Effect of cardiac rehabilitation on neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in ST elevation myocardial infarction patients

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ABSTRACT

Objectives: Cardiac rehabilitation is known to have positive effects on the inflammatory processes. The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) were found to be indicative of inflammation. The purpose of this study is to determine the effects of cardiac rehabilitation on the NLR and PLR ratios of ST elevation myocardial infarction (STEMI) patients.

Methods: The study includes 101 STEMI patients that underwent primary percutaneous coronary intervention (PCI). The patients were randomized into two groups: the cardiac rehabilitation group (CR group, n = 68), and the control group (n = 33). One month after primary PCI, cardiac rehabilitation was applied to CR group with cycle ergometer for 8 weeks (30 sessions). The NLR and PLR parameters were calculated from the complete blood count results from before and after the cardiac rehabilitation application for both groups.

Results: When the baseline values of the two groups were evaluated, the hemoglobin value of the control group (13.10 ± 1.52 g/dL vs. 13.79 ± 1.26 g/dL; $p = 0.03$) and the PLR value of the CR group (122.50 ± 43.89 vs. 92.41 ± 23.70; $p = 0.001$) were significantly higher. The post-cardiac rehabilitation complete blood count parameters, and the NLR and PLR values were similar in both groups. The NLR (3.11 ± 1.95 vs 2.39 ± 1.03; $p = 0.003$) and PLR (122.50 ± 43.89 vs. 108.68 ± 41.83; $p = 0.025$) parameters significantly decreased after the cardiac rehabilitation application in the CR group, whereas there wasn't a change in the control group.

Conclusion: It was found that cardiac rehabilitation applied in STEMI patients caused a significant decrease in NLR and PLR parameters, which are indicators of inflammation.

Keywords: cardiac rehabilitation, myocardial infarction, inflammation, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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Acute myocardial infarction (MI) is a serious disease that develops due to sudden decrease or discontinuation of coronary blood flow due to various causes and results in different degrees of ischemic necrosis of the myocardial tissue associated with the artery. Restoration of coronary blood flow is of great importance in the early stage of the disease, within 12 hours of the onset of symptoms and in patients with persistent ST-segment elevation or possible new left bundle branch block (LBBB). For this purpose, primary percutaneous coronary intervention (PCI) is applied.

Chronic inflammation has an important role in atherosclerosis, coronary artery disease, and STEMI.

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This inflammation is related to the onset and progression of the disease, and plaque rupture and thrombus formation in the AMI process. Leukocytes play an important role in this inflammatory process [1]. The neutrophil-to-lymphocyte ratio (NLR) is one of the important parameters that can be used to determine the severity of this inflammatory process. High NLR levels are one of the most important in-hospital and long-term mortality indicators in acute coronary syndrome (ACS). Platelet-to-lymphocyte ratio (PLR) is also a parameter showing chronic inflammation.

Cardiac rehabilitation (CR) can be defined as all of the activities necessary to ensure that cardiovascular patients are able to regain their physical, mental and social status as early as possible [2]. Numerous studies have documented the efficacy of exercise-based CR after extensive MI. Exercise training in CR after acute coronary syndromes has multifaceted effects. Exercise training appears to be associated with endothelial function, inflammation, cardiovascular autonomic function regulation and risk factor control. Exercise also has benefits related to antithrombotic and ischemic preconditioning.

We have recently published a study about the effects of CR on cardiac autonomic functions; we re-analyzed the study data and evaluate NLR, and PLR. Using these data, we examined the effect of CR on the NLR, PLR and on the inflammatory process in STEMI patients.

