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Prognostic value of red blood cell distribution width in predicting 3-month functional outcome of patients undergoing thrombolysis treatment for acute ischemic stroke

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Abstract

This study was performed to determine whether red blood cell distribution width (RDW) is associated with 3-month poor functional outcome in patients undergoing thrombolytic therapy for acute ischemic stroke.

RDW was measured in patients with thrombolytic therapy in emergency department. Functional outcome was assessed after 3 months and poor functional outcome was defined as modified Rankin scale 3 to 6.

A total of 240 patients were enrolled, and 82 (34.2%) had a poor functional outcome. The median RDW was significantly elevated in patients with a poor functional outcome compare with those with a good outcome. RDW was independently associated with a 3-month poor functional outcome (odds ratio 3.369, 95% confidence interval 2.214–5.125). The optimal RDW cutoff for predicting 3-month poor functional outcome was 12.8%, and the area under the curve for RDW was 0.818 (95% confidence interval 0.761–0.876). The area under the curve for RDW was higher in male patients than in female patients. The RDW correlated positively with the modified Rankin scale score after 3 months and the initial National Institutes of Health Stroke Scale score.

Initial higher RDW level is related to a 3-month poor functional outcome in patients undergoing thrombolytic therapy for acute ischemic stroke.

Abbreviations: AUC = area under the curve, CIs = confidence intervals, CRP = C-reactive protein, ED = emergency department, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, ORs = odds ratios, RDW = red blood cell distribution width, r-tPA = recombinant tissue-type plasminogen activator.

Keywords: cerebral infarction, emergency department, prognosis, red cell distribution width, stroke

1. Introduction

Acute ischemic stroke is the leading cause of disability and mortality throughout the world. The 30-day mortality rate after acute ischemic stroke is 14.2% in stroke unit patients and 20.9% in general ward patients.[1] Intravenous thrombolysis with recombinant tissue-type plasminogen activator (r-tPA) within 4.5 hours after symptom onset is an early effective treatment for patients with acute ischemic stroke.[2] Previous studies have demonstrated that higher National Institutes of Health Stroke Scale (NIHSS) scores and blood glucose levels are associated with a poor outcome for patients with acute ischemic stroke treated with intravenous thrombolysis.[3,4]

Red blood cell distribution width (RDW) is an indicator of the variation in circulating erythrocyte volume and is routinely measured during complete blood count analysis. RDW is commonly used in the differential diagnosis of various types of anemias and iron or vitamin deficiency. Previous studies have reported that elevated RDW is closely associated with inflammatory conditions, including cardiovascular events, multiple myeloma, sepsis, and chronic kidney disease.[5–8] Other recent studies have found that elevated RDW is significantly associated with mortality and a poor functional outcome in patients with acute ischemic stroke.[9–11]

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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However, few studies have focused on RDW as a prognostic marker of functional outcome in patients undergoing thrombolysis for acute ischemic stroke. Therefore, the purpose of our study was to investigate whether RDW is useful for estimating the 3-month functional outcome for patients undergoing thrombolysis for acute ischemic stroke and, if so, to establish a cutoff RDW value.

2. Materials and methods

2.1. Study population

This observational study was undertaken from January 2017 to April 2020 in the emergency department (ED) of Konkuk University Medical Center, an 835-bed tertiary institution in Seoul with about 58,000 ED visits annually.

The inclusion criteria were age ≥19 years and patients with acute ischemic stroke who received intravenous thrombolysis with r-tPA within 4.5 hours of their symptom onset. Acute ischemic stroke was diagnosed as sudden-onset neurological impairment and with magnetic resonance imaging at the ED. The exclusion criteria were a previous neurological disease, infection within the past month, blood transfusion in the past 4 months, current use of iron, vitamin B12, or folate, hepatic or renal disease, hematological disorder, or malignancy. The enrolled patients received intravenous administration of alteplase (0.9 mg/kg, maximum dose <90 mg) in the ED. Ten percent of the total dose was given by intravenous bolus, and the remainder was mixed with 50 mL of 0.9% saline and infused continuously for 1 hour.

