Original Article Ann Med Res 2022;29(10):1062–1066

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Red cell distribution width (RDW) and Alberta stroke programme early computed tomography score (ASPECTS) are correlated in predicting mortality in geriatric ischemic stroke patients

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ARTICLE INFO

Keywords:
Cerebrovascular disease
Stroke
Mortality
Red cell distribution width

Received: Feb 11, 2022
Accepted: Sep 21, 2022
Available Online: 22.10.2022

DOI:
10.5455/annalsmedres.2021.10.573

Abstract

Aim: Ischemic stroke is one of the leading causes of death and disability in elderly people worldwide. The aims of this study were to investigate the relationship of hematologic parameters and Alberta Stroke Programme Early Computed Tomography Score (ASPECTS) with mortality in geriatric patients suffering an ischemic stroke.

Materials and Methods: Geriatric ischemic stroke patients referring to our hospital between May 2016 and May 2019 were retrospectively analyzed. ROC curve analysis was performed to determine the predictive value of hematologic parameters with respect to in-hospital mortality. Multivariate logistic regression analysis was performed to determine the independent predictors of in-hospital mortality.

Results: The neutrophil count, monocyte count, red cell distribution width, neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio were significantly higher, whereas the lymphocyte count was significantly lower in patients who died in the hospital than in those who did not. The areas under the curve for the red cell distribution width, neutrophil-lymphocyte ratio, and monocyte-lymphocyte ratio were 0.720, 0.643, and 0.660, respectively. In the logistic regression analysis, age, female sex, ASPECTS, monocyte-lymphocyte ratio and red cell distribution width were identified as independent predictors of in-hospital mortality. In the correlation analysis, a weak negative correlation was found between the ASPECTS and the red cell distribution width ($r = 0.303$, $p < 0.001$).

Conclusion: The red cell distribution width, monocyte-lymphocyte ratio, and ASPECTS are independent predictors of in-hospital mortality in geriatric ischemic stroke patients. There is a correlation between the ASPECTS and the red cell distribution width.

Introduction

A stroke is a focal neurological condition that develops as a result of the disruption of cerebrovascular blood flow and is the most frequent cause of death in the geriatric age group following myocardial infarction. Stroke refers to a broad group of conditions, including hemorrhage, thrombosis, and embolism. Ischemic strokes, which account for 80–85% of all strokes, are the result of thrombosis and embolism and are among the most frequent causes of disability. Smoking, hypertension, diabetes, coronary artery disease, and atrial fibrillation are modifiable risk factors for ischemic stroke [1,2].

Inflammation plays a role in the formation of brain ischemia and inflammatory processes and makes it easier for life-threatening complications to occur [3]. Proinflammatory chemokines are secreted from ischemic brain tissue and trigger the migration of leukocytes to the inflammation area via trans-endothelial migration [4]. Platelets also play a significant role in the pathogenesis of atherosclerotic diseases. Several studies have investigated the prognostic value of the mean platelet volume (MPV) in myocardial infarction, heart failure, pulmonary embolism, and stroke [5].

Inflammatory reactions are also related prognostic markers [6,7]. Blood hemoglobin levels and the red cell distri-

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bution width (RDW) have been shown to be independent prognostic factors of morbidity and mortality in conditions such as heart failure, myocardial infarction, and stroke [8,9]. A high RDW is associated with mortality and poor prognosis, especially due to heart failure and myocardial infarction [10,11].

For early diagnosis, the Alberta Stroke Program Early CT Score (ASPECTS) is used. This scoring system grades the clinical weight of a stroke and is thus used as a strong prognostic factor. It is also a strong predictor of reperfusion after endovascular thrombolytic treatment [12].

Although, many studies explored clinical and laboratory prognostic markers of ischemic stroke, the results are still inconclusive. Therefore, it is important to continue the research to identify risk factors and prognostic markers. The inexpensive and easily accessible nature of such markers is important in terms of increasing usability in daily practice. We investigated the effects of hematologic parameters on ischemic stroke patient mortality in this study. We also examined whether there was a relationship between the ASPECTS and hematologic parameters in these geriatric patients.

Materials and Methods

This study was approved by the Ethics Committee of Harran University, Şanlıurfa, Turkey (E35548; August 28, 2019). We retrospectively investigated the blood parameters and cranial images of ischemic stroke patients referring to our hospital between May 2016 and May 2019. The study included geriatric patients aged ≥65 years who referred to the hospital within 12 hours of developing stroke symptoms and had blood work and cranial computerized tomography (CT) performed within four hours after referral to the hospital. Patients under the age of 65, patients with malignancy, hematologic diseases, or late-stage liver or kidney diseases, patients who had undergone a blood transfusion up to four months prior to referral, patients suffering a trauma-related ischemic stroke, and pregnant patients were excluded.

