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Orjinal Araştırma / Original Article

Differential Diagnosis of Stroke by Platelet Large Cell Ratio (P-LCR) Levels

Trombosit Büyük Hücre Oranı (P-LCR) Düzeylerine Göre İnmenin Ayırıcı Tanısı

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Abstract

Aim: Platelets play an important role in the pathogenesis of thrombosis and atherosclerosis. Platelet Large Cell Ratio (P-LCR), a routine hemogram parameter, is the largest fraction of platelets that are more closely related to thrombotic events. In this study, for the first time in the literature, P-LCR levels in ischemic and hemorrhagic stroke patients were compared with the levels in transient ischemic attack (TIA) group.

Material and Method: Retrospectively, hospital records between January 2016 and 2019, were searched by ICD-10 codes, and patients aged between 18-70 years who were diagnosed as ischemic stroke, hemorrhagic stroke and transient ischemic attack were included. The P-LCR test results in the first hemogram test of the patients taken at the time of admission to the hospital were included and compared.

Results: Of the 4511 patients, 92.6% (n=4177) were diagnosed with ischemic stroke, 6% (n=271) with hemorrhagic stroke, and 1.4% (n=63) of patients with TIA. The P-LCR levels of the ischemic and hemorrhagic stroke patients were found to be significantly higher than the TIA group (p=0.027; p=0.044, respectively). The Area Under the Curve (AUC) values for ischemic, hemorrhagic and total stroke versus TIA patients were 0.581, 0.568, and 0.580; respectively. The cut-off value of P-LCR was 26.65 ng/L between the ischemic stroke and TIA.

Conclusion: The increase in P-LCR levels can be used to distinguish ischemic and hemorrhagic stroke from TIA.

Keywords: Platelet Large Cell Ratio, stroke, ischemic, hemorrhagic, transient ischemic attack

Öz

Amaç: Trombositlerin tromboz ve ateroskleroz patogenezinde önemli rolleri bulunmaktadır. Rutin hemogramda bakılan bir parametre olan trombosit büyük hücre oranı (P-LCR), trombotik olaylarla daha yakından ilişkili olan trombositlerin, en büyük fraksiyonunun ölçümüdür. Bu çalışmada, literatürde ilk kez, iskemik ve hemorajik inme hastalarının P-LCR seviyeleri, geçici iskemik atak (TIA) hastalarının P-LCR seviyeleri ile karşılaştırılmıştır.

Gereç ve Yöntem: Ocak 2016-2019 tarihleri arasındaki hastane kayıtları retrospektif olarak ICD-10 kodlarına göre taranarak, iskemik inme, hemorajik inme ve geçici iskemik atak tanısı konmuş 18-70 yaş arası hastalar çalışmaya dâhil edilmiştir. Bu hastaların hastaneye başvuru anında yapılan ilk hemogram testlerindeki P-LCR sonuçları alınıp karşılaştırılmıştır.

Bulgular: Çalışmaya dâhil edilen 4511 hastanın %92,6'sının (n=4177) iskemik inme, %6'sının (n=271) hemorajik inme ve %1,4'ünün (n=63) TIA tanılı oldukları belirlenmiştir. İskemik ve hemorajik inme hastalarının P-LCR düzeylerinin, TIA grubuna göre istatistiksel olarak anlamlı yüksek oldukları saptanmıştır (sırasıyla p=0,027; p=0,044). İskemik, hemorajik ve total inme hastaları ile TIA hastaları karşılaştırıldığında, eğri altındaki alan (AUC) değerleri sırasıyla 0,581; 0,568 ve 0,580 olarak tespit edilmiştir. İskemik inme ve TIA arasında P-LCR kesme değeri 26,65 ng/L olarak saptanmıştır.

Sonuç: P-LCR seviyelerindeki artış, iskemik ve hemorajik inmeyi TIA'dan ayırt etmek için kullanılabilir.