The protocol for this study was approved by the ethics committee of the Konkuk University Medical Center, and individual informed consent was waived given the use of routinely measured laboratory data collected during the process of diagnosis and treatment in the ED. We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

2.2. Data collection and assessment

Peripheral venous blood samples were collected within 10 minutes of ED admission. The complete blood count with differential was analyzed using a Sysmex XN-9000 analyzer (Sysmex, Kobe, Japan).

Patient demographic characteristics, clinical features, radiology images, and laboratory data were collected. The initial NIHSS score was assessed before thrombolytic therapy, and the severity of the stroke was classified into 3 groups: mild (NIHSS 1–6), moderate (NIHSS 7–15), and severe (NIHSS ≥16). The functional outcome was determined at 3 months after ED admission; a poor functional outcome was defined as a modified Rankin Scale (mRS) score of 3 to 6. To assess the outcomes after 3 months, a review of the medical records or a telephone interview with the patient was conducted by a physician who was blinded to the clinical information.

2.3. Statistical analysis

IBM SPSS Statistics version 25 (IBM, Armonk, NY) and MedCalc version 19.6 (MedCalc Software, Ostend, Belgium) were used for all statistical analyses. Categorical variables are expressed as frequencies (percentages), and proportions were compared using the χ^2 test. Nonnormally distributed continuous variables are reported as median (25%–75% interquartile range) and were analyzed using the Mann–Whitney *U* test and Kruskal–Wallis test for intergroup differences.

A receiver-operating characteristic curve was applied to identify an optimal cutoff of RDW for predicting a poor functional outcome at 3 months. The area under the curve (AUC) and 95% confidence intervals (CIs) are reported.

Logistic regression analysis was performed to identify independent predictors of a 3-month poor functional outcome after thrombolysis, and the odds ratios (ORs) and 95% CIs were calculated. Spearman correlational analysis was performed to analyze the relationships between RDW, age, mRS score at 3 months, and NIHSS score at ED admission. All statistical testing was 2-sided, and $P < .05$ was considered to be significant.

Table 1

Baseline characteristics and outcomes of the enrolled patients.

Variable	Number (n = 240)
Age, yr	72 (62–80)
Male/female ratio	131/109
Comorbidities, n (%)	
Hypertension	153 (63.8)
Diabetes mellitus	68 (28.3)
Atrial fibrillation	88 (36.7)
Hyperlipidemia	44 (18.3)
Time from onset to ED arrival, min	49 (30–114)
NIHSS score	8 (5–14)
Mild (1–6)	98 (40.8)
Moderate (7–15)	100 (41.7)
Severe (≥16)	42 (17.5)
Vital signs	
Systolic blood pressure, mm Hg	157 (136–176)
Diastolic blood pressure, mm Hg	88 (77–98)
Pulse rate, beats/min	81 (71–93)
Respiratory rate, breaths/min	20 (18–20)
Body temperature, °C	36.6 (36.4–36.8)
Laboratory results	
WBC count, $\times 10^3/\mu L$	7.8 (6.2–9.6)
Hemoglobin, g/dL	13.7 (12.6–14.9)
Hematocrit, %	39.2 (36.6–42.3)
Platelet count, $\times 10^3/\mu L$	22.4 (18.7–25.9)
Blood glucose, mg/dL	127 (111–155)
CRP, mg/dL	0.14 (0.05–0.37)
RDW, %	12.9 (12.1–13.6)
Functional outcome	
Good (mRS score 0–2)	158 (65.8)
Poor (mRS score 3–6)	82 (34.2)
3-month mortality	6 (2.5)

Values are presented as median (25%–75% interquartile range) or number (%).
CRP = C-reactive protein, ED = emergency department, NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin Scale, RDW = red blood cell distribution width, WBC = white blood cell.

3. Results

3.1. RDW and clinical characteristics

Between January 2017 and April 2020, 240 patients were included in the study and observed for 3 months. The demographic and clinical characteristics, laboratory results, and outcomes of the enrolled patients are presented in Table 1. The median age was 72 (62–80) years and 131 (54.6%) patients were males. The median time from symptom onset to ED arrival

Table 2

Comparison of clinical characteristics and laboratory results between male and female patients.