METHODS

Patient Selection and the Procedure

The study includes 101 STEMI patients that admitted to a public University hospital in Turkey in 2014 with STEMI diagnosis, who underwent primary PCI (aged 35-85). CR was applied to 68 of these patients at least 1 month after primary PCI, and 33 were randomised in the control group. The exclusion criteria were as follows: patients with severe valve disease, who were over 85 years of age, respiratory dysfunction, decompensated heart failure, uncontrolled hypertension (HT) and diabetes mellitus (DM), patients with a cerebrovascular disease with orthopedic restriction, and who did not accept the CR program for various reasons. Patients who did not have a sinus rhythm, or were on a pacemaker were also excluded from the study. Patients' anamnesis and physical examination findings, atherosclerosis risk factors, demographic data, height, weight, body mass indexes, biochemical parameters, lipid parameters were recorded. NLR and PLR values before rehabilitation were calculated from the complete blood counts taken at least 1 month after STEMI in patients (CR and control groups). Patients in the CR group were taken to the 8-week CR program at least 1 month after STEMI. Eight weeks of cycling ergometry was performed for an average of 4 sessions per week for 30 minutes (5 minutes warming, 20 minutes aerobic exercise to reach 70-85% of heart rate, 5 minutes cooling) in the direction of heart rate and the watt level. At the end of the rehabilitation, the complete blood count measurement was repeated and the NLR and PLR values were recalculated. Again blood samples were taken from the patients in the control group 1 month after the first blood samples and the NLR and PLR values were calculated. All patients were echocardiographically evaluated using standard techniques using the GE Vivid 7 pro (General Electric Company, Connecticut, USA) instrument with a 3.5 MHz phase-adjusted transducer and in accordance with the recommendations of the American Echocardiography Society guideline.

Statistical Analysis

The data were analyzed using the SPSS (IBM SPSS Statistics Version 22) program. Continuous variables were expressed as mean ± standard deviation, and categorical variables as percent. The normal distribution of continuous variables was assessed by the Shapiro-Wilk normality test. Independent sample T-test or Mann-Whitney U test was used to compare parametric data, and Chi-square or Fisher's Exact test was used to compare categorical variables. Repeated measurements (pre- and post-rehabilitation) were performed with the Wilcoxon signed-rank test. $p < 0.05$ was accepted as significant in all statistical measures.

RESULTS

When the demographic and laboratory findings of the patients were examined, there were no significant differences in age, gender, DM, HT, hyperlipidemia.

Table 1. Baseline characteristics of the study patients

	CR Group (n = 68)	Control Group (n = 33)	*p* value
Age (years)	58.23 ± 9.69	55.48 ± 9.99	0.21
Gender			
Male, n (%)	54 (79.4)	27 (81.8)	0.77
Female, n (%)	14 (20.6)	6 (18.2)	
Diabetes mellitus, n (%)	13 (19.4)	7 (21.9)	0.77
Hypertension, n (%)	24 (35.8)	6 (18.8)	0.08
Smoking, n (%)	31 (46.3)	21 (70)	0.03
Previous PCI, n (%)	7 (10.4)	4 (12.1)	0.80
LVEF (%)	42.13 ± 11.07	42.12 ± 9.13	0.90
Systolic BP (mmHg)	115.80 ± 9.79	111.77 ± 13.81	0.10
Diastolic BP (mmHg)	71.02 ± 7.94	69.03 ± 8.4	0.28
Average HR (beats per minute)	66.23 ± 8.04	69.69 ± 10.31	0.069
WBC count (×10^3)	9.61 ± 2.80	9.5 ± 2.34	0.97
Neutrophil count (×10^3)	6.26 ± 2.39	5.84 ± 2.07	0.40
Lymphocyte count (×10^3)	2.29 ± 0.87	2.62 ± 0.72	0.07
Eosinophil count (×10^2)	2.63 ± 2.21	2.06 ± 1.63	0.20
Hemoglobin (g/dL)	13.10 ± 1.52	13.79 ± 1.26	**0.03**
Thrombocyte count (×10^3)	256.70 ± 83.85	230.41 ± 42.69	0.27
NLR	3.11 ± 1.95	2.41 ± 1.15	0.065
PLR	122.50 ± 43.89	92.41 ± 23.70	**0.001**
Urea (mg/dL)	15.77 ± 4.51	15.51 ± 5.43	0.49
Creatinine (mg/dL)	0.8 ± 0.17	0.79 ± 0.18	0.55
Total colesterol (mg/dL)	179.96 ± 47.41	182.48 ± 41.33	0.51
LDL-C (mg/dL)	120.36 ± 44.61	117.84 ± 35.26	0.70
Sodium (mEq/L)	140.07 ± 2.57	140.64 ± 2.25	0.19
Potassium (mEq/L)	4.43 ± 0.39	4.27 ± 0.45	0.10
Rehabilitation start (days)	62.21 ± 29.33	-	
Drugs			
ASA, n (%)	68 (100)	33 (100)	1.0
Clopidogrel, n (%)	42 (61.8)	17 (51.5)	0.32
Ticagrelor, n (%)	26 (38.2)	16 (48.5)	0.32
Beta blocker, n (%)	66 (98.5)	33 (100)	0.99
ACEI, n (%)	60 (89.6)	30 (90.9)	0.83
ARB, n (%)	6 (9.1)	2 (6.1)	0.60
Statin n (%)	68 (100)	32 (97)	0.99
Spironolactone, n (%)	27 (40.9)	9 (27.3)	0.18
Myocardial infarct area			
Anterior, n (%)	34 (50)	15 (45.5)	0.66
Inferior, n (%)	34 (50)	18 (54.5)	

