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Orginal Article

Platelet large cell ratio (P-LCR) in predicting acute coronary syndromes before aspirin use

Erdal Tekin[1*], Mustafa Bayraktar[2], Muhammet Celik[3], Ibrahim Ozlu[1]

[1]Department of Emergency Medicine, Faculty of Medicine, University of Ataturk, Erzurum, Turkey
[2]Department of Family Medicine, Faculty of Medicine, University of Ataturk, Erzurum, Turkey
[3]Department of Biochemistry, Faculty of Medicine, University of Ataturk, Erzurum, Turkey

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Abstract

Introduction: Platelet large cell ratio (P-LCR) test is one of the test parameters that is routinely calculated in the hemogram test, and expressed as the ratio of platelets with platelet volume greater than 12 fL. Large platelets are relatively younger and contain more intracellular granules, meaning that platelets have more thrombogenic potential. In the literature investigating the relationship between the acute coronary syndrome and P-LCR levels, the use of aspirin in patients and its effects on platelet parameters were ignored. In our study, for the first time in the literature, the relationship between P-LCR levels and acute coronary syndromes were investigated by means of including the patients before they took aspirin which ensures that P-LCR test is not affected by aspirin.

Method: Retrospectively, patients aged 18-70 years were screened and those whose hemogram tests were completed before aspirin usage were included. A total of 109 patients diagnosed with unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) were included and compared in the study.

Results: The mean P-LCR values were 23.61% (95% CI: 21.97-25.25) in UA patients, 28.34% (95% CI: 24.86-31.83) in NSTEMI, and 25.71% (95% CI: 22.07-29.35) in STEMI patients. There was a statistically significant difference between the P-LCR values among the groups ($p=0.022$).

Conclusion: The increase in P-LCR, free of aspirin effects, was found to be statistically significant in acute coronary syndromes.

Introduction

Chest pain is one of the most common causes of all emergency department applications.[1] In the United States, approximately 8 million patients are admitted to the emergency department because of chest pain each year, from whom only 15%-25% are diagnosed with acute coronary syndrome (ACS).[2] Considering the fact that ACS is fatal but it is largely possible to provide full healing when diagnosed early, rapid and accurate management of patients with chest pain becomes even more important.

In ACS, as a multifactorial disease, endogenous and exogenous risk factors are involved in pathogenesis. Platelet activation leads to an increase in platelet consumption in the area of atherosclerotic plaque rupture. This leads to the release of large-sized platelets from the bone marrow during an acute coronary event.[3] Large platelets are relatively younger and contain more intracellular granules, meaning that platelets have more thrombogenic potential.[4] Hemogram is an easy and inexpensive test that can be performed easily in all health systems, including primary care centers. Platelet large cell ratio (P-LCR) test is one of the test parameters that is routinely calculated and given in the hemogram test, and expressed as the ratio of platelets with platelet volume greater than 12 femtolitres (fL). The ratio of normal P-LCR, i.e. large-volume platelets to all platelets, should be less than 30%.[5] Larger platelets which are reflected by high P-LCR levels indicate higher circulating cholesterol and triglyceride levels in serum.[6] There are many studies in the literature that explore the relationship between platelet parameters in the hemogram and the ACS. Although the mean platelet volume was studied frequently in these studies, the P-LCR test was studied in a small number of the studies.[6,7] In one of these studies, Dehghani et al investigated the relationship between platelet parameters between unstable angina (UA), ST elevation MI (STEMI), and non-ACS chest pain.[8] In this study, a significant correlation between P-LCR value elevations and ACS was

***Corresponding Author:** Erdal Tekin, Address: Atatürk University Department of Emergency Medicine, Erzurum, Turkey.
Phone: +90507 117 5956, Email: dret25@gmail.com

found. However, aspirin, a routine anti-thrombotic agent given to chest pain patients, was not taken into account in the studies, and the effects of aspirin on the P-LCR test were neglected. There is no study in the literature evaluating the availability of P-LCR in ACS diagnosis from the point of view of not using aspirin.

In our study, the predictivity of P-LCR test, which is known to play a role in atherogenesis and thrombosis pathogenesis, in the diagnosis of ACS in patients who were not affected by prior aspirin usage, was investigated for the first time in the literature.

Methods

Design of the study, setting and selection of patients

Our study included patients aged 18-70 years old who were admitted to our emergency department with chest pain. The records of the emergency department were retrospectively screened for patients with chest pain over a 3-month period, between November 2019 and February 2020. This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the local ethics committee for the study from Ataturk University, Medical Faculty Ethical Committee. Since this study is a retrospective study, informed consent was not obtained from the patients and/or their relatives.