Variable	Men (n = 131)	Women (n = 109)	*P*
Age, yr	70 (63–78)	72 (65–82)	.682
Time from onset to ED arrival, min	46 (30–102)	53 (30–136)	.345
NIHSS score	8 (5–14)	9 (5–14)	.429
WBC count, $\times 10^3/\mu L$	7.8 (6.2–9.5)	7.9 (6.3–9.7)	.790
Hemoglobin, g/dL	14.6 (13.5–15.7)	12.8 (11.9–13.8)	<.001
Hematocrit, %	41.6 (38.5–44.3)	37.4 (34.5–39.9)	<.001
Platelet count, $\times 10^3/\mu L$	210 (175–253)	231 (192–270)	.022
Blood glucose, mg/dL	128 (111–152)	127 (111–159)	.990
CRP, mg/dL	0.14 (0.06–0.35)	0.15 (0.05–0.44)	.825
RDW, %	12.6 (10.0–13.4)	13.1 (12.3–13.8)	.005
Poor outcome (mRS score 3–6)	38 (29.0)	44 (40.4)	.076

Values are presented as median (25%–75% interquartile range) or number (%).
CRP = C-reactive protein, ED = emergency department, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, RDW = red blood cell distribution width, WBC = white blood cell.

was 49 (30–114) minutes, and the median NIHSS score at ED admission was 8 (5–14).

The initial median clinical characteristics and laboratory results of the male and female patients are presented in Table 2. The median hemoglobin and hematocrit levels were significantly higher in men, and the median platelet count and RDW levels were significantly higher in women.

Enrolled patients were classified into 3 subgroups based on their NIHSS score at ED admission. The group with severe stroke (NIHSS ≥16) accounted for 17.5% (42/240) of all enrolled patients. The median RDW at ED admission was higher in the group with severe (13.1% [12.3–14.0]) and moderate (13.0% [12.2–13.7]) stroke than the group with mild stroke (12.5% [12.0–13.3]) ($P = .009$ and .022, respectively). The median RDW did not differ significantly between the moderate and severe NIHSS score groups ($P = .323$).

3.2. RDW and functional outcome

Six (2.5%) patients died, and 82 (34.2%) patients had a poor functional outcome (mRS score 3–6) at 3 months after intravenous thrombolytic therapy for acute ischemic stroke. The NIHSS score at ED admission was significantly higher in the poor functional outcome group than in the good functional outcome group (11 [7–18] vs 6 [4–11]; $P < .001$).

The median RDW was significantly elevated in patients who had a poor functional outcome (13.7% [13.1–14.5] vs 12.3% [12.0–13.1]; $P < .001$) (Fig. 1). The median white blood cell count and blood glucose and C-reactive protein (CRP) levels were higher in the poor functional outcome group than in the good functional outcome group. Other laboratory results (hemoglobin level, hematocrit, and platelet count) are listed according to the functional outcome in Table 3.

The AUC of RDW for predicting 3-month poor functional outcome was 0.818 (95% CI 0.761–0.876; $P < .001$) (Fig. 2). The optimal cutoff value for a 3-month poor functional outcome was 12.8%. The sensitivity was 86.6%, specificity was 68.4%, positive likelihood ratio was 2.74, negative likelihood ratio was 0.20, positive predictive value was 57.7, and negative predictive value was 90.8. The 3-month poor functional outcome was

