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Original Article

Influence of red blood cell distribution on short-term functional outcome in patients with acute ischemic stroke and atrial fibrillation

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Abstract: *Background and aim:* Accurate risk stratification and prognostication are important for managing patients with atrial fibrillation (AF) and acute ischemic stroke. Red blood cell distribution width (RDW) has previously been found to predict long-term clinical outcomes in these conditions. This study investigated its role in predicting short-term outcomes. *Methods:* This was a retrospective study examining all patients who were admitted to our hospital with a clinical diagnosis of AF and acute ischemic stroke. Baseline characteristics including RDW and short-term outcome variables were recorded. Logistic regression and propensity score-matched analyses were used to identify the independent predictors of outcome variables. *Results:* A total of 258 patients were included in this study, in whom a significant association between RDW and the National Institutes of Health Stroke Scale (NIHSS) scores at admission (r_s = 0.199, $p < 0.001$) was observed. Multivariate analysis confirmed the value of RDW for predicting the occurrence of severe stroke (NIHSS ≥ 8). RDW ≥ 13.1% was associated with a higher modified Rankin Scale score at discharge (3 versus 4, p = 0.007), higher rate of adverse prognosis (75.3% versus 87.6%, p = 0.034), and lower rate of independent ambulation (55.2% versus 37.8%, p = 0.024). Modified Charlson's comorbidity index (CCI) was also an independent factor of mRS scores at discharge (OR = 0.589, 0.451-0.767, $p < 0.001$). *Conclusions:* RDW is an inexpensive marker that can be used to predict stroke severity and short-term functional outcomes in patients with AF and acute ischemic stroke.

Keywords: Red blood cell distribution width, ischemic stroke, atrial fibrillation, severity, outcome

Introduction

Red blood cell distribution width (RDW) is a parameter of complete blood count that quantitatively describes the variability in the size of circulating erythrocytes and plays a role in the differential diagnosis of anemia. It has been recently found a strong predictor in many pathological states, for example coronary deaths, nonfatal myocardial infarction, stroke [1, 2], heart failure [3, 4], peripheral artery disease [5], cancer [6], hemodialysis [7], infection [8] and diabetes mellitus [9]. More recently, RDW has been shown to be an independent predictor of the incidence and clinical outcomes in atrial fibrillation (AF) [10-12]. However, the association between RDW and ischemic stroke remains controversial [11, 13-17]. Ntaio et al. performed a study including 1504 patients with acute stroke, and demonstrated that RDW did not significantly predict the stroke severity and functional outcome [14]. By contrast, other studies showed an association between RDW and the incidence, severity and long term outcomes of stroke [13, 17-19]. While these previous studies have focused on the longer term outcomes, typically at three months or more following acute ischemic stroke events, little is known regarding its association with short-term outcomes. Above all, it remains unclear whether the association is influenced by the interaction between stroke and AF. At that point, the present case-control study was designed to investigate whether RDW might also be predic-

Table 1. Baseline characteristics and clinical data

Characteristic		Study population (n = 258)
Demographic data		
Sex, n (%)	Female	126 (48.8%)
Age, years		78 (70-83)
Medical history		
Hypertension, n (%)		186 (72.1%)
Diabetes mellitus, n (%)		86 (33.3%)
Coronary artery disease, n (%)		217 (84.1%)
Stroke with clinical symptoms, n (%)		58 (22.5%)
Tobacco smoking, n (%)		124 (48.1%)
CCI		7 (6-7)
Laboratory data		
WBC (× 10^9/L)		7.3 (5.9-9.1)
Hemoglobin (g/L)		136 (124-147)
RDW (%)		13.1 (12.5-13.7)
Platelet count (× 10^9/L)		196.5 (163-243)
Total cholesterol (mmol/L)		4.73 (4.08-5.51)
Total glycerol (mmol/L)		1.20 (0.91-1.78)
HDL cholesterol (mmol/L)		1.005 (0.86-1.21)
LDL cholesterol (mmol/L)		2.795 (2.28-3.43)
Fasting blood-glucose (mmol/L)		6.51 (5.46-7.90)
ALT (U/L)		14.3 (9.8-22.1)
AST (U/L)		17.35 (13.4-22.7)
BUN (mmol/L)		6.00 (4.50-7.70)
Creatinine (umol/L)		75.15 (58.60-89.90)
Uric acid (umol/L)		344.75 (282.30-428.90)
Fibrinogen (g/L)		3.160 (2.690-3.788)
Homocysteine (umol/L)		14.245 (11.57-19.21)
HsCRP (mg/L)		9.975 (2.34-19.48)
Clinical data		
NIHSS	Admission	8 (4-14)

CCI, Charlson's comorbidity index; WBC, white blood cell; RDW, red blood cell distribution width; HDL, High density lipoprotein; LDL, Low density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HsCRP, high sensitivity C reactive protein; NIHSS, the National Institutes of Health Stroke Scale.

tive for short-term outcomes in patients with AF and acute ischemic stroke.