Patients who had performed hemogram tests after taking aspirin were excluded from the study in order not to affect the P-LCR test results. Moreover, patients over the age of 70 years old were excluded from the study due to the possibility that hematological diseases, more common in patients over the age of 70, would affect the P-LCR test.

The evaluation of ACS diagnosis of patients admitted to the hospital with chest pain was performed by typical chest pain anamnesis, ECG assessment and cardiac marker measurement of troponin. The patients who were diagnosed as ST-elevated MI, non-ST elevated MI and UA were categorized into different groups and the P-LCR test results of the groups were compared. P-LCR and troponin test results were scanned from the file records of these patients, and patients who lacked these tests were excluded from the study. Troponin levels above 19.8 ng/L, which is the laboratory reference value of our hospital, was considered as high levels.

Statistical analysis

In our study, statistical analyses were performed with IBM SPSS 23.0 package program. Kolmogorov-Smirnov test was used for the normal distribution assessments. Student's *t* test was used for normally distributed variables and Mann Whitney U test was used if the distribution was not normal. When the compared groups were three or more and normally distributed, one-way ANOVA variance test was used, and the Kruskal-Wallis variance test was used if the distribution was not normal. The correlation analysis was performed by Pearson's correlation or Spearman's correlation tests. ROC curve analysis was performed to determine the cut-off value of the P-LCR test for the ACS. Statistical significance was taken as $P<0.05$ in the whole study.

Results

In our study, 109 patients aged 18-70 years who were diagnosed with ACS, having hemogram tests before aspirin usage were included. The average age of patients was 44.66 years (SD: 13.68), whereas 74 (67.9%) were male and 35 patients (32.1%) were female. Sixty-three patients (57.8%) were diagnosed with UA; 26 subjects (23.9%) had NSTEMI; and 20 patients (18.3%) were diagnosed with STEMI. The mortality rates of the patients in the first month were 10.1% (n=11). The mean P-LCR level of all patients was found to be 25.12% (SD: 7.49).

The comparison of the group data according to their diagnoses is given in Table 1. The mean age of UA patients was 41.03 ± 12.49 years, NSTEMI patients were 54.42 ± 10.57 years, STEMI patients were 54.30 ± 12.60 years and there was a significant difference between the groups ($P<0.001$). When considering sex, it was found that men were more frequent in all three groups; 57% in UA patients, 77% in NSTEMI patients, and 90% of STEMI patients were male ($P=0.012$). When low-density lipoprotein (LDL) cholesterol and triglycerides values were analyzed among the groups, STEMI patients had higher LDL-cholesterol levels, while triglyceride levels were found to be higher in NSTEMI patients and statistically significant differences were found between groups ($P<0.001$; $P=0.004$; respectively).

The post-hoc analyzes of the patients are given in Table 2. Accordingly, age distribution and LDL-cholesterol levels were different between UA and NSTEMI, as well as UA and STEMI groups, but there was no significance between NSTEMI and STEMI groups ($P<0.001$; $P<0.001$; $P>0.05$; respectively). In terms of triglyceride values of the patients, a significant difference was found between UA and NSTEMI, and between NSTEMI and STEMI groups, but there was no statistical difference between UA and STEMI groups ($P=0.006$; $P=0.020$; $P=0.954$; respectively).

When the P-LCR values of the patients were compared among the UA, NSTEMI and STEMI groups, the mean P-LCR value of UA patients was 23.61 (95% CI: 21.97-25.25); NSTEMI patients had 28.34 (95% CI: 24.86-31.83); and STEMI group was found to be 25.71 (95% CI: 22.07-29.35). There was a statistically significant difference between the P-LCR values of the groups ($P=0.022$). However, in the post-hoc analysis, only statistical difference was found between UA and NSTEMI groups ($P=0.017$).

Discussion

According to the data obtained in our study, it was found that male patients diagnosed with the ACS were 67.9%; the mean age was 44.66 years, and the final diagnoses were

Table 1. Descriptive values of parameters.

