

STROK ALT GRUPLARINDA LENFOSİT MONOSİT ORANI VE İNFLAMATUAR BELİRTEÇLERDEKİ DEĞİŞİMİN DEĞERLENDİRİLMESİ

Evaluation of Changes in Lymphocyte to Monocyte Ratio and Inflammatory Markers in Stroke Subgroups

İbrahim ÇALTEKİN (0000-0002-3973-0655), Emre GÖKÇEN (0000-0002-6018-6105)

ÖZET

Amaç: Stroke dünya genelinde ciddi morbidite ve mortalite oluşturan hastalıkların başında gelmektedir. Stroke olgularında hematolojik inflamatuvar belirteçlerde değişiklik geliştiğini gösteren bazı çalışmalar vardır. Lenfosit monosit oranı (LMO) ise son zamanlarda gündeme gelen özellikle düşük düzeyi ile birçok malignitede incelenmiş yeni bir hematolojik inflamatuvar belirteç olarak kabul edilmektedir. Çalışmamızda acil servisimize nörolojik bulgular ile başvuran ve stroke tanısı alan hastalarda LMO düzeylerini ve klinik sınıflandırma olan Oxfordshire Community Stroke Project (OCSP) sınıflamasına göre subgruplarda LMO düzeylerini araştırmayı amaçladık.

Gereç ve Yöntemler: Bir üniversite hastanesinin acil servisine Ocak 2017 - Ocak 2019 tarihleri arasında nörolojik bozukluk semptomları ile başvuran ve iskemik inme tanısı alan hastalar geriye dönük olarak incelenmiştir. Stroke hastaları OCSP classificationa göre subgruplara ayrılmış ve klinik ile görüntüleme sonuçları korele edilmiştir. Tüm gruplarda hematolojik inflamatuvar belirteçler incelenmiş, LMO' daki değişimler tespit edilmiştir.

Bulgular: Çalışmamıza 109 (63 bayan, 46 erkek) iskemik stroke hastası, 110 (45 bayan, 65 erkek) kontrol hastası dahil edilmiştir. LMO değeri düşüklüğü strok olgularında kontrol grubuna göre istatistiksel olarak anlamlı bulundu ($p<0.05$). LMO değeri düşüklüğü her dört grupta da kontrol grubuna göre istatistiksel olarak anlamlı bulundu ($p<0.05$). TACI ve POCI gruplarında LMO' da en düşük ortalamalar saptandı. Nötrofil lenfosit oranı ve gama glutamil transferaz (GGT) değerleri yüksekliği ise yine her dört grupta da kontrol grubuna göre istatistiksel olarak anlamlı bulundu ($p<0.05$).

Sonuç: Çalışmamızda stroke subgruplarında kısıtlı inceleme yapılan LMO değeri stroke ve subgruplarının tamamında düşük olarak tespit edilmiştir. Özellikle TACI ve POCI gibi geniş enfarkt alanına sahip klinik durumlarda en düşük seviyedeki ortalamalara ulaşılmıştır. LMO' nun hem stroke hemde subgruplarda mortalite, morbidite ve prognoz belirleyicisi olarak kullanılabileceği düşünülmektedir.

Anahtar kelimeler: *Acil servis; İskemik inme; Lenfosit monosit oranı*

ABSTRACT

Background: Stroke is one of the most important disease causing serious morbidity and mortality worldwide. There are some studies showing the change in hematological inflammatory markers in stroke patients. Lymphocyte to monocyte ratio (LMR) is considered to be a new hematological inflammatory marker that has been recently investigated in many malignancies with its particularly low level. In this study, we aimed to evaluate the levels of LMR in patients presented to our emergency department with neurological findings, diagnosed as ischemic stroke and also we aimed to evaluate the levels of LMR in subgroups according to the Oxfordshire Community Stroke Project (OCSP) classification which is a clinical classification.

Material and Methods: The patients admitted to the emergency department of a university hospital with symptoms of neurological disorders and diagnosed with ischemic stroke between January 2017 and January 2019 were retrospectively analyzed. Stroke patients were divided into subgroups according to OCSP classification and clinical and imaging results were correlated. Hematologic inflammatory markers were examined in all groups and changes in LMR were detected.

Results: 109 (63 female, 46 male) ischemic stroke patients and 110 (45 female, 65 male) control patients were included in the study. The low LMR values were found to be statistically significant in stroke cases compared to the control group ($p<0.05$). The low LMR values were found to be statistically significant in all four subgroups compared to the control group ($p<0.05$). TACI and POCI groups showed the lowest mean in LMR values. Higher NLR and GGT values were found to be statistically significant in all four groups compared to the control group ($p<0.05$).