Cranial CT images were taken from all patients (except for patients in whom CT is not recommended due to pregnancy status and imaging method cannot be performed immediately due to severe general condition deterioration) when they visited the hospital. The scans were performed using adjacent non-contrast axial 5-mm cross sections. The ASPECTS was subsequently determined by at least two radiologists separately, with the final score determined by calculating the average values. The radiologists were blinded to all clinical data.

Clinical data were obtained from the hospital's medical record database. These data were age, sex, comorbid diseases (hypertension, diabetes, coronary artery disease, previous cerebrovascular diseases [CVD]), neutrophil, lymphocyte, and monocyte percentages, hemoglobin concentration, red cell distribution width (RDW), hematocrit, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), mean platelet volume (MPV), and ASPECTS calculated based on CT images. Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), MPV/lymphocyte ratio, and MCV/lymphocyte ratio are calculated after collecting these data. The end point of this study was in-hospital mortality. The patients were divided into two groups: those who died in the hospital and those who did not. Demographic data, hematologic parameters, and ASPECTS were compared between the two groups. For the patients who died in the hospital, the variables were analyzed to determine whether they were independent predictors of mortality and identify possible correlations between them.

Statistical analysis

The data were analyzed using IBM SPSS (Statistical Package for Social Sciences) Statistics 22.0 (IBM SPSS, Chicago, IL, USA). The normality of the data was assessed with the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as means ± standard deviations and compared using Student's t-test. Non-normally distributed continuous variables were expressed as medians (25th–75th percentiles) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-squared test. Pearson and Spearman correlation coefficients were used for correlation analysis. To determine the predictive value of hematologic parameters with respect to in-hospital mortality, receiver operating characteristic (ROC) curve analysis was performed. Multivariate logistic regression analysis with backward elimination was performed to determine the independent predictors of in-hospital mortality. Values of $p \leq 0.05$ were considered statistically significant.

Results

A total of 237 patients, 129 (54.4%) males and 108 (45.6%) females, were included in the study. Their mean age was 73.37 ± 7.67 years. The median time of hospital stay was 5 (range: 3–11) days. The in-hospital mortality rate was 18.1% (43 patients).

Table 1 shows a comparison of baseline characteristics between the patients who died in the hospital and those who did not. The patients who died were older than those who

Table 1. Comparison of baseline characteristics of patients who died in the hospital and those who did not.

	In-hospital mortality (+) (n = 43)	In-hospital mortality (-) (n = 194)	P
Age, years	83.30 ± 7.77	73.61 ± 8.21	<0.001
Female sex (%)	26 (60.5)	82 (42.3)	0.030
Hypertension (%)	29 (67.4)	112 (57.7)	0.241
Diabetes mellitus (%)	13 (30.2)	53 (27.3)	0.700
Previous CVD (%)	15 (34.9)	27 (13.9)	0.001
Cardiovasculer diseases (%)	13 (30.2)	35 (18)	0.072
Hospital stay, days	16 (4-35)	4 (3-9)	<0.001
ASPECTS	6 (4.5-7)	8 (6-8)	<0.001

Values are shown as mean ± standard deviation or median (range between 25-75. quarters). CVD: Cerebrovascular disease, ASPECTS: Alberta Stroke Program Early CT Score.