		Mean	Std. Deviation	95% Confidence Interval for Mean		*P* value
				Lower Bound	Upper Bound	
P-LCR	UA	23,6111	6,51671	21,9699	25,2523	**0,022**
	NSTEMI	28,3423	8,62926	24,8569	31,8277	
	STEMI	25,7100	7,77526	22,0711	29,3489	
	Total	25,1248	7,49295	23,7022	26,5474	
Age	UA	41,03	12,494	37,89	44,18	**0,000**
	NSTEMI	54,42	10,569	50,15	58,69	
	STEMI	54,30	12,599	48,40	60,20	
	Total	46,66	13,682	44,06	49,26	
Total Cholesterol	UA	176,62	124,027	145,38	207,85	0,448
	NSTEMI	199,23	54,767	177,11	221,35	
	STEMI	203,80	46,636	181,97	225,63	
	Total	187,00	100,294	167,96	206,04	
HDL- cholesterol	UA	40,10	6,480	38,46	41,73	0,615
	NSTEMI	39,31	8,019	36,07	42,55	
	STEMI	38,40	6,589	35,32	41,48	
	Total	39,60	6,860	38,29	40,90	
LDL- cholesterol	UA	109,21	33,397	100,80	117,62	**0,000**
	NSTEMI	139,23	32,242	126,21	152,25	
	STEMI	147,05	35,916	130,24	163,86	
	Total	123,31	37,273	116,24	130,39	
Trigliceride	UA	142,33	72,385	124,10	160,56	**0,004**
	NSTEMI	200,92	100,788	160,21	241,63	
	STEMI	136,40	68,258	104,45	168,35	
	Total	155,22	82,731	139,51	170,93	

Note: P-LCR: platelet large cell ratio, UA: unstable angina, NSTEMI; Non-ST elevation myocardial ınfarction, STEMI; ST-elevation myocardial ınfarction, HDL; high-density lipoprotein, LDL: low-density lipoprotein.

57.8% UA, 23.9% NSTEMI and 18.3% STEMI. Although the study had a parallel outcome with the literature, which was more common in men, the average age was lower than the literature due to the fact that the patients older than 70 were excluded from our study.[9]

In our study, it was found that LDL-cholesterol levels were higher in STEMI patients and triglyceride levels were higher in UA patients, and were found to be similar to the literature.[10] These results indicate the importance and the expression of the higher cholesterol levels in accordance with the increase of the P-LCR levels. According to the post-hoc analysis, LDL-cholesterol values differed between UA and NSTEMI and between UA and STEMI patients, whereas its levels did not significantly differ between NSTEMI and STEMI groups ($P < 0.001$; $P < 0.001$; $P > 0.05$; respectively). There was no statistically significant difference between triglyceride levels of UA and STEMI groups ($P > 0.05$). The mean P-LCR level of ACS patients was found to be 25.12 % (SD: 7.49). The mean P-LCR value of UA patients was 23.61 (95% CI: 21.97-25.25); of NSTEMI patients were 28.34 (95% CI: 24.86-31.83); and of STEMI was found to be 25.71 (95% CI: 22.07-29.35). The difference of P-LCR values of the groups were statistically significant ($P = 0.022$). However, interestingly, in the post-hoc analysis, only UA and NSTEMI groups differed statistically ($P = 0.017$).

There are several studies investigating the relationship between P-LCR and ACS in the literature. From these studies, Lv et al investigated the relationship between P-LCR and inflammatory markers in ACS patients and found that P-LCR levels were significantly higher in NSTEMI patients, but they did not find a statistically significance in STEMI patients.[11] These results have yielded similar results with our research. In another study, the relationship between P-LCR and STEMI was investigated, and survival analysis was performed with test results at the time of first arrival, prior to percutaneous intervention.[12] In this study, only STEMI patients were studied and according to the results, P-LCR increase was correlated with high mortality and the cut-off value of P-LCR was obtained as 38.1%. However, it was stated that the patients were given 300 mg of aspirin before they were admitted to the hospital and their blood was taken after aspirin admission, but the effects of aspirin use on P-LCR were ignored. In our study, the patients who were given aspirin were excluded in order to be free from the effects of aspirin on platelet parameters. In a study comparing P-LCR testing in UA, NSTEMI and STEMI patients, the P-LCR value was higher in STEMI patients and the cut-off value was 20.25%.[8] In this study, the AUC value of 0,560 and sensitivity/specificity values were 44%-68%. In this study, all patients were given 300 mg aspirin before

