

ORIGINAL ARTICLE

ÖZGÜN ARAŞTIRMA

THE RELATIONSHIP BETWEEN ERYTHROCYTE DISTRIBUTION WIDTH (RDW) AND FUNCTIONAL STATUS IN PATIENTS WITH ACUTE ISCHEMIC STROKE WHO RECEIVED MECHANICAL THROMBECTOMY

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ABSTRACT

INTRODUCTION: Stroke ranks second among the diseases causing death worldwide and is a severe condition because of significant individual and societal consequences, especially prevalent in developing countries in epidemiological studies. Mechanical thrombectomy is recommended as a safe and effective treatment option for patients with acute ischemic stroke associated with large artery occlusion due to thrombus burden. High RDW (Red Blood Cell Distribution Width) values have been shown in patients with acute ischemic stroke to be associated with early mortality, poor functional recovery, and an increased risk of hemorrhagic transformation after intravenous thrombolytic treatment. In this study, we aimed to investigate the relationship between RDW values and the functional status of patients at discharge and 3 months who underwent mechanical thrombectomy in our region.

METHODS: 51 patients with acute ischemic stroke who presented to the emergency department between January 2018 and March 2022 were included. The discharge modified Rankin Scale (DmRS) and 3rd month modified Rankin Score were calculated, and those with DmRS equal to or less than 3rd month mRS were classified as Group 1 and those with 3rd month mRS greater than DmRS were classified as Group 2. RDW levels were compared between Group 1 and Group 2.

RESULTS: There was no significant difference in age and admission times between Group 1 and Group 2 ($p>0.05$). However DmRS, 3rd month mRS, initial NIHSS score and RDW values were significantly higher in Group 2 ($p<0.05$). A moderate positive correlation was found between difference of DmRS & 3rd month mRS and RDW levels ($p<0.05$, $0.29<r<0.70$).

DISCUSSION AND CONCLUSION: RDW was found to be associated with poor functional outcomes in ischemic stroke patients underwent mechanical thrombectomy in our region,. Larger and more comprehensive studies are needed in the future for the use of RDW in the determination of prognosis.

Keywords: Stroke, mechanical thrombectomy, prognosis, RDW, functional status.

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MEKANİK TROMBEKTOMİ YAPILAN AKUT İSKEMİK İNMELİ HASTALARDA ERİTROSİT DAĞILIM GENİŞLİĞİNİN (RDW) FONKSİYONEL DURUM İLE İLİŞKİSİ

ÖZ

GİRİŞ ve AMAÇ: İnme, dünya genelinde ölüme yol açan hastalıklar içinde 2. sırada yer alan, epidemiyolojik çalışmalarda özellikle gelişmekte olan ülkelerde yaygın, bireysel ve toplumsal sonuçları bakımından ağır bir hastalıktır. Akut iskemik inmede trombüs yükü ile ilişkili büyük arter oklüzyonu olan hastalarda güvenli ve etkin tedavi seçeneği olarak mekanik trombektomi yapılması önerilir. Yüksek RDW (Red Blood Cell Distribution Width) değerlerinin akut iskemik inmeli hastalarda erken dönemde ölüm, kötü fonksiyonel iyileşme, intravenöz trombolitik tedavi sonrası hemorajik transformasyon riskinde artış ile ilişkili olduğu gösterilmiştir. Biz de bu çalışmada bölgemizde mekanik trombektomi yapılan hastalarda RDW değerleri ile hastaların taburculuk sırasındaki ve 3. aydaki fonksiyonel durumu arasındaki ilişkiyi araştırmayı planladık.

YÖNTEM ve GEREÇLER: Ocak 2018 ile Mart 2022 tarihleri arasında hastanemizin acil polikliniğine başvuran 51 akut iskemik inme hastası dahil edilmiştir. Hastaların taburculuk modifiye rankin skoru (TmRS) ve 3. ay mRS hesaplandı, 3. ay mRS'u TmRS'ye eşit olan ve/veya TmRS'den küçük olanlar Grup 1, 3. ay mRS'u TmRS'dan büyük olan hastalar Grup 2 olarak sınıflandı. Grup 1 ve Grup 2 arasında RDW düzeyleri karşılaştırıldı.