Materials and methods

Study population

In this retrospective study, data were obtained from the database for all hospitalized patients with acute stroke in the second hospital of Tianjin Medical University, which is one of the major stroke centers in Tianjin. The study population was based on consecutive patients with a final diagnosis of AF and acute ischemic stroke at discharge between January, 2010 and November, 2016. All patients admitted to the hospital within 72 hours of symptoms onset through the Emergency Department (ED) or the Out-Patient Department were included. For each patient, computed tomography (CT) scan and baseline electrocardiogram (ECG) were performed at admission. Patients initially admitted to the intensive care unit underwent permanent ECG monitoring. Through the method above or the 24-hour Holter ECG, patients without known AF had continuous ECG monitoring for at least 24 hours. The diagnosis of AF at discharge was based on medical history, initial and supplemental ECG during hospitalization, ECG monitoring and 24-hour Holter ECG findings.

Patients were excluded for the following reasons: transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, cerebral sinus venous thrombosis, late admission, trauma or surgery within 3 months, missing information on basal characteristics. The study was approved by the Ethics Committee of the Second Hospital of Tianjin Medical University and written informed consent was obtained from all patients.

Data collection

Baseline characteristics were recorded including demographic data, medical history (hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, symptomatic stroke,

Table 2. Binary logistic regression analysis to identify independent factors of NIHSS ≥ 8 in patients with AF and AIS

Independent variable	Univariate analysis		Multivariate analysis	
	OR	P	OR	P
Sex	2.512 (1.521-4.150)	< 0.001	1.962 (1.120-3.436)	0.018
Age	1.043 (1.016-1.071)	0.002	1.030 (1.001-1.060)	0.043
Coronary artery disease	1.862 (0.942-3.683)	0.074		
Stroke with clinical symptoms	2.775 (1.478-5.210)	0.001	2.919 (1.452-5.865)	0.003
Tobacco smoking	0.521 (0.317-0.854)	0.010	0.535 (0.309-0.927)	0.026
CCI	1.327 (1.105-1.594)	0.002		
WBC	1.149 (1.044-1.266)	0.005	1.169 (1.047-1.306)	0.006
RDW ≥ 13.1%	2.262 (1.374-3.724)	0.001	1.867 (1.074-3.248)	0.027
Fibrinogen	1.535 (1.129-2.088)	0.006		
HsCRP	1.014 (1.002-1.027)	0.019		

AF, atrial fibrillation; AIS, acute ischemic stroke; NIHSS, the National Institutes of Health Stroke Scale; CCI, modified Charlson's comorbidity index; WBC, white blood cell; RDW, red blood cell distribution width; HsCRP, high sensitivity C reactive protein.

tobacco smoking), modified Charlson's comorbidity index [20] and laboratory examinations at ED or admission. The severity of stroke was evaluated by the National Institutes of Health Stroke Scale (NIHSS) score at admission and the functional outcome by the modified Rankin Scale (mRS) score at discharge. All the scoring procedures were performed independently by two neurologists, and disagreements were resolved by negotiation.

Common medical complications associated with acute ischemic stroke during hospitalization were identified by searching the secondary diagnoses from the medical records. Complications were categorized into one of the following categories: infectious (pneumonia, urinary tract infection), gastrointestinal (stress ulcer, alimentary tract hemorrhage), cardiac (acute myocardial infarction), thrombotic (deep vein thrombosis, pulmonary embolism), neurological (symptomatic epilepsy), internal environment (electrolyte disturbance), miscellaneous (pressure ulcer). For most of the statistical analysis, patients were divided into two groups: no medical co-morbidity and those with at least one medical condition.

