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Effects of hematological parameters on long term mortality in acute ischemic stroke patients

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ABSTRACT

Aims: Mortality can be seen in acute ischemic stroke (AIS) in the early or late period. We investigated the role of mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and stroke volume in late-term mortality.

Methods: This retrospective cross-sectional study included 132 AIS patients who applied to the emergency department of a university hospital over a consecutive 12-month period. Some patientswere excluded from the study according to the exclusion criteria. Patients were divided into groupsas survivors and deceased. MPV, NLR, PLR levels in each group were evaluated according to theNational Institutes of Health Stroke Scale (NIHSS) scores. Diffusion-weighted MR images (DWIMRs) were evaluated and the infarct volumes of the patients were calculated.

Results: The data of a total of 83 AIS patients who remained after exclusion were analyzed. The mean age, NIHSS score and infarct volume of the deceased were statistically significantly higher than the survivors ($p<0.01$, $p=0.026$, $p=0.021$, respectively). According to Spearman's analysis, NLR, MPV and PLR were negatively correlated with Glasgow Coma Scale (GCS) at presentation, while they were positively correlated with NIHSS and infarct volume. In ROC curve analysis, the optimal cut-off values of NLR, MPV and PLR as predictors of long-term mortality were determined as 4.68, 7.20and 167.66, respectively. At this level, their sensitivities were 54.84, 48.39, 61.29, respectively, their specificities were 75, 73.08, 73.8, respectively, their positive predictive values were 56.7, 51.7, 57.6, respectively, and their negative predictive values were 73.6, 70.4, 76, respectively, (AUC: 0.64[0.52-0.74 95% CI], 0.64[0.52-0.74 95% CI], 0.66[0.55-0.76 95% CI]).

Conclusion: The results showed that MPV, PLR, infarct volume and mean age were independentpredictors of 3-year all-cause mortality in AIS patients.

Keywords: Ischemic stroke, mean platelet volume, neutrophil/ lymphocyte ratio, plateletlymphocyte ratio, mortality

INTRODUCTION

Acute ischemic stroke (AIS) is sudden onset loss of focal cerebral functions that is clinically longer than 24 hours. AIS is the second leading cause of deaths and dementia worldwide, third long-term disability. 80-85% are of ischemic origin, resulting in complete or partial occlusion of one or more cerebral vessels in the atherothrombotic zone.[1]

Diffusion-weighted MR (DWI MRs) images are a highly sensitive imaging tool for early ischemic changes in the acute phase and demonstrate cerebral ischemic changes within five minutes of onset of symptoms. The lesion volume at DWI MRs is associated with clinical significance scores. It has been accepted that infarct volume in DWI MRs can predict clinical outcome and may be a potential parameter in AIS patients.[2]

Leukocytes that play a major role in the active inflammatory process also have a critical role in atherosclerosis. It has been suggested that hematologic parameters, such as white blood cells (WBC) and neutrophils, can predict infarct size, prognosis, and mortality in acute ischemic events. Neutrophils are the earliest subtype of leukocytes that leak from the ischemic brain area.[3] Platelets have a major effect on the formation of atherosclerotic plaques and are thus known to play an important role in the pathogenesis of atherothrombosis. Mean platelet volume (MPV) is an indicator of platelet function and increased platelet reactivity. MPV levels are known to be significantly higher in hospitalized patients with AIS.[4]

The aim of this study was to investigate the relationship between useful, reliable and cheap hematologic parameters and infarct volume with all-cause 3-year mortality in AIS patients.

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METHODS

Ethical Approval

The study followed the tenets of the Declaration of Helsinki and was approved by the Kahramanmaraş Sütçü İmam University Ethics Committee (Date: 29.08.2018, Desicion No: 2018/15/30).