BULGULAR: Grup 1 ile Grup 2 arasında yaş, işleme alınma süreleri arasında anlamlı bir farklılık tespit edilmezken ($p>0,05$), TmRS, 3. ay mRS, başvuru NIHSS değeri ve RDW değerlerinin Grup 2'de anlamlı olarak yüksek olduğu bulunmuştur ($p<0,05$). 3. ay mRS ile TmRS arasındaki fark ile RDW düzeyleri arasında orta düzeyde pozitif bir ilişki bulunduğu tespit edilmiştir ($p<0,05$, $0,29<r<0,70$).

TARTIŞMA ve SONUÇ: Bölgemizde mekanik trombektomi işlemi uygulanan iskemik inme hastalarında RDW'nin kötü fonksiyonel sonuçlar ile ilişkili olduğu tespit edilmiştir. RDW'nin prognoz tespitinde kullanılabilmesi için ileride yapılacak daha geniş popülasyonlu ve çok sayıda çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: İnme, mekanik trombektomi, prognoz, RDW, fonksiyonel durum.

INTRODUCTION

Mechanical thrombectomy as a safe and effective treatment option in Acute Ischemic Stroke Patients with Large Vessel Occlusion due to thrombus burden is a treatment recommended in the American Heart Association/American Stroke Association (AHA/ASA) treatment guideline with a class I, evidence A level recommendation for up to 24 hours in eligible patients (1).

RDW (Red Blood Cell Distribution Width), which means erythrocyte distribution width, is a value that measures the heterogeneity (anisocytosis) in the volume and size of circulating erythrocytes and can be obtained from a routine hemogram without any additional cost. It is calculated with the formula "Standard deviation of the red blood cell (RBC) /mean corpuscular volume (MCV) $\times 100$ ". High RDW value is an objective marker for anisocytosis (2). It is an indicator of the increase or ineffective production of erythrocytes and deterioration in erythrocyte structures that occur during the differentiation and maturation of erythrocytes as a result of chronic inflammation and oxidative stress (2-4).

Various studies in the literature have shown that high RDW values are associated with early death, poor functional recovery, and an increased

risk of hemorrhagic transformation after intravenous thrombolytic therapy in patients with acute ischemic stroke and that it is an independent potential risk factor for these conditions (5-10).

In the only multicenter study in the literature conducted in our country, it was also reported that high RDW is an independent indicator of poor functional prognosis in patients with acute ischemic stroke treated with mechanical thrombectomy (11).

In this study, we planned to research the relation between RDW values and the functional status of patients at discharge in patients who underwent mechanical thrombectomy in our region.

METHODS

Study order: Between January 2018 and March 2022, the data of patients who applied to the Emergency Polyclinic and were diagnosed with ischemic stroke based on anamnesis, clinical findings, and radiological examinations, in whom large vessel occlusion of the anterior system was detected on CT/catheter angiography, and who were treated with mechanical thrombectomy and admitted to the Neurological Intensive Care Unit were examined retrospectively. Approval for the

study was received from Inonu University Ethics Committee on 28/09/2022 with protocol number 2022/107. The study was carried out in accordance with the Ethical Standards of the Helsinki Declaration.

At our university hospital, a computerized data system (automation system) is used in all polyclinics and services, biochemistry and microbiology laboratories, including the radiology department, which provides access to patients' outpatient clinic examinations, laboratory information, consultations, and all other examinations.

Demographic, clinical, biochemical/hematological data and neuroradiological imaging of the patients were accessed using this automation system in our hospital, which is in routine use.

Inclusion or exclusion criteria of the patients in the study: The basic criteria in the study were that a definitive acute ischemic stroke diagnosis was made by excluding other possible causes (intracerebral hemorrhage, mass, trauma, cerebral venous thrombosis, etc.) in neuroradiological imaging and that the onset of stroke symptoms was within the first 6 hours from the time the patient was last seen well.