Short-term outcome variables included discharge destination, length of stay (LOS) and mRS at discharge. Discharge destination was analyzed as discharge to rehabilitation center or home, hospice, death or others (i.e. left against medical advice or transferred to another hospital). Adverse prognosis was defined as mRS ≥ 3. In the ordinal logistic model for mRS scores, patients were divided into four groups (0, 1 to 2, 3 to 5 and 6). As a secondary outcome, independent ambulation was defined as ambulation without assistance from another person, with or without the use of a walking aid, and the analysis was restricted to patients with documented ability to ambulate independently prior to symptom onset (10 patients excluded).

Statistical analysis

Continuous variables are reported as median (interquartile range), and categorical variables were reported as counts (percentage value). Comparison between groups was performed with independent-sample t tests (for normally distributed variables), Wilcoxon's two-sample nonparametric test or Kruskal-Wallis test (for continuous variables and ordinal variables), Chi-square test, or Fisher's exact test for categorical and dichotomous variables, respectively. Spearman Rank correlation was used to determine the correlation between different variables. Binomial or ordinal logistic regression was performed to evaluate independent effects of RDW on stroke severity or functional outcome, respectively, with adjustment for basal characteristics and clinical variables. Variables with $p < 0.10$ in the univariate analysis were entered the multivariate logistic regression. Receiver operating characteristic (ROC) curves were constructed to assess the predictive value of RDW. The optimal cut-off value was identified by Youden index. To bal-

Table 3. Baseline characteristics, clinical data and discharge status of patients classified according to RDW levels before matched

Characteristic		RDW < 13.1%	RDW ≥ 13.1%	P
Patients		118	117	
Newly diagnosed AF, n (%)		15 (12.7%)	12 (10.3%)	0.555
Demographic data				
Sex, n (%)	Female	50 (42.4%)	64 (54.7%)	0.059
Age, years		75 (65-81)	79 (73-84.5)	0.003
Medical history				
Hypertension, n (%)		87 (73.7%)	85 (72.6%)	0.852
Diabetes mellitus, n (%)		46 (39.0%)	33 (28.0%)	0.080
Coronary artery disease, n (%)		98 (83.1%)	100 (85.5%)	0.611
Stroke with clinical symptoms, n (%)		19 (16.1%)	34 (29.1%)	0.017
Tobacco smoking, n (%)		59 (50.0%)	53 (45.3%)	0.471
CCI		6 (5-7)	7 (6-8)	0.005
Laboratory data				
WBC (× 10^9/L)		7.4 (6.2-9.1)	6.7 (5.6-9.2)	0.192
Hemoglobin (g/L)		139 (128-151)	131 (116-143)	< 0.001
Platelet count (× 10^9/L)		205 (168-243)	189.5 (155-239)	0.065
Total cholesterol (mmol/L)		4.86 (4.27-5.58)	4.61 (3.85-5.42)	0.081
Total glycerol (mmol/L)		1.235 (0.91-1.84)	1.19 (0.93-1.88)	0.875
HDL cholesterol (mmol/L)		1.03 (0.88-1.21)	1.00 (0.84-1.22)	0.418
LDL cholesterol (mmol/L)		2.97 (2.43-3.39)	2.68 (2.27-3.37)	0.153
Fasting blood-glucose (mmol/L)		6.61 (5.45-8.21)	6.49 (5.46-7.86)	0.562
ALT (U/L)		15.5 (10.4-23.7)	13.5 (9.5-20.2)	0.167
AST (U/L)		17.05 (13.2-22.0)	17.7 (13.9-23.8)	0.351
BUN (mmol/L)		5.95 (4.50-7.50)	6.10 (4.50-7.90)	0.394
Creatinine (umol/L)		76.00 (59.90-85.10)	73.90 (58.10-93.30)	0.848
Uric acid (umol/L)		334.95 (264.30-396.90)	371.10 (306.40-450.10)	0.007
Fibrinogen (g/L)		3.010 (2.670-3.521)	3.416 (2.724-4.110)	0.008
Homocysteine (umol/L)		13.325 (10.23-17.78)	15.41 (12.55-20.56)	0.001
HsCRP (mg/L)		9.305 (1.91-15.41)	9.31 (2.45-21.59)	0.115
Clinical data				
NIHSS	Admission	6 (3-11)	9 (5-16)	0.001
Discharge status				
Discharge destination, n (%)*	Died/Hospice	13 (11.0%)	24 (20.5%)	0.046
	Rehabilitation/Home	105 (89.0%)	93 (79.5%)	
mRS*	Discharge	3 (2-5)	5 (3-5)	< 0.001
Adverse prognosis, n (%)*	mRS ≥ 3	80 (67.8%)	106 (90.6%)	< 0.001
Independent ambulation, n (%)†		68 (58.6%)	36 (33.0%)	< 0.001
Length of stay, days*		14 (11-16)	14 (10-16)	0.609
Medical complications/Type, n (%)*	≥ 1	51 (43.2%)	71 (60.7%)	0.007