Conclusion: In our study, the LMR value, which was limited investigated in stroke subgroups, was found to be low in all stroke and subgroups. Especially in clinical situations with large infarct sizes such as TACI and POCI groups, the lowest means were reached. It is thought that LMR can be used as a predictor of mortality, morbidity, and prognosis in both stroke and its subgroups.

Keywords: *Emergency department; Ischemic stroke; Lymphocyte to monocyte ratio*

Yozgat Bozok Üniversitesi Tıp Fakültesi
Acil Tıp A.D. Yozgat, Türkiye

İbrahim ÇALTEKİN, Dr. Öğr. Üyesi
Emre GÖKÇEN, Dr. Öğr. Üyesi

İletişim:

Dr. Öğretim Üyesi İbrahim ÇALTEKİN,
Bozok Üniversitesi Tıp Fakültesi Acil Tıp
A.D. Yozgat, Türkiye
Adres Yozgat Bozok Üniversitesi
Erdoğan Akdağ Yerleşkesi Atatürk Yolu
7. Km 66100
Merkez / YOZGAT
Tel: +90530-528 3677
e-mail:
drkaltekin@gmail.com

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BACKGROUND

Stroke is one of the most important disease causing serious morbidity and mortality worldwide (1). There are studies showing changes in hematological inflammatory markers especially in stroke patients. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) are some of these hematological inflammatory markers (2). Lymphocyte to monocyte ratio (LMR) is considered to be a new hematological inflammatory marker which has been recently investigated in many malignancies with its particularly low level (3). In addition, it is determined in assessments that low LMR levels were associated with poor prognosis in stroke patients (4).

The Oxfordshire Community Stroke Project (OCSP) classification, a fast, safe and valid clinical classification, is used to evaluate patients with stroke. This clinical classification divides stroke patients into four groups after imaging methods exclude intracranial hemorrhage. Total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), and posterior circulation infarct (POCI) are the four subgroups (5, 6).

To the best of our knowledge, no study in stroke subtypes was found investigating LMR in literature which is an example of a hematological inflammatory evaluation. In this study, we aimed to evaluate the levels of LMR in patients presented to our emergency department with neurological findings, diagnosed as ischemic stroke and also we aimed to evaluate the levels of LMR in subgroups according to the Oxfordshire Community Stroke Project (OCSP) classification which is a clinical classification.

METHODS

In this study, the patients applied to the emergency department of a university hospital with symptoms of neurological disorders and diagnosed with ischemic stroke between January 2017 and January 2019 were retrospectively analyzed and the study is conducted in accordance with the principles of the Declaration of Helsinki Declaration. The study was approved by the Ethics Committee of our institution. In this period, it was found that 316 stroke cases applied to

our emergency department. After excluding patients with exclusion criteria, the study population consisted of 109 patients who presented to our emergency department with ischemic stroke. In addition, 110 patients were composed as a control group. All patients over the age of 18 years who were diagnosed as stroke, followed up and blood was taken at first visit, were included in our study. Medical examination records, electronic files and radiological imaging of the patients were investigated from the hospital information system. Blood hematological parameters of the patients; hemoglobin, hematocrit, leucocyte, neutrophil, monocyte, red blood cell distribution width (RDW), mean platelet volume (MPV), platelet levels were examined from the blood sample which taken in the first admission. In addition, C-reactive protein (CRP) which known marker of inflammatory conditions (7) and oxidative stress marker gamma-glutamyl transferase (GGT) (8) were also investigated. NLR, PLR, LMR values were obtained by examining these analysis. Stroke patients were divided into subgroups according to OCSP classification and clinical and imaging results were correlated. Hematologic inflammatory markers were examined in all groups and changes in LMR were detected.

Patients whose examination records, epicrisis and electronic records were missing, could not be detected any blood tests and could not be reached any information, were excluded from the study. In addition, patients who were diagnosed with hemorrhagic stroke as a result of radiological examinations were excluded from the study. However, patients who had infection, sepsis, inflammatory, cardiac events and hepatobiliary system pathologies that could affect both inflammatory and oxidant parameters were also excluded from the study, even if blood was taken.