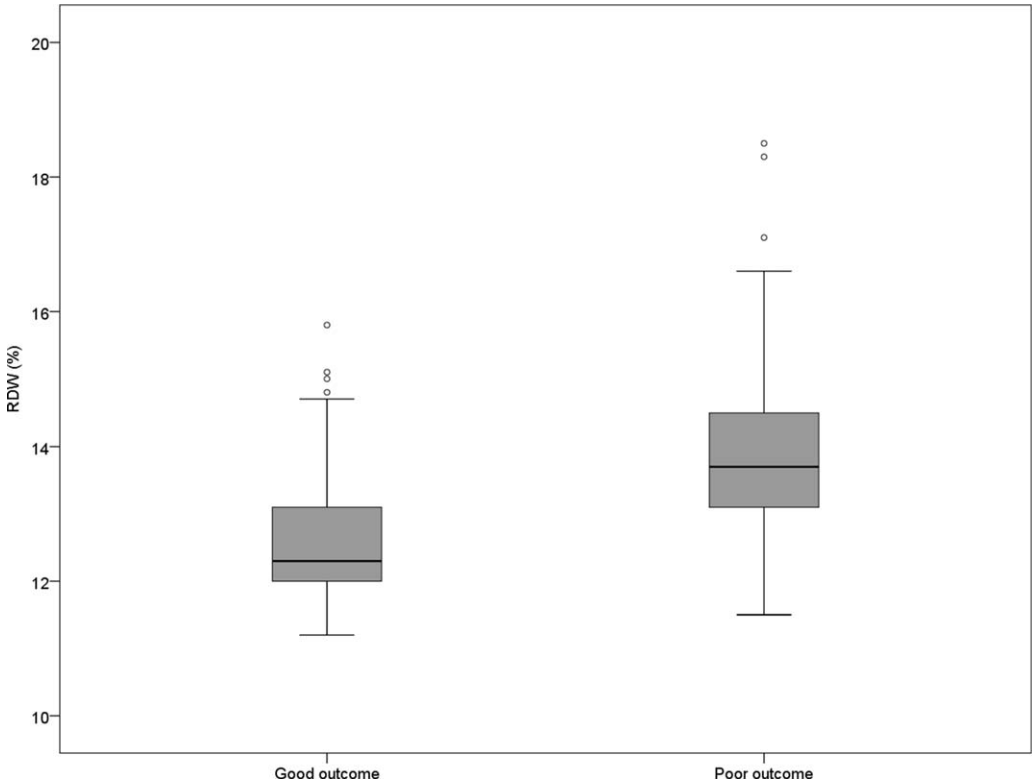

Figure 1. Differences in RDW according to functional outcomes. RDW = red blood cell distribution width.

Table 3

Clinical characteristics and laboratory results according to functional outcomes.

Variable	Good outcome (n = 158)	Poor outcome (n = 82)	*P*
Age, yr	68 (59–77)	78 (70–84)	<.001
Men/women	93/65	38/44	.076
Time from onset to ED arrival, min	46 (30–113)	53 (29–120)	.784
NIHSS score	6 (4–11)	11 (7–18)	<.001
WBC count, $\times 10^3/\mu L$	7.5 (6.2–9.1)	8.7 (6.3–10.4)	.044
Hemoglobin, g/dL	13.7 (12.9–15.1)	13.2 (11.8–14.5)	.008
Hematocrit, %	39.8 (37.5–42.8)	38.6 (34.3–41.7)	.008
Platelet count, $\times 10^3/\mu L$	228 (190–253)	210 (171–269)	.391
Blood glucose, mg/dL	124 (109–149)	133 (114–166)	.046
CRP, mg/dL	0.11 (0.04–0.29)	0.20 (0.07–0.75)	.003
RDW, %	12.3 (12.0–13.1)	13.7 (13.1–14.5)	<.001

Values are presented as median (25%–75% interquartile range) or number.

CRP = C-reactive protein, ED = emergency department, NIHSS = National Institutes of Health Stroke Scale, RDW = red blood cell distribution width, WBC = white blood cell.

58.7% in the higher RDW (>12.8%) group, and 9.2% in the lower RDW (≤12.8%) group ($P < .001$).

The AUC for RDW in male patients was 0.835 (95% CI 0.760–0.894; $P < .001$). The optimal cutoff value for 3-month poor outcome was >12.9%, with a sensitivity of 84.2% and specificity of 74.2%. The AUC for RDW in female patients was 0.783 (95% CI 0.694–0.857; $P < .001$). The optimal cutoff value in female patients >12.8%, with a sensitivity of 88.6% and specificity of 61.5%.

The AUC of the NIHSS score at ED admission for predicting 3-month poor functional outcome was 0.722 (95% CI 0.656–0.788; $P = .034$). The AUC was significantly higher for the RDW than for the NIHSS score at ED admission ($P = .033$).