RDW, indicates red blood cell distribution width; AF, atrial fibrillation; CCI, modified Charlson's comorbidity index; WBC, white blood cell; HDL, High density lipoprotein; LDL, Low density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HsCRP, high sensitivity C reactive protein; NIHSS, the National Institutes of Health Stroke Scale; mRS, modified Rankin Scale. *, Excluding patients whose discharge destination were categorized into others. †, Excluding patients whose discharge destination were categorized into others and those without independent ambulation prior to symptom onset.

ance the characteristics of patients classified according to the median of RDW, a propensity score was created with a 0.15 caliper width and a matching ratio 1:1. Statistical analysis was performed by IBM SPSS 23.0 software. Two-sided < 0.05 was considered significant.

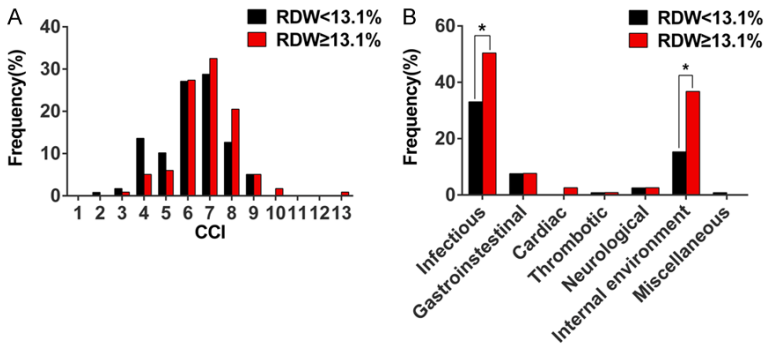

Figure 1. Distribution of modified Charlson's comorbidity index and medical complication type in patients classified by the median of red blood cell distribution width. Distribution of modified Charlson's comorbidity index (A) and medical complication type (B) in patients classified by the median of red blood cell distribution width (excluding whose discharge destination were categorized into others). Results are shown as frequency (%). *indicates $p < 0.05$.

Results

The study population consisted of 258 patients with a final diagnosis of AF and acute ischemic stroke, of which on admission 227 patients had known AF and 31 patients with newly diagnosed AF. Baseline characteristics and clinical data are shown in **Table 1**. A significant association was found between RDW *levels* and the NIHSS scores at admission (r_s = 0.199, $p < 0.001$). Univariate logistic regression was performed to identify the predictor factors for the NIHSS scores at admission. NIHSS scores were classified into two groups using the median, into 0-7 and ≥ 8, and RDW levels into RDW < 13.1% and RDW ≥ 13.1%. A stepwise multivariate analysis showed that RDW ≥ 13.1% remained significantly associated with stroke severity after adjusting for confounders (**Table 2**).

To determine the relationship between RDW and discharge status variables, patients whose discharge destinations were categorized into others were excluded. The baseline characteristics, clinical data, and discharge status of patients classified by the median of RDW are showed in **Table 3**. Age, proportion of symptomatic stroke and CCI (**Figure 1A**) were significantly increased in patients with RDW ≥ 13.1%, whilst LOS was similar between the two groups. RDW was found to be significantly associated with discharge destination (r_s = 0.131, p = 0.045), mRS score at discharge (r_s = 0.272, $p < 0.001$) and medical complication (r_s = 0.188, p = 0.004). Among those types of medical complications, infection and electrolyte disturbance were the top two and occurred more frequently in patients with RDW ≥ 13.1% (**Figure 1B**).

Furthermore, in the ordinal logistic regression analysis for mRS scores, the parameters significantly associated with functional outcome were diabetes mellitus, CCI, RDW ≥ 13.1% and NIHSS scores at admission (**Table 4**). To enable comparison of the strength of association, multivariate logistic regression for dichotomized mRS scores was performed. This demonstrated quartiles of RDW were independent factors for both adverse outcome (odds ratio [OR] 2.198, 95% confidence interval [CI] = 1.410-3.427, p = 0.001) and independent ambulation (OR = 0.666, 95% CI = 0.465-0.954, p = 0.026). The ROC curves of RDW for predicting adverse outcome and independent ambulation yielded an AUC of 0.717 (95% CI = 0.634-0.801, $p < 0.001$) and 0.643 (95% CI = 0.570-0.715, $p < 0.001$) respectively (**Figure 2**). The best cut-off value was 12.45% with a sensitivity of 0.833 and specificity of 0.531 for adverse outcome, and 12.95% with a sensitivity of 0.653 and specificity of 0.625 for no independent ambulation.