Data are shown as mean±standard deviation or number (%). ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, ASA = acetilsalysilic acid, BP =blood pressure, CR = cardiac rehabilitation, HR =heart rate, LDL-C= low density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, NLR = neutrophil-to-lymphocyte ratio, PCI = percutaneous coronary intervention, PLR = platelet-to-lymphocyte ratio, WBC = white blood cell

Table 2. Comparison of the hemogram parameters after rehabilitation between groups

	CR Group (n = 68)	Control Group (n = 33)	*p* value
WBC count (×10^3)	8.75 ± 2.36	8.85 ± 1.32	0.81
Neutrophil count (×10^3)	5.40 ± 1.49	5.23 ± 1.63	0.61
Lymphocyte count (×10^3)	2.47 ± 0.83	2.49 ± 0.68	0.91
Eosinophil count (×10^2)	2.30 ± 1.49	1.93 ± 1.12	0.22
Hemoglobin (g/dL)	13.54 ± 1.26	13.95 ± 1.23	0.13
Thrombocyte count (×10^3)	245.74 ± 57.29	230.74 ± 39.09	0.19
NLR	2.39 ± 1.03	2.23 ± 0.96	0.48
PLR	108.68 ± 41.83	99.65 ± 32.88	0.29

Data are shown as mean±standard deviation. CR = cardiac rehabilitation, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, WBC = white blood cell

There was no significant difference in echocardiographic findings. Among the complete blood count parameters, the hemoglobin value was significantly higher in the control group (13.10 ± 1.52 g/dL vs 13.79 ± 1.26 g/dL; $p = 0.03$), and the PLR was significantly higher in the CR group (122.50 ± 43.89 vs 92.41 ± 23.70; $p = 0.001$) (Table 1). There was no difference between the groups in terms of MI region and applied treatments (Table 1). NLR and PLR values of the whole blood count parameters after the rehabilitation period were similar in both groups (Table 2).

Complete blood count parameters, NLR and PLR values of the CR group and the control group were analyzed before and after rehabilitation. Leukocyte and neutrophil counts in the CR group were significantly higher than those before CR, while hemoglobin values were significantly lower (Table 3). NLR (3.11 ± 1.95 vs 2.39 ± 1.03; $p = 0.003$) and PLR (122.50 ± 43.89 vs. 108.68 ± 41.83; $p = 0.025$) ratios of the CR group were significantly decreased with CR (Table 3). There was no significant difference in NLR and PLR values of the control group before and after CR period (Table 3).

Table 3. Rehabilitation group and control group; comparison of hemogram parameters before and after rehabilitation