2.2. Statistical analysis

Statistical analyses were completed using the Statistical Package for Social Sciences (SPSS Inc; Chicago, IL, USA) version 20.0 software. Characteristics of the study population were described as means \pm SD and standard descriptive statistics were used to analyze the hematological parameters in stroke groups. The Chi-square test or Fischer's exact test (when chi-square

test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare the proportions in different groups. The distribution of the variable data was determined using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). The Mann-Whitney U test was utilized for the non-parametric numerical data while the Student t-test was adopted for the parametric numerical data between control and stroke groups. Additionally, the Kruskal Wallis test was utilized for comparison between OCSP classification and control groups, and the significance between groups was evaluated by using post-hoc comparison test. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

109 (63 female, 46 male) ischemic stroke patients and 110 (45 female, 65 male) control patients were included in the study. The mean age of the two groups was 72.71 ± 10.67 in the case group and 63.25 ± 11.62 in the control group. In addition, 22 (20.2%) of all ischemic stroke cases had a history of stroke. Variables and demographic parameters of stroke cases and control group are shown in Table 1. The low LMR values were found to be statistically significant in stroke cases compared to the control group ($p < 0.05$). GGT, CRP values were also examined and found statistically significant higher in the stroke group compared to the control group ($p < 0.05$).

Table 1. Variables and demographic parameters of main groups

	Control	Case	p
Gender			0,012
Male	45(40,9%)	63(57,8%)	
Female	65(59,1%)	46(42,2%)	
Age	63,25±11,62	72,71±10,67	<0,001
Hematological parameters			
Wbc (10³uL)	7,42±1,46	9,64±3,99	<0,001
Neutrophil (10³uL)	4,47±1,25	6,72±3,57	<0,001
Lymphocyte (10³uL)	2,21±0,58	1,97±1,01	,001
Monocyte (10³uL)	0,55±0,13	0,69±0,31	,001
Hb (g/dl)	14,16±1,5	13,91±1,77	,249
Htc (%)	42,59±4,18	42,31±5,12	,658
MCV (fl)	86,1±4,97	86,58±6,46	,221
MCHC (g/dl)	33,26±1,08	32,87±1,45	,026
RDW (%)	13,35±1,06	14,17±1,8	<0,001
PLT (10³uL)	276,05±60,43	246,85±91,08	<0,001
MPV (fl)	10,2±0,78	10,55±1,02	,018
GGT (U/L)	17,95±10,47	34,93±29,92	<0,001
CRP (mg/dl)	2,51±1,24	20,68±43,91	<0,001
LMR	4,21±1,37	3,07±1,28	<0,001
NLR	2,18±0,88	4,62±4,36	<0,001
PLR	134,43±48,23	158,14±121,25	,934
Hb: hemoglobin; Htc: hematocrit; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; RDW: Red blood cell distribution width; PLT: platelet; MPV: mean platelet volume; GGT: gamma-glutamyltransferase; CRP: C-reactive protein; LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio			

When the stroke patients divided to four group according to OCSP classification, 29 (26,60%) patients were in TACI group, 19 (17,40%) patients were in POCI group, 37 (33,90%) patients were in PACI group, 24 (22%) patients were in LACI group (Table 2, Figure 1).

Table 2. Distribution of OCSP classification according to subgroups

OCSP	(%)	n
TACI	26,60%	29
POCI	17,40%	19
PACI	33,90%	37
LACI	22%	24
Total	100%	109

OCSP: Oxfordshire Community Stroke Project; TACI: total anterior circulation infarctions; POCI: posterior circulation infarctions; PACI: partial anterior circulation infarctions; LACI: lacunar infarctions

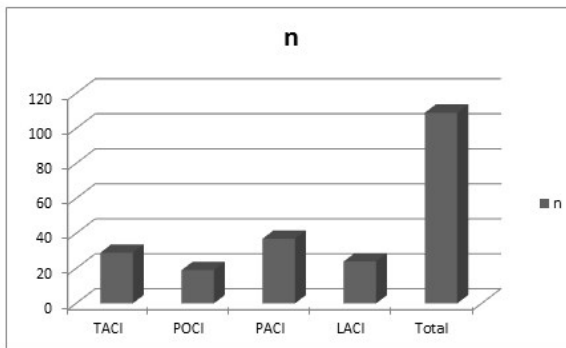


Figure 1. Distribution of OCSP subgroups

The low LMR values were found to be statistically significant in all four subgroups compared to the control group ($p < 0.05$). TACI and POCI subgroups showed the lowest mean in LMR values. Higher NLR and GGT values were found to be statistically significant in all four groups compared to the control group ($p < 0.05$). Higher mean GGT levels in TACI, PACI and POCI groups were detected compared to LACI group.

When the CRP value was examined, a statistically significant difference was found in PACI group patients compared to the control group ($p < 0.05$), but there was no statistically significant difference between the other three groups compared to the control group ($p > 0.05$). When the PLR values were examined, no statistically significant difference was observed between the four groups and the control group ($p > 0.05$) (Table 3).