Patients who had a stroke for the first time, NIHSS (National Institutes of Health Stroke Scale Scores) ≥ 6 and < 25 , and ASPECT (The Alberta stroke program early CT score) ≥ 6 were included in the study.

Intravenous thrombolytic therapy was administered to eligible patients who were admitted within the first 4.5 hours.

Patients with nutritional anemias (iron deficiency, B12, folic acid deficiency, and B6 deficiency), other hematological diseases (such as sickle cell anemia and thalassemia) that are known to affect the RDW value, and patients with any history of malignancy, chronic (liver, kidney, etc.) and autoimmune disease, or patients who received one of these diagnoses during hospitalization were not included in the study.

Evaluation of functional and dependency status of the patients: The modified Rankin scale (mRS) is a standardized disability scale used in the follow-up of stroke patients, determining stroke severity, detecting dependency, and assessing functional improvements (12).

The last neurological examination (T-mRS) scores of the patients when they were discharged

from the clinic were calculated for the study. If the 3rd month neurological examination or mRS after discharge was recorded in the file, the 3rd month-modified Rankin scores (3rd month mRS) were calculated by considering this information. Patients' T-mRS and the 3rd month mRS evaluations were performed by the same neurologist.

In terms of functional status, patients were classified as Group 1, whose 3rd month mRS is equal to T-mRS and/or less than T-mRS, and Group 2, whose 3rd month mRS is more than T-mRS.

The groups were compared in terms of age, mRS, RDW, mechanical thrombectomy starting time, and NIHSS values.

Laboratory analysis: RDW values, a hematological parameter, were obtained from the hemogram taken from the patients' peripheral venous blood samples during their first admission. In our hospital, hemogram analyses are evaluated by an automatic nephelometric method using the Sysmex Corporation 1-5-1 Wakinahama-kai Gandari Chuo-ku, Kobe, 651-0073, Japan analyzer system.

Statistical analysis: SPSS Statistics 26.0 (Version 26.0, SPSS Inc., Chicago, IL, USA) package program was used for statistical analysis when assessing the findings obtained in the study. Continuous variables that follow normal distribution were expressed as mean \pm standard deviation, continuous variables that do not follow normal distribution were expressed as median (minimum-maximum), and categorical data were expressed as numerical values (%).

Kolmogorov-Smirnov test was used to analyze the data's suitability for normal distribution. Wilcoxon Test was used to analyze not-normally distributed data. RDW and mRS correlation analysis was performed with Spearman's correlation test. The statistical significance level was accepted as $p < 0.05$.

RESULTS

51 patients who met the criteria were included in the study. The mean age of the patients was 72.80 ± 13.77 years and 28 of them (54.9%) were women. While the mean value of TmRS was 4.14 ± 1.18 , the mean value of 3rd month mRS was 4.53 ± 1.9 . The number of patients who received intravenous thrombolytic therapy was 13 (25.5%) and those who did not receive was 38 (74.5%).

While the number of patients in whom complete recanalization was achieved was 26 (51%), those in whom complete recanalization was not achieved was 25 (49%). The number of patients with 3rd month mRS equal to and/or less than TmRS was 22 (%43.2), and the number of patients with 3rd month mRS greater than TmRS (Group 2) was 29 (51%) (Table 1). The average NIHSS value of the patients was 13.98±3.69, and the average RDW value was 14.46±2.07. The average time for patients to be taken to the procedure was determined as 184.12±73.98 minutes (Table 2).

While no significant difference was detected between age and taking to procedure time between Group 1 and Group 2 (p>0.05), TmRS, 3rd month mRS, admission NIHSS value and RDW values were found to be significantly higher in Group 2 (p<0.05) (Table 2).

It was determined that there was a moderate positive relationship between the difference between 3rd month mRS and TmRS and RDW levels. (p<0.05, 0.29<r<0.70) (Table 3).

ROC curve analysis method was used to determine RDW value separating Group 1 and

Group 2, using the Youden index maximization method. For RDW, the area under the ROC curve (AUC) was calculated as 0.701 (95% Confidence interval (CI) 0.521-0.792) (Figure). In the ROC curve analysis for patients with 3rd month mRS higher than TmRS, the cut-off value for RDW was determined as 14.15, specificity was 58.6%, sensitivity was 77.3% and accuracy was 66.7% (Table 4).