Age, sex, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, time from symptom onset to ED arrival, NIHSS score at ED admission, white blood cell count, hematocrit, levels of hemoglobin, blood glucose, and CRP, and RDW were included in a logistic regression analysis to identify the independent predictors of 3-month poor functional outcome. In the univariable analysis, the following variables were associated with 3-month poor functional outcome: age (OR 1.069, 95% CI 1.041–1.098; $P < .001$); hypertension (OR 2.282, 95% CI 1.259–4.137; $P = .007$); NIHSS score at ED admission (OR 1.148, 95% CI 1.090–1.209; $P < .001$); hemoglobin level (OR 0.812, 95% CI 0.692–0.953; $P = .011$); hematocrit (OR 0.920, 95% CI 0.864–0.980; $P = .009$); CRP level (OR 1.370, 95% CI 1.083–1.733; $P = .009$); and RDW (OR 2.878, 95% CI 2.062–4.017; $P < .001$). In the multivariable analysis, the following variables were identified as independent predictors of 3-month poor outcome: age, NIHSS score at ED admission, CRP level, and RDW (Table 4).

The Spearman correlation coefficients were 0.305 ($P < .001$) for the association between RDW and age, 0.130 ($P = .004$) for

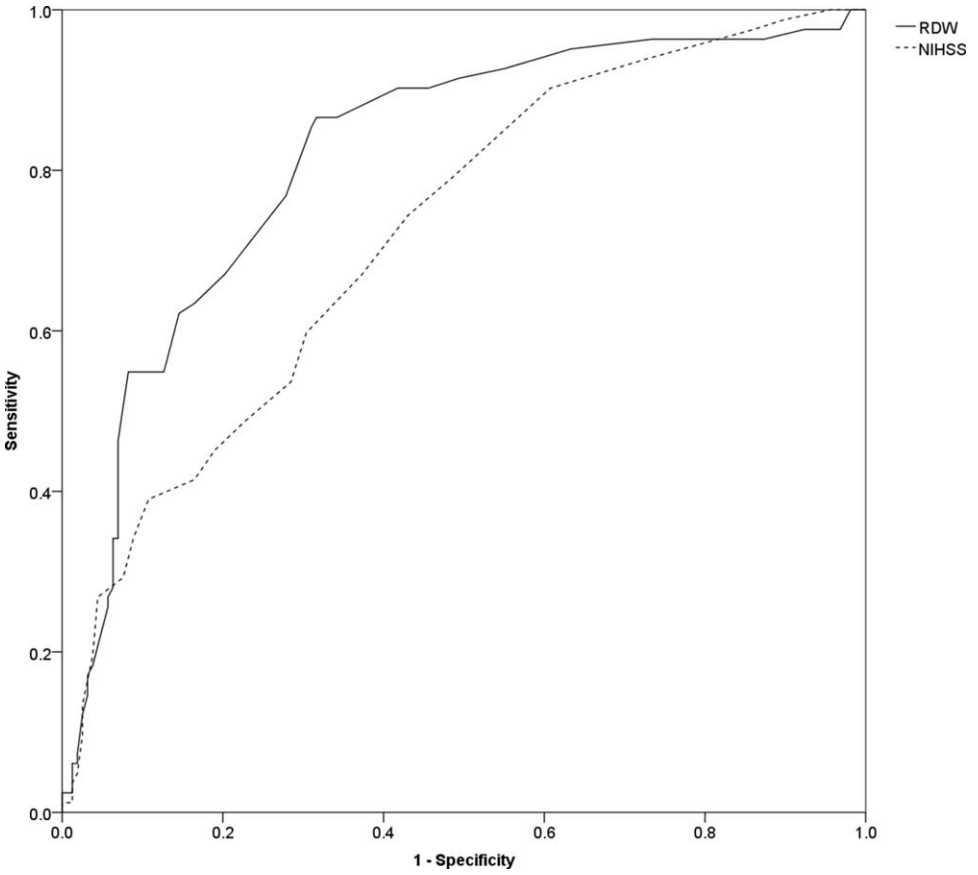

Figure 2. The receiver-operating characteristic curves of red blood cell width (RDW) for 3-month poor functional outcome. NIHSS = National Institutes of Health Stroke Scale, RDW = red blood cell distribution width.

Table 4

Multivariable logistic regression analysis to predict 3-month poor outcome.

Variable	Adjusted odds ratio (95% CI)	P
Age	1.057 (1.022–1.093)	.001
NIHSS	1.140 (1.071–1.213)	<.001
CRP	1.343 (1.027–1.758)	.031
RDW	3.369 (2.214–5.125)	<.001

CI = confidence interval, CRP = C-reactive protein, NIHSS = National Institutes of Health Stroke Scale, RDW = red blood cell distribution width.

the association between RDW and NIHSS score at ED admission, and 0.321 ($P < .001$) for the association between RDW and mRS score at 3 months.

