Siemens Healthcare Diagnostics, Deerfield, Illinois, United States). Finally, the normal reference range for RDW was set at 11.5% to 14.5%.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional ethics Committee of the Second Affiliated Hospital of Nantong University (No. 2020KN088) and informed consent was taken from all the patients.

Statistical analysis

The measurement data were presented as means ± standard

Table 2 Comparison of the general clinical information between the two groups according to HAS-BLED score

Variables	No-high risk (n=205)	High risk (n=46)	P value
Average age (year-old)	66.44±10.36	68.56±7.18	0.251
Female, n (%)	95 (46.3)	27 (58.6)	0.130
Hypertension, n (%)	85 (41.5)	29 (63.0)	0.008
Type II diabetes, n (%)	31 (15.1)	8 (17.4)	0.701
Stroke, n (%)	15 (7.3)	10 (21.7)	0.003
Bleeding history, n (%)	8 (3.9)	1 (2.2)	0.569
Labile INR, n (%)	10 (4.9)	3 (6.5)	0.649
Drugs/alcohol use concomitantly, n (%)	18 (8.7)	8 (17.4)	0.083
Hematocrit	0.411±0.437	0.371±0.438	0.000
MCH (Pg)	30.26±1.96	30.39±2.05	0.739
MCHC (g/L)	334.11±9.50	332.29±10.08	0.330
MCV (fL)	90.61±5.03	90.60±4.95	0.993
RDW (%)	13.08±1.03	13.96±0.93	0.000
Hemoglobin (g/L)	137.38±15.37	121.80±14.31	0.000
PLT ($\times 10^9$/L)	189.31±53.03	174.37±51.28	0.154
MPV (fL)	10.88±1.21	11.13±1.41	0.336
PDW (%)	13.58±2.83	14.00±3.49	0.478
NT-ProBNP (ng/L)	364.51±659.72	673.89±811.08	0.084
ALT (U/L)	23.31±25.39	27.65±20.06	0.403
Tb (mmol/L)	15.31±5.31	16.71±6.31	0.781
Scr (mmol/L)	69.81±14.81	73.98±23.81	0.201
Cystatin (mg/L)	1.01±0.19	1.15±0.26	0.001

Drugs use concomitantly: concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs)/antiplatelet drugs. INR, international normalized ratio; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width; PLT, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; NT-ProBNP, N terminal pro B type natriuretic peptide; ALT, alanine aminotransferase; Tb, total bilirubin; Scr, serum creatinine.

deviation, while the enumeration data were presented as percentage or frequency. Independent-sample *t*-test and chi-square test were applied in comparing the measurement data and the enumeration data in the two groups, respectively, and bivariate Spearmen was used for the correlation analysis. The predictive values of RDW on a high HAS-BLED score was completed through receiver-operating characteristic (ROC) analyses and multiple logistic regression analysis was used to evaluate the relationship between variables and a high HAS-BLED score. Variables with a P value <0.1 in univariate logistic regression analysis were included in a multivariate logistic regression model and the results of the regression analysis were presented as odds ratios and 95% confidence intervals. The data analysis was completed with SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA) and MedCalc (version 11.2.1; MedCalc, Mariakerke, Belgium) and a difference of P<0.05 was deemed as statistically significant.

Results

Comparison between the characteristics in the two groups showed hypertension (%), stroke (%), RDW, and cystatin were higher in the high-risk group than the no-high risk group (P<0.05), while the hematocrit and hemoglobin levels were lower than those in the no-high risk group (P<0.05) (*Table 2*).

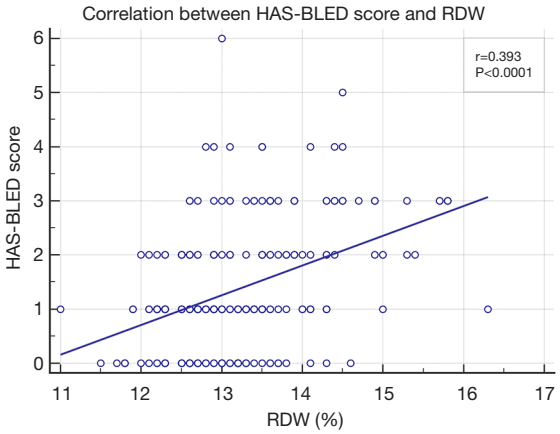

Figure 1 Correlation analysis between RDW and HAS-BLED scores showed the RDW was positively correlated with HAS-BLED score, with r=0.393 (P<0.0001). RDW, red cell distribution width.