Anahtar Kelimeler: trombosit büyük hücre oranı, inme, iskemik, hemorajik, geçici iskemik atak

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INTRODUCTION

Stroke is a neurological dysfunction caused by occlusion or rupture of the vascular structure of the central nervous system. As a pathophysiological basis, stroke is divided into two as ischemic and hemorrhagic. Both types of strokes have common risk factors. These risk factors are: hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, asymptomatic carotid stenosis, physical inactivation, smoking and alcohol consumption. Many of the risk factors that can be modifiable are based on atherosclerosis pathogenesis. Early detection or prevention of atherosclerosis risk is important in predicting the predisposing factors of stroke and in monitoring the prognosis.[1]

Platelets play an important role in the pathogenesis of thrombosis and atherosclerosis. Larger platelets have been associated with increased reactivity, increased cardiovascular risk, and higher complication rates after coronary stenting. The elevation of mean platelet volume (MPV) test, which indicates platelet volume increase, was evaluated as an independent risk factor for cardiovascular ischemic events.[2] Although increased platelet volume (MPV) has been found to be associated with platelet activation, and myocardial infarction and stroke[3,4] MPV testing has limitations due to many factors, such as age, sex, blood storage duration and ambient temperature[5] which hampers the routine use of MPV.

The Platelet Large Cell Ratio (P-LCR) test, which is another test in routine hemogram test, is defined as the largest fraction of platelets that are more closely related to thrombotic events. P-LCR levels were found to be significantly higher in patients with dyslipidemia, prone to thromboembolic ischemic events. [6] There are studies in the literature investigating the role of P-LCR in cardiovascular events. In a study investigating the availability of P-LCR testing as a prognostic factor in acute myocardial infarction, it was found to be significantly associated with P-LCR increase and mortality at the time of application.[7,8]

There are no studies in the literature that investigate the role of P-LCR levels in cerebrovascular events. Hemogram test is the most easily accessible test in all health care institutions, including primary care, as it is easy, cheap and quick to produce results. If the hemogram test determines the availability of stroke diagnosis, a fairly easy and fast test will reduce the time required to start treatment of stroke. In this study, for the first time in the literature, the relationship of the P-LCR test with stroke was studied, and its use in the diagnosis and distinction of hemorrhagic-ischemic stroke versus TIA was investigated.

MATERIAL AND METHOD

Ethical approval was taken from Atatürk University, Faculty of Medicine, Clinical Researches of Ethical Committee (Date: 07.11.2019, Decision No: 07/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Within the scope of our study, hospital records between January 1, 2016 and January 1, 2019 were searched by ICD-10 codes and patients aged between 18-70 years who were diagnosed as stroke were included in our study. ICD-10 codes of ischemic stroke, hemorrhagic stroke and transient ischemic attack were G45, G46, I60, I61, I62, I64, I65, I66, I67, I68, I69 and their subgroups. Since our study was planned retrospectively, no informed consent was obtained. Patients over 70 years of age were excluded from the study in order not to be affected by hematological abnormalities or problems that increase with age and the patients below 18 years of age or missing P-LCR test results were also excluded from the study in accordance with the exclusion criteria. Flow chart of the study was given in **Figure 1**. Ischemic or hemorrhagic stroke diagnoses were mandatory to be given as the definite diagnosis, since the preliminary diagnoses were neglected.

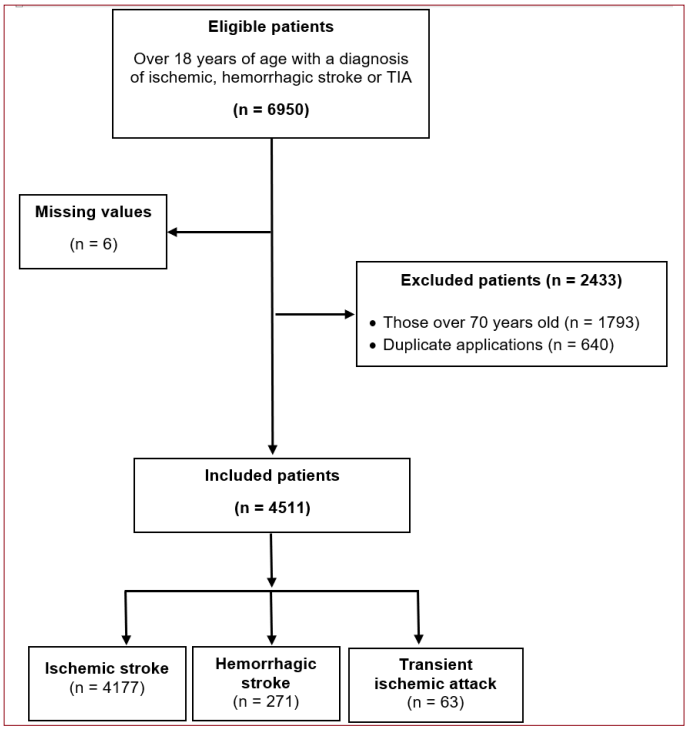

Figure 1. Flow chart of the study

In the study, statistical analyses were performed with SPSS 23.0 (IBM, USA) program. Kolmogorov-Smirnov test was used for the normal distribution assessment. If the groups were normally distributed, the Student–t test and one–way ANOVA test were taken for the analysis of two or more groups respectively. If the normal distribution was not determined, the Mann Whitney U test, and the Kruskal Wallis variance test was taken depend on the number of groups. The correlation analysis uses Pearson's correlation if there is a normal distribution, and Spearman's correlation test if there is no normal distribution. ROC curve analysis was performed to determine the cut-off value of the P-LCR test for stroke. Statistical significance was taken as $p<0.05$ in the whole study.