Study Population and Protocol

This study is descriptive and retrospectively reviews the AIS diagnosed patients with the diagnostic codes in ICD-10 (G46, G46.8, I67, I67.8, I67.9, I68, I68.8, I69, I69.8) over a consecutive 12-month period. Their demographic and clinical characteristics, laboratory results, comorbities, subtype of acute stroke, inital symptoms, Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS), hospital stay, 3-year mortality rates after stroke and also the infarct volumes in DWI MRs were recorded in the standard data format that wascreated.

Computerized Tomography (CT) and DWI MRs were reviewed by the Radiologist. Patients with intracranial hemorrhage (epidural, subdural, subarachnoid, intracerebral, intracerebellar, etc.) in the CT were not included in the study. Thus, while the study started with 132 patients, 49 patients were excluded from the study with this exclusion. Finally, 83 patients diagnosed with AIS who fulfilled inclusion criteria and were admitted to the Emergency Department within the first 48 hours after the onset of symptoms were included (Figure 1).

Inclusing Criteria

Gender: Males/Females.

Age Range: 18 years and above. Ischemic stroke

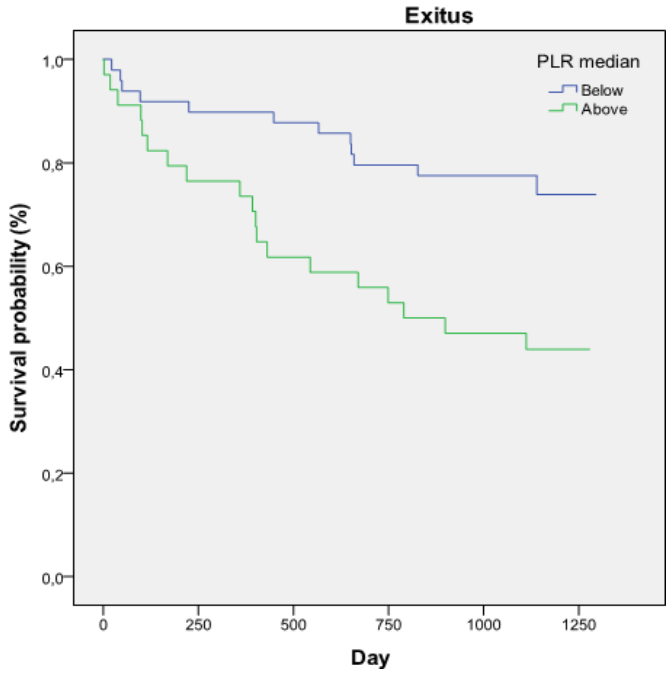

Figure 1. Kaplan-Meier survival curve according to the PLR (platelet/lymphocyte ratio) medianvalue.

Exclusing Criteria

Those who applied more than 48 hours after the onset of symptoms, cerebral venous sinus thrombosis, thrombocytopenia, hereditary platelet disease,

Drug use that can affect the number of platelets (antiplatelet agents, antineoplastic agents,hydroxyurea),

Hemorrhagic stroke in CT,

Unknown onset of symptoms (common neurological disorder and dementia, noncommunicable patients, relatives who do not have adequate knowledge, or patients who cannot be relatives),

Hematologic disorder, Immunosuppressive drug use (steroids),

Have an infection history within 2 weeks before stroke,Patients with high fever and infection,

Stroke stories in the last 6 months,

Patients with missing data (laboratory results, medical history),

Outcome measures were assessed by the NIHSS score and GCS on admission. Finaldiagnosis of AIS was performed by a senior neurologist (C.B.T.Y.) and radiologist (K.D.).