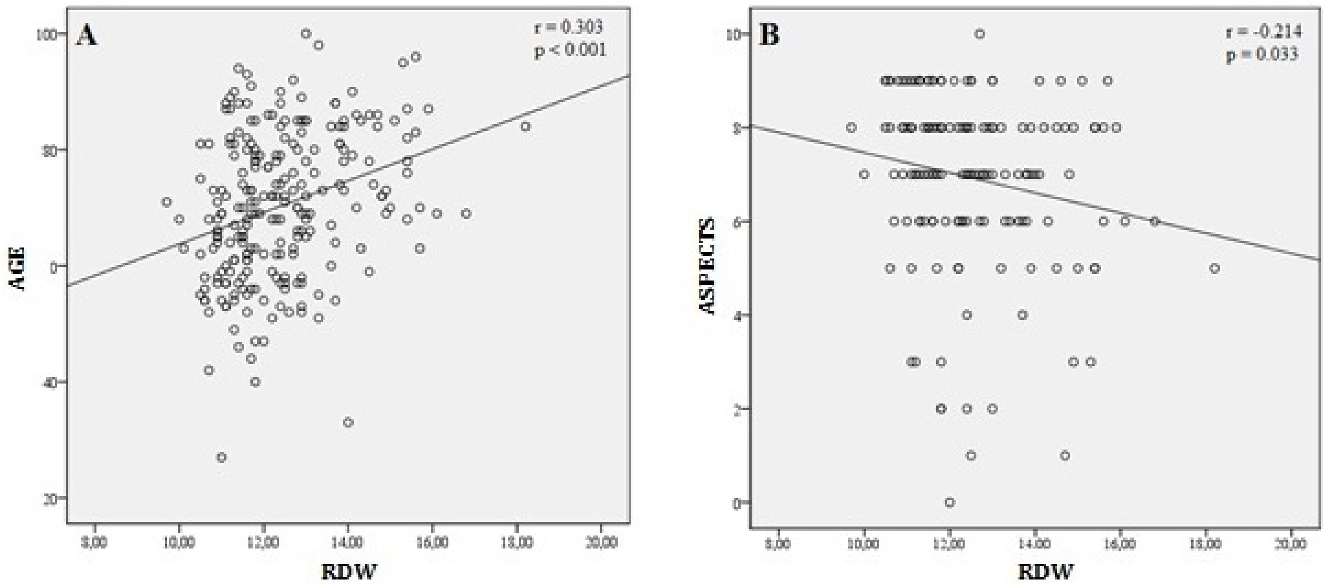

Figure 1. A: Correlation analyse between age and RDW. B: Correlation analyse between age ASPECTS and RDW.

Table 2. Comparison of hematological parameters of patients who died in the hospital and those who did not.

	In-hospital mortality (+) (n = 43)	In-hospital mortality (-) (n = 194)	P
Neutrophil, × 10^3/μL	7.10 (5.10-11.60)	5.70 (4.50-7.90)	0.005
Lymphocyte, × 10^3/μL	1.70 (1.20-2.90)	2.20 (1.60-2.80)	0.033
Monocytes × 10^3/μL	0.73 ± 0.40	0.57 ± 0.21	0.019
Hemoglobin, g/dL	13.82 ± 2.15	14.04 ± 1.93	0.500
Hematocrit (%)	42.62 ± 6.05	42.71 ± 5.63	0.928
MCV, fL	89.72 ± 5.93	88.70 ± 7.33	0.395
MCH, pg	29.27 ± 2.71	29.37 ± 3.62	0.864
MCHC,g/dL	32.59 ± 1.68	32.88 ± 1.80	0.328
RDW (%)	13.35 ± 1.60	12.22 ± 1.28	< 0.001
MPV, fL	8.18 ± 1.31	7.93 ± 1.64	0.350
Platelets, × 10^3/μL	235.78 ± 75.93	236.93 ± 70.53	0.929
Neutrophil/Lymphocyte ratio	3.93 (2.24-9.25)	2.58 (1.75-4.33)	0.003
Platelet/ Lymphocyte ratio	148.35 ± 95.16	123.78 ± 68.07	0.139
Monocyte/ Lymphocyte ratio	0.36 (0.22-0.56)	0.25 (0.19-0.33)	0.001
MPV/Platelet ratio	0.03 (0.02-0.04)	0.03 (0.02-0.04)	0.735
MPV/ Lymphocyte ratio	4.8 (3.4-6.4)	3.6 (2.6-4.9)	0.017
MCV/Platelet ratio	0.38 (0.31-0.49)	0.38 (0.33-0.46)	0.974
MCV/ Lymphocyte ratio	56.7 (32.5-73.3)	40.4 (30.7-55.1)	0.028

Values are shown as mean ± standard deviation or median (range between 25-75. quarters) MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, MPV: mean platelet volume.

did not ($p < 0.001$). The in-hospital mortality rate was significantly higher in female than in male patients ($p = 0.030$). The frequency of previous CVDs was higher ($p = 0.001$), and hospital stay duration was longer ($p < 0.001$), whereas the ASPECTS was significantly lower ($p < 0.001$) in patients who died in the hospital than in those who did not.

Table 3. Independent predictors of in-hospital mortality.