RESULTS

Of the 4511 stroke patients, 4177 (92.6%) patients with ischemic stroke, 271 (6%) patients with hemorrhagic strokes and 63 (1.4%) patients with TIA were identified. General characteristics of the patients were given in **Table 1**.

The mean age of 4177 patients with ischemic stroke was 45.29±14.62 years; 60.2% were female; and they were hospitalized for 6.8±8.94 days. The mean P-LCR test result of the patients with ischemic stroke was 28.15±7.43 ng/L. Female patients had significantly higher P-LCR test results than men (p<0.001). The Kruskal Wallis test of the P-LCR test according to age was not significant (p=0.088).

The mean age of 271 patients with hemorrhagic stroke was 47.96±15.25 years; the rate of male patients was higher (63.5%) and mean hospital stay was 10.38±12.16 days. The mean P-LCR test result of the patients with hemorrhagic stroke was 27.88±7.82 ng/L. In the analysis of P-LCR according to gender, t–test analysis of female patients showed a statistically significant higher P-LCR value (p =0.04). However, there was no significant difference in age–based analysis (p=0.276).

The mean age of 63 patients with transient ischemic attack (TIA) was 49.78±13.77 years; with the rate of male patients 57.1% and the mean hospital stay was 5.46±7.75 days. The mean P-LCR test result of the patients with TIA was 25.74±6.37 ng/L. In the analysis of P-LCR test by gender, it was higher in female patients, but not statistically significant (p=0.12). Similarly, no statistical difference was found in the analysis by age (p=0.198).

Comparisons of patients with ischemic, hemorrhagic stroke and TIA are given in **Table 2**. Accordingly, when the P-LCR test results of the ischemic stroke patients and the results of the TIA patients were compared, the P-LCR level of the ischemic stroke patients was found to be significantly higher (p=0.027). Spearman's correlation analysis showed a positive correlation between P-LCR and ischemic stroke (r=0.034). A statistically significant difference was found between the ages of patients with ischemic stroke and TIA (p=0.019). Ischemic stroke patients were mostly female, whereas TIA patients were mostly male (r=0.005). The duration of hospitalization in both groups was not significant (p=0.578).

When the P-LCR values of the patients with hemorrhagic stroke and TIA were compared, the P-LCR levels of the hemorrhagic stroke patients were statistically significantly higher (p=0.044). In Pearson correlation analysis, a positive correlation was found (r=0.110). The age and sex distribution of the two groups were not statistically different (p=0.385; p=0.352, respectively). However, the duration of hospitalization was significantly higher in the group with hemorrhagic stroke (p=0.002).

There was no statistically significant difference in the comparison of P-LCR test in patients with ischemic and hemorrhagic stroke (p=0.549). A statistically significant difference was observed between the average ages of two groups (p=0.002). Similarly, a significant difference was found in the duration of hospitalization (p<0.001). Ischemic stroke was more common in females and hemorrhagic stroke was more frequent in males and was statistically significant (p<0.001).

When all patients with ischemic and hemorrhagic strokes were taken as total stroke and P-LCR results of stroke group were compared with TIA, P-LCR values of stroke patients were significantly higher (p=0.029). In Spearman's correlation analysis, P-LCR height and stroke were positively correlated (r=0.033). A statistically significant difference was found between the age and sex of stroke patients and TIA patients (p=0.024 and p=0.011, respectively). There was no significant difference between the duration of hospitalization (p=0.372).

When the Receiver Operating Characteristic (ROC) curve analysis of the P-LCR test was performed, the Area Under the Curve (AUC) values for ischemic stroke vs TIA; hemorrhagic stroke vs TIA; ischemic vs hemorrhagic Stroke; and total stroke vs. TIA were 0,581; 0,568; 0,511 and 0,580; respectively (**Table 3**). The cut-off value between the ischemic stroke and TIA was 26.65 ng/L (p=0.027), and the cut-off value between the total stroke group and TIA was also 26.65 ng/L (p=0.029). Besides, the sensitivity and specificity of the cut-off values were relatively low (54.9 and 54% relatively) However, P-LCR cut-off value between hemorrhagic stroke and TIA and ischemic stroke and hemorrhagic stroke was not statistically significant (p>0.05). The ROC curve analyses are given in **Figure 2**.