According to DWI MRs images, patients were divided into 2 groups as infratentorial infarct and supratentorial infarct. The supratentorial infarct group was divided into 2 groups as lacunar (≤1.5cm) and non-lacunar (> 1.5cm) infarcts.[3] Later, the non-lacunar infarct group wasalso divided into 2 groups as (1) cardioembolic stroke (AF rhythm ECG, valvular heart disease, ECO or TEE thrombus formation)[2] and atherosclerotic stroke (Aortic calcific plaque without documented carotid artery disease or evident hearth disease).[3]

Patients underwent DWI MRs imaging using the Philips Ingenia 1.5 Tesla magnetic resonance device (Philips Healthcare Nederland). For DWI MRs, echo-planar imaging was made in the transverse plane over the spinecho sequence, and imaging parameters were used as TR/TE:3100/100; matrix:192x192; NEX:3; section thickness:5 mm; inter-section gap:1.5 mm; examination time:4-5 minutes and FOV:230x230 mm. Diffusion gradients were taken in three planes perpendicular to one another and ADC maps were attained by using 2 different b values (500 and 1.000 sec/mm^2). Lesions that met both hyperintense features on DWI images and hypointense features on ADC images were accepted as acute ischemia. In the measurement of ischemia volume (AxBxC)/2 formula was used. The largest dimension in the axial plane was the longest dimension, the other dimension perpendicular to it was A and B values, and the C value was taken into account when considering the vertical axial section thickness. Infarct volumes of the patients were also calculated by the defined formula.[2]

The in-hospital mortality of patients was determined according to the epicrisis reports. The 3- year mortality of out-of-hospital mortality was found out by using Turkiye Republic Ministry of Health, General Directorate of Public Health, Death Notification System using the ID numbers of the patients. The time of stroke-till-death in all patients was

calculated as days. The patients were divided into 2 groups as alives and deaths.

Laboratory Data

Laboratory data at the time of admission (within 48 hours after onset of symptoms), consisted of the platelet count (PLT, 10ˆ9/L), mean platelet volume (MPV, fL), platelet distribution width (PDW, fL), WBC, 10ˆ9/L, neutrophyl count/L), lymphocyte count (10ˆ9/L), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), liver, renal function tests and glucose (mg / dL).

Hemogram and routine biochemical panel were assessed using peripheral venous blood samples taken when the patients applied to emergency department. Hemogram samples were collected in calsium ethylenediaminetetra-acetic acid tubes. Laboratory data were automatically analyzed using XN-3000 Hematology Analyzer (SYSMEX Corporation, Korea, Japan) and Advia 1800 Chemistry Instrument (SIEMENS, Erlangen, Germany).

Statistical Analysis

SPSS 17.0 program was used in the analysis of the data. The normal distribution relevance of the data was tested by the Shapiro-Wilk test and by the Levene test of variance homogeneity. The independent sample t test was used for normally distributed data and Mann- Whitney U test was used not normally distributed data to compare two independent groups. Pearson correlation analysis was used to examine the correlations of the normally distributed variables and Spearman's rho for not normally distributed variables. The quantitative data in tables are expressed with mean±std (standard deviation) or median [interquartile range (IQR)]. Cox regression analysis was used to determine 3-year mortality determinants. Age, gender, hypertension, diabetes mellitus, glucose levels, creatinin, infarct volume, NIHSS, GCS, NLR, MPV and PLR were included as independent variables in this regression model. Optimal cut-off points of all clinical variables (NLR, MPV, PLR, age, NIHSS and others) of patients who alive and deaths were assessed by receiver operating characteristic (ROC) analysis. Maximum value of sensitivity specificity were determined by calculating the area under the curve (AUC) of the relevant tests. Sensitivity, specificity and positive and negative predictive values were also assessed at the best cut-off value for each clinical variable. Categorical data are expressed as n (number) and percent (%). The data were analyzed at 95% confidence level and those with a p- value less than 0.05 were considered significant.

RESULTS

The mean age of 83 consecutive patients with AIS diagnosis was 67.49±15.30. Forty-three (51.8%) were male and 40 (48.2%) were female. Seventy (84.3%) of the cases were atherosclerotic, 13 (15.7%) were cardio embolic. Median ischemic volume was 5.50 (IQR: 1- 40). Median NLR, MPV and PLR levels of all patients were 3.69 (IQR: 2.15-5.99), 6.40 (IQR: 5.80- 8.20) and 154.11 (IQR: 109.05-221.64), respectively. Median NIHSS and GCS values at the time of admission were 4 (IQR: 2-8) and 15 (IQR: 13-15), respectively. The three-year mortality rate was calculated as 37.3% (n = 31).