Table 1. Frequency distributions.

Gender (n) (%)	
Male	23 (45.1%)
Female	28 (54.9%)
Age distribution (n) (%)	
<= 60	8 (15.7%)
61 - 75	16 (31.4%)
76 - 85	18 (35.3%)
85 +	9 (17.6%)
Modified Rankin Scale (n) (%)	
Group 1	26(56.8%)
Group 2	25 (43.2%)
Intravenous thrombolytic therapy	
Applied	13(25.5%)
Not-applied	38(74.5%)
Complete recanalization	
Provided	26 (51%)
Not-provided	25 (49%)
Total	51 (100%)

Table 2. Analyses of variables (Mean±SD/Min-Max).

	Group 1(n=25) (49%)	Group 2 (n=26) (51%)	Total (n=51) (100%)	p
Age (year)	68.45±15.66/27-86	76.1±11.35/47-90	72.8±13.77/27-90	0.051
TmRS	3.27±1.32/1-5	4.79±0.41/4-5	4.14±1.18/1-5	0.000*
3rd month mRS	2.59±1.3/1-5	6±0/6-6	4.53±1.9/1-6	0.000*
RDW	13.75±1.63/11.6-18.1	15±2.22/11.9-21.7	14.46±2.07/11.6-21.7	0.015*
Admission NIHSS**	12.5±3.84/7-18	15.1±3.19/8-24	13.98±3.69/7-24	0.023*
Starting Time (minutes)**	177.27±81.19/60-330	189.31±69.02/90-330	184.12±73.98/60-330	0.493

*Statistically significant at 0.05 level** Shows normal distribution. T Test, all other variables were analyzed by Mann Whitney U Test. Abbreviations: mRS: modified Rankin scale, TmRS: modified Rankin scale at discharge, NIHSS: National Health Stroke Scale, RDW: Red blood cell distribution width.

Table 3. Discharge with RDW-3rd-month mRS values relationship Spearman Correlation Test (r (p)).

	RDW
TmRS	0.44 (p=0,001*)
3rd-month mRS	0.43 (p=0,001*)
TmRS-3rd-month mRS %	0.30 (p=0,032*)

*Statistically significant at 0.05 level. Abbreviations: TmRS: modified Rankin scale at discharge, RDW: Red blood cell distribution width.

Table 4. Group 1/Group 2 RDW level ROC analysis.

Cut-off	14.15
Specificity	58.6%
Sensitivity	77.3%
Accuracy	66.7%
Area Under the Curve (AUC)	0.701
%95 CI	0.521-0.792
p	0.025*

*Statistically significant at 0.05 level.

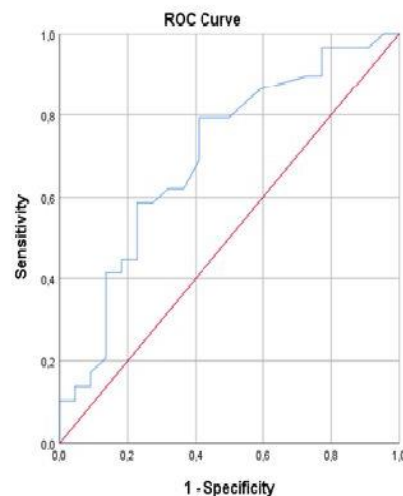


Figure. Group 1/Group 2 RDW level ROC curve graph.

DISCUSSION AND CONCLUSION

As a result of our study, we found that RDW is associated with poor functional outcomes in ischemic stroke patients who underwent mechanical thrombectomy in our region.

Stroke is a common disease that ranks second among the diseases, which causes death worldwide and is severe in terms of individual and social consequences. Its incidence is reported to be increased in young people aged 20-54, especially in developing countries and in older individuals in epidemiological studies (13). However, today there is no treatment method other than intravenous thrombolytic therapy and mechanical thrombectomy that targets reperfusion in the acute phase treatment of ischemic stroke and can only be applied within a narrow period and to patients who meet certain criteria (14,15). With mechanical thrombectomy, intraarterial plasminogen activators directly affect the clot and restore perfusion (16). Endovascular mechanical thrombectomy can restore vascular patency of these vessels between 41% to 54% of the time and can be used as an alternative and synergistic method to restore blood flow (17,18).