As the study was non-randomized, a propensity score matching was performed, yielding 89 matched pairs of patients (excluding those categorized into others). Characteristics of matched patients were shown in **Table 5**. There was no significant difference in the variables generally considered to determine outcome variables (sex, age, diabetes mellitus, CCI, hemoglobin, total cholesterol, creatinine, uric acid, fibrinogen, homocysteine and NIHSS), except for RDW (12.4%, 12.0%-12.7%; 13.6%, 13.3%-14.2%; $p < 0.001$). Patients with different levels of RDW showed no significant difference in the LOS whether before or after matching. The proportion of discharge to home/hospice and at least 1 type of medical complication both became similar after matching. Only the mRS score at discharge, the proportion of adverse prognosis and independent

Table 4. Ordinal logistic regression analysis to identify independent factors of mRS scores in patients with AF and AIS

Independent variable	Univariate analysis		Multivariate analysis	
	OR	P	OR	P
Sex	1.630 (0.955-2.781)	0.073	0773 (0.414-1.442)	0.418
Age	0.955 (0.931-0.981)	0.001	0.997 (0.965-1.030)	0.874
Diabetes mellitus	0.575 (0.328-1.008)	0.053	0.460 (0.228-0.928)	0.030
Stroke with clinical symptoms	2.240 (1.167-4.301)	0.015	1.160 (0.530-2.541)	0.710
CCI	0.547 (0.449-0.667	< 0.001	0.589 (0.451-0.767)	< 0.001
WBC	0.930 (0.866-0.999)	0.045	1.010 (0.931-1.096)	0.815
RDW ≥ 13.1%	3.368 (1.891-5.998)	< 0.001	2.060 (1.090-3.893)	0.026
Fasting blood-glucose	0.910 (0.836-0.990)	0.029	0.931 (0.839-1.034)	0.183
AST	0.974 (0.953-0.996)	0.020	0.982 (0.959-1.006)	0.133
Fibrinogen	0.766 (0.559-1.048)	0.096	1.198 (0.839-1.711)	0.321
NIHSS/Admission	0.788 (0.742-0.835)	< 0.001	0.812 (0.762-0.865)	< 0.001

MRS, modified Rankin Scale; AIS, acute ischemic stroke; AF, atrial fibrillation; CCI, modified Charlson's comorbidity index; WBC, white blood cell; RDW, red blood cell distribution width; AST, aspartate aminotransferase; NIHSS, the National Institutes of Health Stroke Scale.

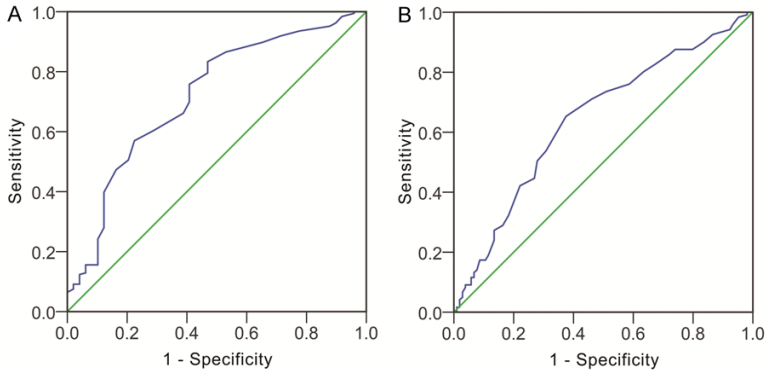

Figure 2. Receiver operating characteristic curves analysis of red blood cell distribution width. ROC curve analysis of red blood cell distribution width for predicting adverse outcome (A) and independent ambulation (B).

ambulation remained significantly higher in matched patients.