Table 2. Post-hoc analyses of the study

			P value
P-LCR	UA	NSTEMI	**0.017**
		STEMI	0.503
	NSTEMI	UA	**0.017**
		STEMI	0.448
	STEMI	UA	0.503
		NSTEMI	0.448
Age	UA	NSTEMI	**0.000**
		STEMI	**0.000**
	NSTEMI	UA	**0.000**
		STEMI	0.999
	STEMI	UA	**0.000**
		NSTEMI	0.999
Sex	UA	NSTEMI	0.153
		STEMI	**0.016**
	NSTEMI	UA	0.153
		STEMI	0.598
	STEMI	UA	**0.016**
		NSTEMI	0.598
Death in first month	UA	NSTEMI	**0.026**
		STEMI	**0.006**
	NSTEMI	UA	**0.026**
		STEMI	0.779
	STEMI	UA	**0.006**
		NSTEMI	0.779
Total Cholesterol	UA	NSTEMI	0.600
		STEMI	0.545
	NSTEMI	UA	0.600
		STEMI	0.987
	STEMI	UA	0.545
		NSTEMI	0.987
HDL-cholesterol	UA	NSTEMI	0.876
		STEMI	0.605
	NSTEMI	UA	0.876
		STEMI	0.898
	STEMI	UA	0.605
		NSTEMI	0.898
LDL-cholesterol	UA	NSTEMI	**0.001**
		STEMI	**0.000**
	NSTEMI	UA	**0.001**
		STEMI	0.715
	STEMI	UA	**0.000**
		NSTEMI	0.715
Triglyceride	UA	NSTEMI	**0.006**
		STEMI	0.954
	NSTEMI	UA	**0.006**
		STEMI	**0.020**
	STEMI	UA	0.954
		NSTEMI	**0.020**

Note: P-LCR: platelet large cell ratio, UA: unstable angina, NSTEMI; Non-ST elevation myocardial ınfarction, STEMI; ST-elevation myocardial ınfarction, HDL; high-density lipoprotein, LDL: low-density lipoprotein.

their blood was taken and the effects of aspirin were also ignored. High P-LCR levels were found statistically significant in a study that investigated the relationship between the P-LCR levels and coronary tortuosity; the finding showing the presence of myocardial ischemia even if coronary artery disease was not present.[13] The most important point of this study is the exclusion of aspirin-treated patients, unlike other ACS studies.

The effects of the aspirin on platelet parameters should be considered in the studies. In a research investigating the relationship of aspirin and clopidogrel with MPV in ACS patients, a paradoxical increase in MPV was found after anti-platelet therapy.[14] The increase in MPV levels may also lead to higher P-LCR levels. So, this result proposes that P-LCR levels from all aspirin-treated patients may have an increase caused by aspirin, not just ACS itself. Therefore, studies exploring the relationship between the P-LCR increase and ACS should be investigated by eliminating confounder variables such as prior aspirin usage. Our study was the first in the literature which investigated and determined the relationship between ACS and high P-LCR levels, by excluding patients who were given aspirin.

Limitations of the study

Our study is a retrospective single-centered study, and prospective comprehensive studies are needed. Although there have been studies investigating the relationship between P-LCR and ACS, there is a need to compare P-LCR levels between groups in patients who have been given aspirin and patients who have not been given aspirin, to identify effects of aspirin on P-LCR.

Conclusion

The most notable limitation of the studies in the literature investigating the relationship between P-LCR levels and ACS is that the hemogram test results are influenced by the aspirin that patients take. Aspirin is likely to have different effects on P-LCR levels. In our study, for the first time in the literature, the relationship between P-LCR elevations and ACS in patients who had hemogram tests before aspirin usage was investigated and a statistically significant difference was found.

Conflict of Interest

The authors have no conflict of interest to declare.

Ethical Approval

The study protocol was approved by the ethical committee of Atatürk University, Faculty of Medicine Ethics Committee (Number: 07/50, date: 07.11.2019).

Author's contributions

Study design, ET, MB, IO; Study conduct, MB, MC; Writing, ET, MB, MC; Analysis, ET, MB, IO; Critical review and article

Study Highlights

What is current knowledge?

- There are several studies investigating the relationship between P-LCR and ACS in the literature. From these studies, Lv et al investigated the relationship between P-LCR and inflammatory markers in ACS patients and found that P-LCR levels were significantly higher in NSTEMI patients, but they did not find a statistically significance in STEMI patients. In another study, the relationship between P-LCR and STEMI was investigated, and survival analysis was performed with test results at the time of first arrival, prior to percutaneous intervention.In this study, only STEMI patients were studied and according to the results, P-LCR increase was correlated with high mortality and the cut-off value of P-LCR was obtained as 38.1%

What is new here?

- In our study, for the first time in the literature, the relationship between P-LCR elevations and ACS in patients who had hemogram tests before aspirin usage was investigated and a statistically significant difference was found.

search, MC, MB; data gathering, ET, MB, MC, IO.

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