Table 3. Hematological and inflammatory biomarkers of OCSP subgroups

	OCSP				CONTROL	p
	TACI	POCI	PACI	LACI	Mean±Std	
LMR	3,07±1,43	2,68±1,03	3,16±1,32	3,23±1,32	4,21±1,37 ^a	<0,001
NLR	5,22±5,88	5,37±4,71	4,00±3,08	4,27±3,61	2,18±,88 ^a	<0,001
PLR	160,84±142,69	178,09±165,66	157,32±103,16	140,37±73,77	134,43±48,23 ^a	,941
GGT	48,07±47,07	33,89±25,33	29,95±18,38	27,54±12,60	17,95±10,47 ^a	<0,001
CRP	12,78±20,50	17,37±34,87	27,17±49,46	22,84±60,00	2,51±1,24 ^b	<0,001

OCSP: Oxfordshire Community Stroke Project; TACI: total anterior circulation infarctions; POCI: posterior circulation infarctions; PACI: partial anterior circulation infarctions; LACI: lacunar infarctions; LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; GGT: gamma-glutamyltransferase; CRP: C-reactive protein

^a There was a significant difference between the control group and all OCSP groups in post-hoc comparison.
^b There was a significant difference between the control group and PACI group in post-hoc comparison.

DISCUSSION

In our study, hematologic inflammatory markers were examined in stroke patients. Another important point of evaluating these markers was to detect the course of these markers in stroke subgroups. In the light of the data obtained, unlike inflammatory parameters such as NLR and CRP, low LMR was found to be significant for stroke patients and subgroups, and this was consistent with a few counts of literature investigation.

It is known that there is a relationship between prognosis and inflammatory markers in patients with stroke (9). Sometimes it is difficult to determine the stroke etiology (10). Some classifications like OCSF classification and Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria are used to determine the subgroups of stroke patients (6, 11). These classifications make it easier to predict the etiology, prognosis and mortality in stroke patients.

Like CRP, NLR and PLR have been investigated in many studies as inflammatory markers. (12-14). It has been reported that increased levels of NLR and PLR is a predictor of ischemia and prognosis in patients with stroke (15, 16) It is also known that the level of inflammation increases as the level of these markers increases (9). In a study, NLR and PLR levels and OCSF classification were evaluated according to carotid intima media thickness of ischemic stroke patients and no difference was found between subgroups. However, when these markers were examined among subgroups, the highest levels of NLR have been found in POCl group and the lowest levels of NLR have been found in LACI group (17). Similarly, in our study, these parameters were higher in all subgroups than in the control group. In addition, with large volume involvement higher mean values were found in TACI and POCl patients than LACI patients.

On the other hand, LMR is another marker for determining inflammation status, unlike to NLR and PLR low levels of LMR is also valuable for stroke and coronary events (18). It is known that lymphocytes and monocytes, which play a role especially in inflammatory processes, also play a role in secondary brain injury after stroke. However, cortisol secretion

due to immunosuppression and endocrine response in stroke cases causes destruction of lymphocytes and decrease in absolute lymphocyte count. Monocyte migration is a condition that can be detected secondary to inflammation observed in the post-ischemic infarct area, but monocytosis is considered to be a poor prognostic marker in ischemic stroke (19). Ren et al., in another study found that ischemic stroke severity and poor prognosis were significant with low LMR levels (4). Another study examining cases of acute pulmonary embolism revealed low LMR as an independent risk factor for in-hospital and short-term mortality (20). In our study, similar findings were obtained with literature. It was found that lymphocyte ratios of stroke patients were lower than the control group and monocyte ratios of stroke patients were higher than the control group. LMR values were lower in all stroke patients and in each subgroup compared to the control group. In clinical situations with large infarct areas such as TACI and POCl, the lowest mean levels of LMR were obtained.

GGT was found to be high in both stroke and coronary artery disease as an oxidant stress marker, and this was associated with the role of glutathione and thiol mediated oxidative processes in intracellular mechanisms (21-23). In a study conducted by Gurbuz et al., found a significant difference in GGT levels between stroke patients and the control group, and between PACI group with large infarct sizes and LACI group with small infarct sizes (23). In our study, GGT levels were found to be higher in all four groups compared to the control group, and even GGT levels in the TACI, PACI and POCl groups were found to have higher averages than the LACI group.

CONCLUSION

There are many studies examining the relationship between hematological inflammatory markers and stroke in literature. However, the number of studies with new markers such as LMR seems to be limited. In our study, the LMR value, which was limited investigated in stroke subgroups, was found to be low in all stroke and subgroups. Especially in clinical situations with large infarct sizes such as TACI and POCl groups, the lowest means were reached. It is thought that LMR

can be used as a predictor of mortality, morbidity, and prognosis in both stroke and its subgroups.

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