The mean age, NIHSS and infarct volume of non survivors were statistically higher than survivors (p<0.01, p=0.026, p=0.021, respectively). The mean GCS in the non survivors group was statistically significantly lower than the surviving group (p=0.009). There was a statistically significant difference between the surviving and non surviving patients in terms of median NLR, MPV and PLR levels (p=0.033, p=0.034, p=0.011, respectively). The demographic and clinical characteristics of all patients are summarized in Table 1.

The location and characteristics of the lesions in the radiological evaluation are shown in a table (Table 2).

According to correlation analysis, NLR, MPV, and PLR were negatively correlated with the GCS at admission and were positively correlated with NIHSS and infarct volume (Table 3).

When 3 years of survival of patients are examined according to median NLR, PLR and infarctvolume, Kaplan-Meier survival curves were significantly different between the two groups. (p=0.017, p=0.004, p=0.001, respectively; Figure 1 and Figure 2).

Cox regression analysis revealed that MPV, PLR and infarct volume variables were significant independent risk factors for death (p=0.016, p=0.024, p=0.008, respectively).

Optimal cut-off values of NLR, MPV and PLR were determined as 4.68, 7.20 and 167.66 as long-term mortality predictors in ROC curve analysis, respectively. At this level sensitivities were 54.84, 48.39, 61.29; specificities were 75.0, 73.08, 73.8; positive predictive values were 56.7, 51.7, 57.6 and negative predictive values were 73.6, 70.4, 76.0, respectively. (AUC: 0.64 [0.52-0.74% 95 CI], 0.64 [0.52-0.74% 95 CI], 0.66 [0.55-0.76% 95 CI])

DISCUSSION

In this study, in the group that died of acute ischemic stroke, the mean age, NIHSS score and we found that the infarct volume was statistically significantly higher than the surviving group.

We also found and share the cut-off values for NLR, MPV and PLR levels in objectively assessing the probability of survival and death in cases of acute ischemic stroke.

Despite the results at the probability level in different studies, this study shows that mortality can be predicted with statistically significant data. This is a very significant contribution to the literature and clinical practice.

It has been reported that the inflammatory process plays an important role in the development of ischemic injury and develops within 6-24 hours.[3] Leukocyte-endothelial cell activation whichis the rate-determining step in inflammation is almost absent in normal healthy cerebral microcirculation, however it occurs mainly after the onset of brain ischemia. The rapid increase of leukocytes and other blood cells (e.g. platelets) can be attributed to the increased release of adhesion molecules in both cerebral endothelial cells and circulating blood cells. These adhesion molecules allow the release of different inflammatory cell populations (initially neutrophils, then mononuclear leukocytes) and also platelets in a coordinated sequenceto the cerebral microvascular structure

Table 1. Demographics and laboratory findings of survived and non survived patients