Discussion

Stroke is one of the most common causes of disability and death around the world. A better understanding of the factors that may have an impact on the clinical outcomes is necessary for accurate risk stratification and prognostication, which may provide great help for managing patients as well as communicate with patients and families about the condition. For the past few years, red cell distribution width (RDW) has been found an independent factor for predicting clinical outcomes in patients with ischemic stroke. Several studies demonstrated that RDW was significantly associated with neurological improvement, 3-month unfavorable outcome and 1-year all-cause mortality in patients with ischemic stroke [17, 21]. To the best of our knowledge, this study is the first to demonstrate a significant association between RDW and functional outcomes (mRS scores, adverse prognosis or independent ambulation) at discharge in patients with AF and acute ischemic stroke. Adjustment for multiple potential confounders attenuated but did not eliminate the association between higher RDW levels and the adverse clinical outcomes. As RDW is a simple and cost-effective laboratory test assessed rapidly by automated cell counters, its predictive value for the functional outcome at discharge may provide a novel means for prognostication in acute stroke.

In addition, our data demonstrated RDW as a marker for stroke severity (NIHSS scores at admission), which was not shown in the previous study [14]. This difference may be attributed to differing cohorts studied. Many studies have demonstrated significant increases in RDW in patients with AF [10, 12], indicating that AF may have a potentially confound-

Table 5. Baseline characteristics, clinical data and discharge status of patients classified according to RDW levels after matched

Characteristic		RDW < 13.1%	RDW ≥ 13.1%	P
Patients		89	89	
Newly diagnosed AF, n (%)		5 (5.6%)	10 (11.2%)	0.177
Demographic data				
Sex, n (%)	Female	45 (50.6%)	46 (51.7%)	0.881
Age, years		77 (70-82)	79 (70-84)	0.250
Medical history				
Hypertension, n (%)		69 (77.7%)	68 (76.4%)	0.859
Diabetes mellitus, n (%)		33 (37.1%)	29 (32.6%)	0.529
Coronary artery disease, n (%)		76 (85.4%)	74 (83.1%)	0.681
Stroke with clinical symptoms, n (%)		16 (18.0%)	21 (23.6%)	0.356
Tobacco smoking, n (%)		44 (49.4%)	44 (49.4%)	1.000
CCI		6 (6-7)	7 (6-8)	0.207
Laboratory data				
WBC (× 10^9/L)		7.7 (6.4-9.1)	6.95 (5.5-9.0)	0.161
Hemoglobin (g/L)		136 (126-147)	133 (119-144)	0.387
Platelet count (× 10^9/L)		204 (166-246)	286 (153-238)	0.136
Total cholesterol (mmol/L)		4.85 (4.29-5.60)	4.67 (4.04-5.42)	0.188
Total glycerol (mmol/L)		1.19 (0.91-1.77)	1.16 (0.93-1.75)	0.941
HDL cholesterol (mmol/L)		1.08 (0.96-1.22)	1.04 (0.87-1.23)	0.154
LDL cholesterol (mmol/L)		2.97 (2.49-3.31)	2.71 (2.41-3.46)	0.327
Fasting blood-glucose (mmol/L)		6.51 (5.45-7.79)	6.35 (5.44-7.97)	0.937
ALT (U/L)		13.8 (10.0-23.7)	13.6 (9.9-20.4)	0.632
AST (U/L)		17.2 (13.7-21.7)	17.6 (13.4-23.8)	0.624
BUN (mmol/L)		6.00 (4.50-7.70)	6.00 (4.30-7.60)	0.881
Creatinine (umol/L)		74.50 (58.90-89.90)	73.50 (58.10-87.30)	0.807
Uric acid (umol/L)		339.50 (269.90-399.30)	361.10 (293.60-438.40)	0.144
Fibrinogen (g/L)		3.090 (2.750-3.550)	3.290 (2.660-3.990)	0.329
Homocysteine (umol/L)		13.48 (10.20-18.85)	15.23 (12.34-19.45)	0.065
HsCRP (mg/L)		11.50 (2.29-15.41)	10.16 (2.90-24.55)	0.230
Clinical data				
NIHSS	Admission	6 (3-14)	8 (5-15)	0.162
Discharge status				
Discharge destination, n (%)*	Died/Hospice	10 (11.2%)	19 (21.3%)	0.068
	Rehabilitation/Home	79 (88.8%)	70 (78.7%)	
mRS*	Discharge	3 (2-5)	4 (3-5)	0.004
Adverse prognosis, n (%)*	mRS ≥ 3	63 (70.8%)	78 (87.6%)	0.006
Independent ambulation, n (%)†		49 (56.3%)	31 (37.8%)	0.016
Length of stay, days*		14 (12-18)	14 (9-15)	0.179
Medical complications/Type, n (%)*	≥ 1	43 (48.3%)	49 (55.1%)	0.368