	Odds ratio	95% CI	P
Age	1.058	1.007 - 1.112	0.025
Female sex	3.421	1.145 – 10.223	0.028
ASPECTS	0.667	0.511-0.872	0.003
Monocyte/Lymphocyte ratio	1.039	1.016 – 1.063	<0.001
RDW	1.451	1.144 – 2.015	0.034

Included parameters: age, sex, hypertension, diabetes mellitus, previous cerebrovascular diseases, Neutrophil/Lymphocyte Ratio, Monocyte/Lymphocyte Ratio, RDW, MPV/Lymphocyte ratio, MCV/Lymphocyte ratio, ASPECTS ASPECTS: Alberta Stroke Program Early CT Score, RDW: Red cell distribution width.

Table 2 shows a comparison of hematologic parameters between the patients who died in the hospital and those who did not. The neutrophil count ($p = 0.005$), monocyte count ($p = 0.019$), RDW ($p < 0.001$), NLR ($p = 0.003$), MLR ($p = 0.001$), MPV/lymphocyte ratio ($p = 0.017$), and MCV/lymphocyte ratio ($p = 0.028$) were significantly higher, while the lymphocyte count ($p = 0.033$) was significantly lower in patients who died in the hospital.

The correlation analysis revealed a weak negative correlation between the ASPECTS and the RDW ($r = -0.214$, $p = 0.033$) and a positive correlation between age and the RDW ($r = 0.303$, $p < 0.001$; Figure 1).

In the ROC curve analysis, the areas under the curve (AUC) for the RDW, NLR, MLR, MPV/lymphocyte ratio, and MCV/lymphocyte ratio were 0.720, 0.643, 0.660, 0.617, and 0.607, respectively (Figure 2).

The multivariate logistic regression analysis with backward elimination was performed to determine the indepen-

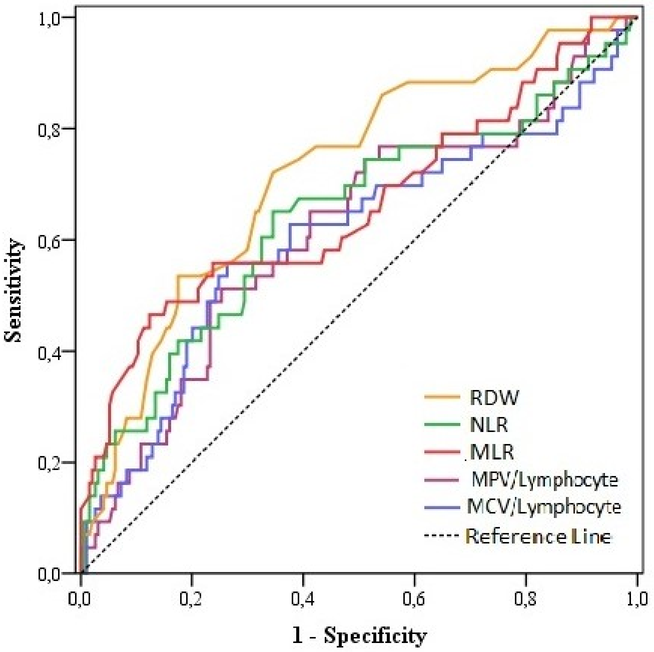

Figure 2. Determination of predictive values of hematological parameters in showing in-hospital mortality by ROC curve analysis.

dent predictors of in-hospital mortality. in-hospital mortality. Age, sex, hypertension, diabetes mellitus, previous cerebrovascular diseases, Neutrophil/Lymphocyte Ratio, Monocyte/Lymphocyte Ratio, RDW, MPV/Lymphocyte ratio, MCV/Lymphocyte ratio and ASPECTS were included into full model. It was found that age, female sex, ASPECTS, MLR, and RDW were independent predictors of in-hospital mortality (Table 3).

Discussion

In this study, we examined the relationship between hematologic parameters and in-hospital mortality in acute ischemic stroke patients, as well as the relationship between the ASPECTS and hematologic parameters. RDW, MLR, and ASPECTS were found to be independent predictors of in-hospital mortality. The RDW was determined to be the strongest predictor. Also, a correlation between the ASPECTS and the RDW was observed.

Ischemic strokes are prevalent worldwide and are among the most frequent causes of disability and death in the geriatric age group. Age and sex are significant factors in its epidemiology, with age being the stronger factor. The mean age of ischemic stroke patients ranges between 63 and 72 years in the literature [13]. The incidence of stroke is higher in males than in females, but the older the age, the more frequently it is seen in women and the higher the mortality rate [14]. Accordingly, in our study, ischemic strokes were more frequent in males, but the in-hospital mortality rate was higher among females.