Demographic and laboratory	Survived (n=52)	Nonsurvived (n=31)	p
Age, year, median (IQR)	65.5 (28-84)	80 (46-93)	0.000
Gender, F/M	23/29	17/14	0.349
Hypertension, %	35 (67.3%)	24 (77.4%)	0.326
Diabetes mellitus, %	17 (32.7%)	9 (29%)	0.681
AF, %	9 (17.3%)	5 (16.1%)	0.890
CAD, %	12 (23.1%)	8 (25.8%)	0.779
Dislipidemia, %	38 (73.1%)	14 (45.2%)	0.011
Smoking, %	10 (19.2%)	7 (22.6%)	0.715
Sistolic BP, mmHg, median (IQR)	140 (107-250)	145 (85-220)	0.695
Diastolic BP, mmHg, median (IQR)	85 (54-150)	90 (50-100)	0.765
HR, /min, median (IQR)	85 (51-114)	88 (68-117)	0.042
GCS, median (IQR)	15 (8-15)	14 (7-15)	0.009
NIHSS, median (IQR)	3 (0-17)	5 (1-18)	0.026
Infarct volume, mmt, median (IQR)	3.5 (0.1-202.5)	12 (0.1–262.5)	0.021
WBC,10^3/μL, median (IQR)	8.9 (4.2-25)	8.7 (4.2 – 24.8)	0.770
Neutrophil, 10^3/μL, median (IQR)	6.28 (2.17-22)	5.83 (2.21-20.90)	0.519
Lymphocyte, 10t/μL, median (IQR)	1.7 (0.8–5.8)	1.3 (0.3 – 3.5)	0.033
Platelet, 10^9/L, median (IQR)	258.5 (103-587)	249 (94-561)	0.713
RDW, fL, median (IQR)	14 (12.3–22.7)	15.2 (12.7-18.4)	0.000
NLR, median (IQR)	3.2 (1.1 – 12.6)	4.9 (0.9-36)	0.033
MPV, median (IQR)	6.3 (5.2 – 12.5)	7 (5.5-13)	0.034
PLR, median (IQR)	129.2 (34.5-460.8)	190.2 (27-652.3)	0.011
Glucose, mg/dL, median (IQR)	115.5 (76-518)	127 (50-293)	0.713
Creatinin, mg/dL, median (IQR)	0.8 (0.3–12.7)	0.8 (0.2–1.7)	0.865
ALT, U/L, median (IQR)	26 (16-90)	25 (13-89)	0.436
AST, U/L, median (IQR)	21 (8-84)	15 (5-67)	0.007
Hospitalization time, median (IQR)	7 (1-46)	8 (1-97)	0.038

Abbreviations: F/M, females/males; AF, atrial fibrillation; CAD, coronary artery disease; BP,blood pressure; HR, heart rate; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cell count; RDW, red cell distribution width; NLR, neutrophil/lymphocyte ratio; MPV, mean platelet volume; PLR, platelet/lymphocyte ratio; ALT,alanin aminotransferaz; AST, aspartat aminotransferaz; IQR, interquartile range.

Table 2. Location and characteristics of lesions between two groups in radiological evaluation

Location and characteristics of lesions	Survived	Nonsurvived
Supratentorial, n, %	47 (62.7%)	28 (37.3%)
Infratentorial, n, %	2 (50%)	2 (50%)
Supra-infratentorial, n, %	3 (75%)	1 (25%)
Lacunar, n, %	20 (69%)	9 (31%)
Nonlacunar,n, %	32 (59.3%)	42 (40.7%)

after ischemia-reperfusion. These increased inflammatory blood cells make cerebral microvascular perfusion even more dangerous and contribute to the development of ischemic infarction.[5] Leukocytes are thought to contribute to brain ischemia and tissue damage associated with reperfusion, and neutropenic animals have been advocated for studies that have improved infarcts and neurological outcomes. It has been reported that neutrophils may accumulate in ischemic and reperfused areas in initial response to injury in inflammatory diseases of the central nervous system such as stroke.[3]

Neutrophils have a mixed effect in animal models of stroke, with some studies correlating the presence of neutrophils with injury, while other studies have shown that pre-stroke neutrophil infiltration reduces disease severity. In ischemic stroke, most published studies on the induction and increase of leukocytes have focused on the early injury response and have emphasized the importance of neutrophils.[6] However, most animal studies have focused on the role of cerebral microvascular dysfunction and lymphocytes in tissue injury that occurs several days afterischemic stroke injury.[3] Our study supported these studies and found that neutrophil counts were high and lymphocyte counts were low in the non-surviving group.