Many studies on RDW have been conducted to date, and its predictive role in the prognosis and diagnosis of various vascular diseases such as myocardial infarction, coronary artery disease, atrial fibrillation, pulmonary embolism, deep venous thrombosis, and cerebral venous thrombosis has been investigated (19-23).

Studies have been conducted on stroke, showing that it is generally predictive of prognosis and functional outcomes (24). Mohindra et al. found a significant relationship between neurological function status severity and RDW levels in acute ischemic stroke patients (25). Another study by Ani et al. showed that basal RDW values of ex-ischemic stroke patients were higher than other patients (8), and Ye et al. showed that high RDW values were an independent biomarker for mortality in patients treated with intravenous thrombolysis (26). High RDW value was shown to be an independent prognostic factor associated with 3rd-month functional outcomes and 30-day mortality in stroke patients (27). Another study in the literature found that the risk of haemorrhagic transformation after thrombolytic treatment increased with the increase in RDW value (28).

A multicentre study by Akpınar et al. found

that increased RDW value was associated with poor functional outcomes in ischemic stroke patients who underwent mechanical thrombectomy (11). It was also demonstrated that the RDW value is significantly higher in ischemic stroke patients with high NIHSS. The results of our study carried out in our region also supported the literature.

Although pathophysiological mechanisms underlying RDW causing poor functional outcomes in stroke patients are not clear, it is predicted that inflammation and oxidative stress play important roles. Inflammatory cytokines associated with chronic inflammatory conditions such as IL-1, tumor-necrosis alpha, and interferon gamma affect the production and maturation of red blood cells in the bone marrow, causing anisocytosis development and an increase in RDW. Erythrocytes with high RDW circulate less in the microcirculation, leading to a decrease in tissue oxygenation. As a result, this facilitates penumbra loss, which leads to poor functional outcomes. It is known that inflammation shortens red blood cell lifespan and causes red cell damage by inhibiting its production (29), and erythropoiesis impairment worsens ischemic symptoms (30). Another mechanism is that in the case of anisocytosis, nitric oxide activity is inhibited and the ability of vasodilation in the arteries is lost (31). Oxidative stress is also thought to cause damage to protein and lipid structures, a decrease in red blood cell fragility, and an increase in the RDW value by causing red blood cell damage (32). It was shown that as abnormal increases in RDW value accelerate erythrocyte destruction and ineffective erythrocyte production, it also accelerates atherosclerosis and leads to thickening of the carotid intima (33). It was demonstrated that high RDW values are positively correlated with the cholesterol content in the erythrocyte membrane, which causes atherosclerotic plaque rupture (34). Considering this information, it can be thought that high RDW values can trigger ischemic events.

RDW cut-off value associated with poor functional outcomes in patients who underwent mechanical thrombectomy was determined as 14.15, its specificity was 58.6%, and its sensitivity was 77.3% in our study. In the literature, although there are studies on acute treatment of ischemic

stroke in which ROC curve analysis was used only in relation to iv thrombolytic application (26,35), a comparison could not be made as there is no ROC curve analysis on the poor functional outcomes of patients who underwent mechanical thrombectomy.

There are various limitations in our study. While the single-center nature of the study is one of these limitations, another one is that blood loss, infection, and inflammation, which are common in intensive care patients, can lead to an increase in RDW value, which can be confusing. Lack of repeated measurements of RDW is another reason for the limitation.

Consequently, it was proven that high RDW values are associated with poor functional outcomes in ischemic stroke patients who underwent mechanical thrombectomy. For the use of RDW in detecting stroke patients with a poor prognosis, future studies with larger populations and larger numbers are needed to be made.

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Ethics

Ethics Committee Approval: The study was approved by Ethical Committee of İnönü University (Date: 28.09.2023, No: 2022/107).

Informed Consent: The author declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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