4. Discussion

The present study evaluated the ability of RDW at ED admission to predict 3-month poor functional outcome (mRS score of 3–6) in patients undergoing thrombolytic therapy for acute ischemic stroke. The RDW at ED admission was significantly elevated in patients who subsequently had a poor functional outcome and seemed to be an independent predictor of 3-month poor functional outcome.

RDW is used mainly to help diagnose various types of anemia, but it has also been reported as a prognostic marker in hospitalized patients.[12] The mechanism underlying the association between a high RDW and poor outcome in patients with acute ischemic stroke remains unclear. The inflammatory response and oxidative stress are known to play an important role in ischemic stroke. Inflammation may affect iron metabolism and bone marrow function, and induce the premature release of large reticulocytes into the peripheral circulation.[13] Oxidative stress may lead to an increase in osmotic fragility and membrane damage of red blood cells, which may contribute to the increase in RDW.[14]

Previous studies have found that elevated RDW correlates consistently with older age. Cheng et al[15] reported that RDW tended to increase in parallel with age in a large healthy control group. Our study also found a significant association between increasing RDW and age ($r = .305$). Interestingly, in another study, RDW was an independent predictor of 1-year survival in older patients (≥75 years) with ischemic stroke treated with thrombolysis but not in younger patients (<75 years).[16] By contrast, Patel et al[17] reported a significant trend toward an increased risk of all-cause mortality with higher RDW in both middle-aged (45–64 years) and older adults (>65 years).

Kara et al[18] reported a significant association between elevated RDW and the severity of stroke, as indicated by the NIHSS score, in patients with acute stroke. Mohindra et al[19] also showed that stroke severity, as assessed by the initial NIHSS score, was related to higher RDW. By contrast, other studies have reported that RDW was not associated with stroke severity, as evaluated by the baseline NIHSS score.[11,20] In addition, Pinho et al[16] found no significant relationship between the initial NIHSS score and RDW in patients with ischemic stroke treated with intravenous thrombolysis. In our study, the RDW at ED admission was higher in the groups with moderate or severe stroke than that in the group with mild stroke but did not differ significantly between the moderate and severe groups ($P = .323$).

Several laboratory markers have been studied for their prognostic value in patients with acute ischemic stroke. Tu et al[21] reported that serum 25-hydroxyvitamin D level was an independent prognostic marker for death and functional outcome within 90 days in Chinese patients with acute ischemic stroke. Zhang et al[22] demonstrated that a higher neutrophil–lymphocyte ratio was associated with poor functional outcome at 3 months after ischemic stroke. Another study showed that serum sirtuin1 was significantly elevated in patients with acute ischemic stroke but did not correlate with functional outcome after 1 year.[23]

The main focus of our study was whether there is a relationship between RDW and functional outcome in patients who received thrombolytic therapy after acute ischemic stroke. In the present study, 34.2% of patients had a poor functional outcome at 3 months, and RDW was markedly elevated in the patients who later had a poor functional outcome. Age, initial NIHSS score, and CRP level were also related to a poor functional outcome at 3 months. Cong et al[24] reported that 38% of patients had a poor outcome after 90 days and that a high RDW (≥13.15%) and NIHSS score at 24 hours after ED admission were independent predictors of a poor outcome in patients who received thrombolytic treatment. In the study by Pinho et al,[16] a higher percentage of patients (55%) than in our study had a poor outcome, and the frequency of a poor outcome after 3 months was higher in patients with a high RDW. These finding suggest that differences in outcome between patients receiving thrombolytic therapy may be related to the severity of stroke at ED admission. By contrast, Shahsavarinia et al[25] reported that the baseline RDW did not correlate with outcome after a 3-month follow-up in patients who received tPA treatment. Ye et al[26] found that RDW was not associated with clinical outcome after 1 year but was significantly related to all-cause mortality.

Our study was included only patients given thrombolytic treatment and several studies have included all patients treated after acute ischemic stroke. A recent meta-analysis reported that elevated RDW is associated with a poor functional outcome at discharge and after 3 months.[10] By contrast, Ntaios et al[20] found that the RDW was not associated with stroke severity 1-year poor functional outcome in patients with acute ischemic stroke with 24 hours after last-well time.