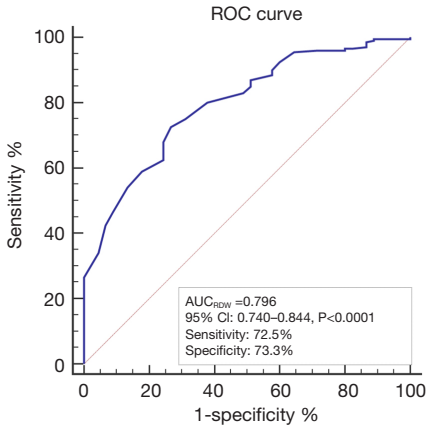

Figure 2 The ROC AUC of RDW in predicting a high HAS-BLED score was 0.796, with the cut-off level of 13.3%, 95% CI of 0.740–0.844, sensitivity of 72.5%, and specificity of 73.3% (P<0.0001). RDW, red cell distribution width. ROC, receiver-operating characteristic; AUC, area under the curve.

Correlation analysis between RDW and HAS-BLED scores showed the RDW was positively correlated with HAS-BLED score, with r=0.393 (P<0.0001) (*Figure 1*), while the area under the ROC curve of RDW to predict a high HAS-BLED score was 0.796, with the cut-off level of 13.3%, 95% CI of 0.740–0.844, sensitivity of 72.5%, and specificity of 73.3% (P<0.0001) (*Figure 2*).

Multiple logistic regression analysis showed that RDW (OR: 1.33, 95% CI: 1.10–1.56, P=0.031), stroke (OR: 3.13, 95% CI: 1.65–4.35, P=0.003), hemoglobin (OR: 0.93, 95% CI: 0.88–0.98, P=0.040), and hypertension (OR: 2.30, 95% CI: 1.25–3.99, P=0.022) were independent predictors of a high HAS-BLED score (*Table 3*).

Table 3 Multiple logistic regression analysis to detect the independent predictors of high HAS-BLED score in patients with AF

Variables	OR, 95% CI	P value
Hemoglobin	0.93 (0.88–0.98)	0.040
RDW	1.33 (1.10–1.56)	0.031
Hypertension	2.30 (1.25–3.99)	0.022
Stork	3.13 (1.65–4.35)	0.003

RDW, red cell distribution width; AF, atrial fibrillation.

Discussion

The results showed that the RDW value in the high HAS-BLED score group was significantly higher than in the no-high HAS-BLED score group and was positively correlated with a HAS-BLED score. In addition, RDW could be used as an independent predictive factor of high HAS-BLED scores.

Atrial mural thrombi can cause cerebral embolism and stroke, and patients with atrial fibrillation have a higher fatality rate, invalidism rate, and hospitalization stay duration than those without. Different strategies for anticoagulation management may be used according to the evaluation of CHA2DS2-VASc scores on thromboembolism risk. RDW reflects the dispersion degree of red blood cells in peripheral blood and in the past, was mainly used for the morphological classification of anemia including the differential diagnosis of iron-deficiency anemia clinically (13). Lee *et al.* (9) showed that the incidence rate of CHA2DS2-VASC scores and cerebral arterial thrombosis increased with an increasing RDW value. While preventing thrombus, bleeding risk should also be evaluated in the process of using anticoagulant drugs and at present, the HAS-BLED scoring system is the most widely used scoring system. Research has shown that RDW was also correlated to HAS-BLED scores, and can be used as an independent predictive factor of high HAS-BLED scores.

An increased RDW has been shown to be associated with high blood pressure and could be used as a predictive factor of high blood pressure organ damage (14). A large-scale cohort study of Hoffmann (15) showed that RDW was age dependent and tended to increase with age, while Lippi

et al. (16) studied RDW and creatinine values in a large sample of outpatients and found that RDW was negatively correlated with renal function. In addition, correlation between high RDW values with abnormal liver function and ischemic stroke has been demonstrated in several studies (17-19). High blood pressure, age, abnormal hepatorenal function, and stroke are the major factors which constitute the HAS-BLED score system and this may explain the predictive value of RDW on high HAS-BLED scores. At present, an increase in the RDW value is believed to be correlated with factors such as a lack of nutrients, including folic acid and vitamin B12, which cause anemia, and the resulting changes to hemopoietin cause impaired renal function, activation of the neuroendocrine system, oxidative stress, and *in vivo* neuroendocrine system changes (20-26).

Limitations

The major limitations to this study are its small sample size, short follow-up period, and that it was limited only to the correlation between RDW and HAS-BLED.

Conclusions

RDW values are easy to obtain, have a strong predictive value for high HAS-BLED scores, and can be used as an auxiliary index to evaluate bleeding risk in the process of atrial fibrillation anticoagulation therapy.

Acknowledgments

We acknowledge the assistance of all doctors, nurses, technicians, ambulance paramedics, and hospital staff who cared for our patients.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at http://dx.doi.org/10.21037/jtd-21-567

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-21-567

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-21-567). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional ethics Committee of the Second Affiliated Hospital of Nantong University (No. 2020KN088) and informed consent was taken from all the patients.

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(English Language Editor: B. Draper)

Cite this article as: Cai HL, Chen H, Wang J, Xie L, Zheng KL, Zhang Q. Relation of red cell distribution width with HAS-BLED score in patients with non-valvular atrial fibrillation. J Thorac Dis 2021;13(5):3070-3075. doi: 10.21037/jtd-21-567