It is emphasized that increased NLR is independently associated with coronary artery disease (CAD) severity and may lead to poor prognosis in patients during the 3-year follow-up period.[7] It has been argued that in patients with peripheral arterial disease, high neutrophil counts may add prognostic information to traditional atherothrombotic risk factors and other inflammatory parameters, which may indicate a greatly increased risk for atherosclerotic cardiovascular events.[8] It was also emphasized that high NLR increases the risk of long-term mortality in patients undergoing percutaneous coronary intervention (PCI).[9] Despite the fact that the total

Table 3. A linear relationship among NLR, MPV, PLR, infarct volume and the othercontinuous variables

	NLR		MPV		PLR		Infarct volume	
Variables	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Age	.087	.432	.112	.313	.218	.048	.097	.385
NIHSS	.342	.002	.026	.819	.232	.035	.429	.001
Infarct volume	.204	.065	.167	.131	.122	.270	-	-
GCS	-.352	.001	-.069	.536	-.137	.218	-.426	.001
Glukoz	.311	.004	.028	.803	.015	.896	.161	.145
Creatinin	.066	.553	-.103	.353	-.005	.964	-.030	.786
Sistolic BP	.106	.340	-.115	.301	.034	.763	.003	.977
Diastolic BP	.007	.949	-.006	.956	.031	.778	-.052	.641
Hospitalization time	.184	.096	.135	.225	.148	.182	.454	.001

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale;BP, blood pressure; NLR, neutrophil/lymphocyte ratio; MPV, mean platelet volume; PLR, platelet/lymphocyte ratio; p, level of statistical significance; r, sperman correlation coefficient.

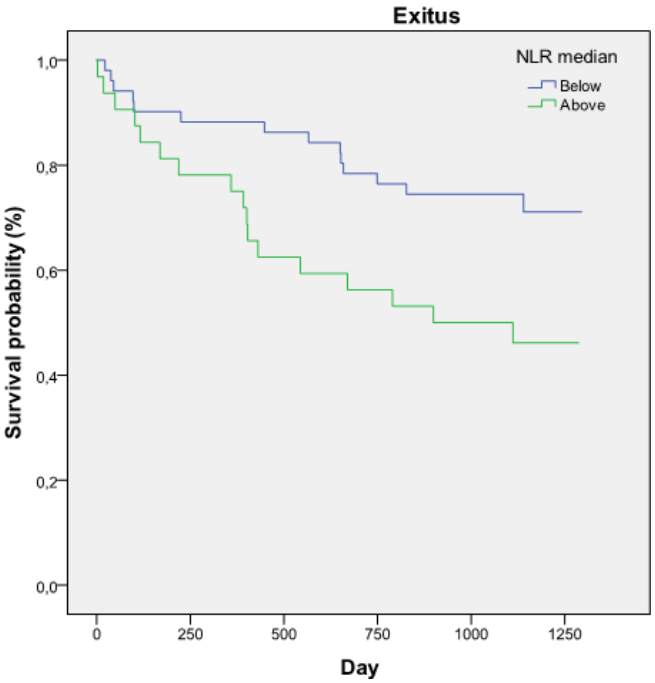

Figure 2. Kaplan-Meier survival curve according to the NLR (Neutrophil/lymphocyte ratio)median value.

number of WBCs was reported to be an independent decisive factor about mortality in patients with high risk CAD, NLR was more predictive about long-term mortality and it was reported to have significant effects on CAD risk assessment.[9,10] Similarly, it has been suggested that NLR is an independent effect of mortality and morbidity in AIS patients.[7,11] It has also been reported that NLR at the time of admission may be a predictor of short-term mortality independently of infarct volume in AIS patients.[3] In our study, NLR was found to be statistically significantly higher in the non survived group, but in regression analysis it was reported that NLR was not a predictor of long term mortality.