Table 1. General features of patients.

	Ischemic Stroke	Hemoragic Stroke	TIA
Patients (n. %)	4177 (92.6%)	271 (6%)	63 (1.4%)
Age (Mean. Std. Dev.)	45.29±14.62	47.96±15.25	49.78±13.77
Sex	60.2% Women	63.5% Men	57.1% Men
Hospital staying (days)	6.8±8.94	10.38±12.16	5.46±7.75
P-LCR (ng/L) (Mean. Std.Dev.)	28.15±7.43	27.88±7.82	25.74±6.38

Table 2. Statistical differences between groups

	Age (p)	Sex (p)	Hospital staying (p)	P-LCR (p)	Correlation
Ischemic Stroke vs. TIA	0.019	0.005	0.578	0.027	r=0.034
Hemorrhagic stroke vs. TIA	0.385	0.352	0.002	0.044	r=0.110
Ischemic vs. Hemorrhagic Stroke	0.002	<0.001	<0.001	0.549	-
Ischemic + Hemorrhagic stroke vs. TIA	0.024	0.011	0.372	0.029	r=0.033

Table 3. ROC analysis and cut off values of P-LCR.

	p	AUC	95% CI	Cut-off (ng/L)	Sens.%	Spec.%
Ischemic Stroke vs. TIA	0.027	0.581	0.513-0.648	26.65	54.9	54
Hemorrhagic stroke vs. TIA	0.090	0.568	0.495-0.642	26.65	54.2	54
Ischemic vs. Hemorrhagic Stroke	0.549	0.511	0.474-0.548	27.55	49.9	49.4
Ischemic + Hemorrhagic stroke vs. TIA	0.029	0.580	0.513-0.647	26.65	54.9	54

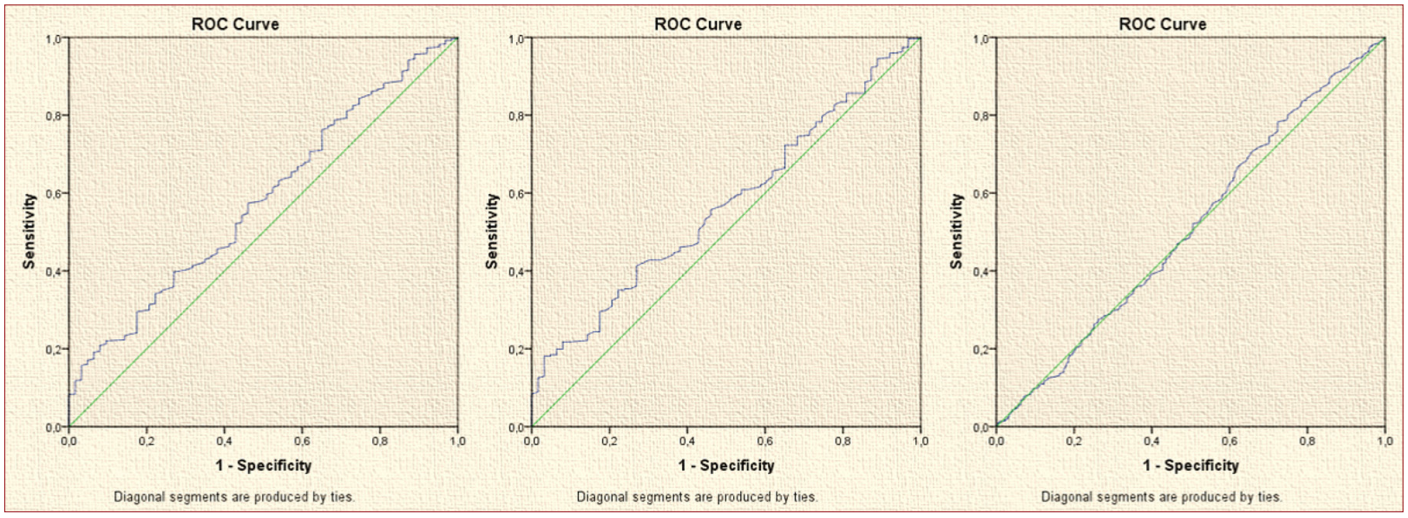

Figure 2. ROC curve graphics of (1) Ischemic stroke versus TIA; (2) Hemorrhagic stroke versus TIA; (3) Ischemic versus hemorrhagic stroke, respectively