Few studies have reported an optimal cutoff value of RDW for predicting outcomes in patients with acute ischemic stroke undergoing thrombolytic therapy. In our study, the AUC of the RDW for predicting 3-month poor outcome was 0.818. The optimal cutoff RDW for predicting 3-month poor outcome was determined as 12.8%, with 86.6% sensitivity and 68.4% specificity. These results suggest that the accuracy of the prediction of 3-month outcome was significantly higher in our study than the AUC of 0.663 reported by Cong et al,[24] who included 196 patients treated with r-tPA thrombolysis. They reported a suitable RDW cutoff of 13.15% for predicting 90-day poor functional outcome, with a sensitivity of 64.0% and specificity of 60.7%. The percentages of patients with a poor outcome were 34.2% in our study and 30% in the study of Cong et al, which suggests that the functional outcomes did not differ between studies.

To our knowledge, no studies have compared the prognostic value of RDW between male and female patients who received thrombolytic treatment. Some studies have found slightly higher RDW values in females than in males,[27,28] whereas others have reported no sex difference in RDW values between males and

females.[11,29] In our study, female patients had a slightly but significantly higher RDW value than male patients (13.1% vs 12.6%; $P = .005$). We found that the AUC value of RDW for 3-month poor outcome was higher in male patients than in female patients: 0.835 (95% CI 0.760–0.894) vs 0.783 (95% CI 0.694–0.857), respectively. For a cutoff value of >12.8% for RDW in female patients, the sensitivity and specificity for 3-month poor outcome were 88.6% and 61.5%, respectively. For a cutoff value of >12.9% for RDW in male patients, the sensitivity was 84.2%, which was lower than in female patients, but the specificity (74.2%) was higher than in female patients.

A previous study reported a significant correlation between the RDW and NIHSS score at ED admission ($r = .322$).[30] We found similar relationships, in that the RDW correlated with the NIHSS score at ED admission and with the mRS score after 3 months.

Hemoglobin and hematocrit levels are generally inversely correlated with RDW. Studies have reported an association between hemoglobin or hematocrit level and the outcome of ischemic stroke. In 1 study, a high hemoglobin level on admission was significantly associated with disability at the time of hospital discharge, but a low hemoglobin level was not associated with disability.[31] Kellert et al[32] reported that a low hemoglobin level was associated with a poor outcome at 3 months after ischemic stroke. A high hemoglobin level increases blood viscosity and can indicate iron overload, which may increase resistance to blood flow and decrease oxygen delivery, which in turn could worsen the prognosis after ischemic stroke. A low hemoglobin level reflects systemic inflammation and is associated with a poor outcome after ischemic stroke.[33] By contrast, Ozaita et al[34] reported that hematocrit was not associated with the short-term outcome of patients with cerebral infarction. In the univariable analysis in our study, hemoglobin level, hematocrit, and RDW were associated with a poor outcome. However, in the multivariable analysis, only RDW was associated with a poor outcome. We have not been able to analyze these results, and a large-scale prospective study will be needed in the future.

Our study has some limitations. First, this study was conducted at a single tertiary hospital and included a small number of patients. Therefore, the outcomes may not be generalized to all patients treated with intravenous thrombolysis. Second, RDW was measured only once at the time of ED arrival, and there were no further measurements. In addition, the CRP level was measured in this study, but other inflammatory biomarkers, such as platelet distribution width, neutrophil-to-lymphocyte ratio, and procalcitonin level, were not measured.

5. Conclusions

In conclusion, in our study, a higher RDW at ED admission, even if within the normal range, correlated independently with 3-month poor functional outcome after thrombolytic therapy. We found that the prognostic value of RDW in male patients was equal or superior to that of female patients. Although careful interpretation is needed because of the limited sensitivity and specificity, the RDW may be a useful marker for predicting 3-month functional outcome in patients undergoing thrombolytic treatment for acute ischemic stroke.

Author contributions

Conceptualization: Dae Young Hong.
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Investigation: Dae Yong Kim, Sin Young Kim.
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Supervision: Dae Young Hong.
Validation: Dae Young Hong, Kyeong Ryong Lee, Kwang Je Baek.
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Writing – review & editing: Dae Young Hong.

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