There are also some publications in rat stroke models demonstrate that antineutrophil treatment is useless despite the fact that many molecules altering leukocyte infiltration in ischemic regions have been shown to reduce infarct size.[12] Acute inflammation, which can be followed by peripheral inflammatory parameters in AIS patients, may affect the magnitude of the infarct and is positively correlated with infarct volume and NLR.[3] It has been reported that increased NLR can predict infarct size independently of ethology.[3] The positive correlation of NLR with infarct volume and NIHSS and negative correlation of NLR with GCS in our study are compatible with other studies. In addition, the infarct volume was found to be statistically significantly higher in the non survived group that it could be a predictor of long term mortality. Löuvbld et al.[2] also reported that the DWI MRs imaging infarct volume is correlated with the clinical severity and outcome of the disease in the AIS patients and indicated that it could be a predictor of long term mortality.

MPV is considered to be a marker of platelet activation and associated with systemic inflammatory responses. Although it is generally accepted that increased platelet activation is associated with ischemic stroke and coronary heart disease, some studies suggest that there is noassociation between MPV and ischemic stroke.[13-15] Similar to the findings of Mohammed et al,[16] the association between NIHSS score and elevated MPV in AIS patients, resulted in an increase in morbidity and cardiovascular mortality in patients with high MPV after ischemic stroke. Ray et al.[17] reported that MPV increases and platelet count reduces in both of acute and nonacute phases of cerebral ischemia. Domaç et al.[14] reported that MPV levels, that reflect platelet reactivity, increased just before stroke in patients with severe stroke. Löuvbld et al.[2] reported that in the AIS patients, the DWI MRs imaging infarct volume correlated with the clinical severity and outcome of the disease and indicated that it could be a predictor. There was a similarity with literature and MPV value was found statistically higher in the non survived group in our study. MPV may be a predictor of long-term mortality in AIS patients. In addition, positive correlation was found among MPV, ischemia volume and NIHSS and negative correlation with GCS.

PLR is an easily obtained biomarker that combines the prognostic value of platelet and lymphocyte counts with systemic inflammatory burden in cardiovascular diseases. Platelets play an important role in the development, destabilization, and rupture of atherosclerotic plaques. It is thought that increased PLR may accelerate restenosis and plaque instability, thus contributing to the progression of atherosclerosis. This is associated with poor prognosis in

ischemic events. Stable CAD patients undergoing elective stent implantation with high PLR have been reported to have a higher mortality rate. PLR has also been suggested to be a predictor of long-term mortality in CAD.[18] Temiz et al. [19] reported that increased PLR is an independent predictor of in-hospital cardiovascular mortality in patients with ST-elevation AMI, and the threshold value of PLR is 144. The relationship between increased platelet count and cardiovascular mortality hasbeen shown in many studies.[20-22] It has been suggested that increased PLR ratios in stroke patients may indirectly predict infarct volume. The possible pathophysiological mechanism of this relationship is the migration of inflammatory mediators to the penumbra and an increase in the infarct area.[23] Altintas et al.[1] reported that AIS patients had better functional outcomes with low PLR values than with high PLR values. It was also found that mortality rates increased four to five times when PLR was higher than 145 (PLR>145). Similarly, in our study, PLR was statistically significantly higher in the non-survivor group. It was determined that PLR could be a predictor of long-term mortality. In addition, PLR was found to be positively correlated with infarct volume and NIHSS and negatively correlated with GCS.

Limitations

This current study has many limitations. First, the study was retrospective in nature. Since the density of data in the electronic medical record system is always high, the number of lost data is high. This can also lead to prejudice. Second, we could not obtain blood samples to compare prognostic significance of early and late hematologic parameters. In addition, these parameters were compared only with the survival and non survival group, and no comparison with the healthy control group was made. Third, in-hospital mortality, short-term and long-term mortality were not comparable to hematologic parameters because the number of cases was not sufficient.

CONCLUSION

MPV and PLR values were found as an independent predictor for 3 year mortality of AIS patients. Additionally infarct volume and average age were an independent predictor for 3 year mortality of AIS patients, too.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study followed the tenets of the Declaration of Helsinki and was approved by the Kahramanmaraş Sütçü İmam University Ethics Committee (Date: 29.08.2018, Decision No: 2018/15/30).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtainedfrom patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis ofthe paper, and that they have approved the final version.

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