DISCUSSION

In this study, for the first time in the literature, P-LCR test results of ischemic and hemorrhagic stroke patients and P-LCR test results of TIA patients were statistically compared. In our study, the effectiveness of P-LCR test in the diagnosis of ischemic and hemorrhagic stroke and differential diagnosis of ischemic-hemorrhagic stroke was investigated. As one of the parameters of the P-LCR test on the hemogram, easy, inexpensive, fast and feasibility can be an important advantage.

As a result of our study, it was found that P-LCR values of both ischemic and hemorrhagic stroke patients were statistically higher than TIA patients. It was determined that P-LCR test correlated positively but weakly with stroke. According to ROC analysis, P-LCR had a cut-off value of 26.65 ng/L. Thus, it was concluded that the height of the P-LCR test is an indicator that can support the diagnosis of stroke. This is the case with stroke patients who have to make quick diagnosis and referral, with only a simple hemogram test, easy and fast diagnosis will be obtained.

In the study, the P-LCR test in the differentiation of ischemic-hemorrhagic stroke was not found to be statistically significant. This suggests that the P-LCR value cannot be used as an indicator for the differential diagnosis of ischemic-hemorrhagic stroke.

Male gender and advanced age in stroke are considered as unmodifiable risk factors.[1] Due to the protective effect of estrogen, stroke is less common in premanopausal women, whereas, this ratio increases in postmenopausal and older ages, and the rate of stroke increases in females since they live longer.[9,10] However, studies show that female stroke rates are higher than men at all ages.[11] In our study, although the stroke patients older than 70 years were excluded, 58.8% of the ischemic and hemorrhagic stroke patients were female, which is similar to the literature. The mean age of stroke patients was 45.5 years in the study, which is a non-reflective result due to the absence of stroke patients over 70 years of age. Likewise, the reason for the higher incidence of ischemic stroke in our study (92.6%) than in the literature is that stroke patients older than 70 years of age were not included in the study.

In the literature, the relationship between P-LCR elevation and atherosclerotic vascular diseases has been mostly investigated in coronary artery diseases, and different opposite results were obtained in these studies. In a study performed by Khandekar et al. in acute myocardial infarction, unstable angina and stable angina groups, they found that P-LCR value was significantly higher in these patients.[12] Cerit et al. compared the platelet parameters with the coronary tortuosity associated myocardial ischemia and found that the P-LCR test of these patients was significantly higher than the control group.[13]

In another study investigating the relationship between coronary artery disease and P-LCR levels, it was found that there was no association between P-LCR levels, and P-LCR elevation could not be used as a marker for coronary events.[14] Yet again, in a study investigating the relationship between periprocedural myocardial infarction and P-LCR, no association with elevated P-LCR levels was found.[15] The remarkable point of this study was that, P-LCR elevation was found to be associated with a previous cerebrovascular event. However, according to our research, there are no studies investigating the relationship between P-LCR and stroke in the literature. In our study, for the first time in the literature, patients with the diagnosis of acute ischemic and hemorrhagic strokes were found to have elevated P-LCR at the time of first admission, and a conclusion that the P-LCR test was a diagnostic indicator in stroke.

Limitations: As a limitation of our study, due to the fact that it was a retrospective study, no history of drug use affecting platelet parameters of patients could be questioned. Also, in our study, patients aged between 18-70 years were screened and it was aimed to ignore the false results of P-LCR test due to the more frequent occurrence of hematological diseases

over 70 years of age. However, as a retrospective study, it is not known and could not be questioned whether patients included in the study have any hematological diseases or using any drugs affecting P-LCR test, which is as another limitation of our study.

CONCLUSION

The P-LCR test, which is one of the parameters measured in the hemogram test, was significantly higher in patients with ischemic and hemorrhagic stroke compared to TIA patients and the cut-off value of P-LCR was found to be 26.65 ng/L. This shows that the P-LCR test can be used as an indicator for stroke diagnosis. P-LCR test is fast, easy, inexpensive and accessible, and further studies are needed to prove its diagnostic effectiveness in stroke and even evaluate it among stroke risk factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was taken from Atatürk University, Faculty of Medicine, Clinical Researches of Ethical Committee (Date: 07.11.2019, Decision No: 07/08).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

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