RDW, red blood cell distribution width; AF, atrial fibrillation; CCI, modified Charlson's comorbidity index; WBC, white blood cell; HDL, High density lipoprotein; LDL, Low density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HsCRP, high sensitivity C reactive protein; NIHSS, the National Institutes of Health Stroke Scale; mRS, modified Rankin Scale. *, Excluding patients whose discharge destination were categorized into others. †, Excluding patients whose discharge destination were categorized into others and those without independent ambulation prior to symptom onset.

ing effect on the association between RDW and acute ischemic stroke. The previous study by Ntaio et al. did not specifically focus on the confounding effect of AF [14], whereas the present study excluded patients without AF, which may exclude the confounding effect of AF and lead to more homogenous results in the latter. The disagreement exactly points towards a complex relationship between RDW, AF and ischemic stroke.

Moreover, the present study showed that higher RDW levels are associated with higher proportions of death/hospice destination and more than 1 type of medical complication, but the association diminished after adjustment for various confounders. It might be due to a relatively small sample size. Although we could not come to the conclusion that RDW was predictive for in-hospital mortality and medical complications during hospitalization, it reminded us of the possible association between RDW and those outcome variables. Studies with a larger sample size should be conducted to get a better understanding.

RDW is conventionally calculated by the ratio of the standard deviation (SD) and the mean of erythrocyte volumes, which reflects the degree of heterogeneity of erythrocyte volume, in other words, anisocytosis. Although the clinical significance of RDW has been studied in many conditions, the underlying mechanisms have not been fully elucidated. An increased RDW mirrors a dysregulation of erythrocyte homeostasis that may be attributed to telomere shortening, higher oxidative stress, increased inflammation, poor nutritional status, dyslipidemia, hypertension, erythrocyte fragmentation and impaired erythropoietin function. In fact, many of these metabolic abnormalities are involved in the pathogenesis of both AF and ischemic stroke. Impaired erythropoiesis, abnormal erythrocyte survival, and delayed erythrocyte clearance might be important control points in the pathogenesis [22, 23]. RDW may be a simple marker of an underlying disrupted homeostasis.

There may be causal association between RDW and a cardiovascular disorder. Anisocytosis is associated with higher levels of cholesterol content in erythrocyte membrane, which participates in the formation and growth of the atherosclerotic plaques [24]. Enhanced inhibition of nitric oxide bioactivity and reduced erythrocyte deformability [25] caused by anisocytosis might ultimately result in reduced flow-dependent artery dilatation and oxygenation in peripheral organs, thus triggering or amplifying the adverse consequence of ischemic damage [26]. In summary, RDW is a simple and inexpensive marker for predicting the prognosis and risk stratification in patients with those pathologies including AF and ischemic stroke [22, 27, 28].

Other than RDW, the modified Charlson's comorbidity index (CCI) was also found to be an independent factor of mRS scores at discharge (OR = 0.589, 0.451-0.767, $p < 0.001$). CCI is a weighted comorbid disease severity score composed of 17 comorbid conditions, which was initially developed as an applicable method for classifying comorbid conditions associated with the risk of mortality in longitudinal studies. It has been extensively used in clinical research to assess the confounding influence of comorbidities and predictor of outcomes. In clinical practice, comorbidity was common in patients with AF and ischemic stroke, as both diseases affect the elderly mainly. For that reason, we used CCI as a measure of the overall condition of patients and burden of disease including baseline risk of developing in-hospital complications. These were not included in most of the previous studies. Our data support that CCI is a predictive factor for mRS scores at discharge. The association might indicate the possible influence of comorbidities on clinical outcome, particularly in the elderly.

There are some limitations in our study. First, although multiple ECG measurements were taken, some patients with AF might have been undetected. Second, the proportion of death or hospice destination and medical complication were higher but not significant after matching, which may be attributed to the small sample size. Larger prospective studies are needed to better elucidate these issues further.

Our study demonstrates the prediction value of RDW in identifying stroke severity and functional outcome in patients with AF and acute ischemic stroke. However, the mechanism of RDW involved remains unclear, and further investigations are needed to establish a more convenient and accurate system for risk stratification to better guide management of these patients.

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Disclosure of conflict of interest

None.

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