In recent years, the number of studies on the prognostic factors of ischemic stroke has increased. The most important reason for this is that prognosis guides the treatment approach. Several prognostic factors have been identified thus far [15]. Hemogram examination is the most widely accepted factor, as it is an inexpensive, objective, and easy-to-perform test, and its parameters are strong inflammatory markers.

No mechanism has been clearly identified that explains the prognostic ability of hematologic parameters. Some studies have associated them with the effect of inflammation. Several studies have reported that the RDW and NLR positively correlate with clearly defined inflammation parameters, such as C-reactive protein and the erythrocyte sedimentation rate [2,7,16,17]. Inflammation response is accepted as one of the significant factors participating in the pathophysiological process of ischemic stroke [18]. Ischemic brain tissues release strong proinflammatory chemokines that activate leukocytes and promote their migration to the trans-endothelial inflammation zone [4]. After an ischemic stroke, the secretion of proinflammatory cytokines and leakage of immune cells lead to disruption of the blood-brain barrier and progression of secondary neuronal injury, which makes brain edema and the infarction volume more severe [19]. In our study, while the RDW, MLR, and NLR differed significantly between the patients who died in the hospital and those who did not, multivariate regression analysis indicated only the RDW and MLR as independent predictors of in-hospital mortality.

In line with our findings, several studies have reported that the mean RDW is higher in patients suffering a stroke than healthy individuals. A broad-scoped meta-analysis including 11.827 patients found a significant relationship between high RDW values and mortality [20], estimating that for each 1% increase in RDW, the mortality rate increased by 14%. While this increase was associated with many comorbid situations, it was also observed in elderly patients with no medical conditions. The authors thus concluded that the RDW combined with an advanced age has a significant effect on mortality. Similarly, age was one of the independent risk factors in our study. There was also a positive correlation between age and the RDW. While the mechanism whereby the RDW increases with age has not been clearly explained, it has been associated with inflammation and oxidative stress. Inflammation and oxidative stress increase the cholesterol level in the erythrocyte membrane and lead to erythrocyte malformation. Moreover, they disrupt iron metabolism, inhibit erythropoietin production or response, and reduce the lifespan of erythrocytes. These effects are thought to lead to an increase in RDW [21].

The MLR, the other independent predictor of mortality among hematologic parameters in our study, is a marker that could be used in stroke-related immunosuppression [22], as it is known that immunomodulatory treatment increases survival.

Clinical data suggest that high leukocyte and neutrophil counts increase the severity of stroke at the early stages of ischemia. A high neutrophil count has been associated with poor prognosis, especially in the third month, while a low lymphocyte count has been identified as an indicator of poor prognosis in the first week [23]. Our results are consistent with these findings.

The ASPECTS is a scoring system used to determine the size of the ischemic and stroke areas. Based on this, information is gathered about the suitability of the patient for thrombolytic treatment. In patients suffering a stroke, the

ASPECTS is among the factors that determine treatment effectiveness and complication development. Two studies found that two different scores (8–10 and 0–7) changed the effect of endovascular thrombolytic treatment [24,25]. In both studies, only patients with high scores (8–10) derived a benefit from endovascular revascularization treatment. Also, these studies reported that a high ASPECTS is an indicator of good prognosis. Similarly, a low ASPECTS was found to be a predictor of in-hospital mortality in our study. It is known that with prolonged time after a stroke, the ongoing ischemic process increases the injury to cerebral tissue. Previous studies have found changes in CT images, and therefore the ASPECTS, with prolonged time. For this reason, we included only cases with CT scans obtained at the early stage.

To our knowledge, no previous studies have examined the relationship between the ASPECTS and hematologic parameters and thus inflammation. The observed correlation between the ASPECTS and the RDW has significant clinical implications.

Conclusion

This study shows that the RDW, MLR, and ASPECTS are independent predictors of in-hospital mortality. It also reveals a correlation between the ASPECTS and RDW (but a weak correlation), which further increases the prognostic value of the latter. Future studies could use the RDW along with the ASPECTS to determine the treatment protocol for ischemic stroke.

Limitations

The most important limitation of our study is its retrospective, single-center design. Some data could not be accessed in the patient files and more data could not be included in the multivariate regression analysis. More robust data could be obtained by broad-scoped prospective studies with larger patient cohorts.

Ethics approval

This study was approved by the Ethics Committee of Harran University, Şanlıurfa, Turkey (E35548; August 28, 2019).

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