	CR Group (n = 68)			Control Group (n = 33)		
	Before rehabilitation	After rehabilitation	*p* value	Initial	Control	*p* value
WBC count (×10^3)	9.61 ± 2.80	8.75 ± 2.36	**0.016**	9.5 ± 2.34	8.85 ± 1.32	**0.017**
Neutrophil count (×10^3)	6.26 ± 2.39	5.40 ± 1.49	**0.007**	5.84 ± 2.07	5.23 ± 1.63	0.180
Lymphocyte count (×10^3)	2.29 ± 0.87	2.47 ± 0.83	0.067	2.62 ± 0.72	2.49 ± 0.68	0.068
Eosinophil count (×10^2)	2.63 ± 2.21	2.30 ± 1.49	0.219	2.06 ± 1.63	1.93 ± 1.12	0.395
Hemoglobin (g/dL)	13.10 ± 1.52	13.54 ± 1.26	**< 0.001**	13.79 ± 1.26	13.95 ± 1.23	0.059
Platelet count (×10^3)	256.70 ± 83.85	245.74 ± 57.29	0.38	230.41 ± 42.69	230.74 ± 39.09	0.739
NLR	3.11 ± 1.95	2.39 ± 1.03	**0.003**	2.41 ± 1.15	2.23 ± 0.96	0.686
PLR	122.50 ± 43.89	108.68 ± 41.83	**0.025**	92.41 ± 23.70	99.65 ± 32.88	0.161

Data are shown as mean±standard deviation. CR = cardiac rehabilitation, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, WBC = white blood cell

DISCUSSION

In our study, the NLR and PLR values in patients who had STEMI had significantly decreased after a CR program that was applied one month after the primary CPI. When this value is evaluated as an inflammation parameter, it can be said that CR has a positive effect on the cardiac inflammatory process. Chronic inflammation plays an important role in the pathogenesis of atherosclerosis. As a result, a large number of intracoronary atherosclerotic plaques form. Plaques include a fibrous capsule, a nucleus composed of necrotic tissue and cholesterol, smooth muscle cells, calcification, and cells involved in inflammation. Mild or moderate stenotic plaques were detected in 3/4 of the patients with myocardial infarction in the responsible lesion area, and the concept of vulnerable plaques become prominent as this condition does not develop only in areas with severe stenosis. Vulnerable plates are probably already in an inflammatory process that has already begun. This process facilitates the plaque rupture [3]. It is known that calcification is not a feature of vulnerable plaques. In a study published in 2014, it was found that NLR value correlated with the presence of noncalcified plaques in the patient [4].

In a meta-analysis published in 2018; patients with higher NLR values had more frequent in-hospital angina, advanced cardiac insufficiency, arrhythmia, major cardiovascular events, death due to cardiac causes, all-cause mortality, stent thrombosis, non-fatal myocardial infarction, and no-reflow phenomena. In addition, long-term mortality, cardiac mortality and major cardiovascular events were significantly more frequent; but there was no difference in non-fatal myocardial infarctions [5]. Thus, cardiovascular outcomes correlate with inflammation level. The ability of the NLR level to predict this may suggest that this parameter may be useful in terms of clinical follow-up.

The NLR used in various chronic diseases is an important parameter showing the chronic inflammation used in patients with coronary artery disease and ACS. Different cut-off levels were determined for this value in different studies. In general, a high value has been shown to be associated with poor cardiovascular outcome. In a study published in 2014 that was conducted with 250 patients, it was determined that an NLR value above 7.4 is an independent indicator of short- (< 30 days) and long-term (< 2 years) deaths [6]. In our study, the NLR value was initially 3.11, and 2.39 afterward. These findings were statistically significant. Cardiac rehabilitation is known to decrease proinflammatory cytokine levels and consequently has an inflammation-reducing effect by reducing oxidative stress. When evaluated in this respect, this value can not be considered as high risk in the beginning or after rehabilitation. However, it might have a positive effect on chronic inflammation and its cardiovascular effects. This decline in value supports this notion. It can be said that; the higher the NLR value, the greater the efficacy of cardiac rehabilitation. Additional research is needed to confirm this.

PLR value is also a parameter showing chronic inflammation like NLR. Azab *et al*. [7] conducted a study in 619 patients with non-STEMI. It has been shown that high PLR value increases mortality; and that among patients with PLR > 176, double-antiplatelet therapy reduced mortality compared to single-antiplatelet treatment. In our study, PLR value decreased from 122 to 108 after rehabilitation, and this result is statistically significant. From this point of view, it can be predicted that chronic inflammation can be regressed with cardiac rehabilitation. Further studies with larger samples are required to support these findings.

Limitations

Among the limitations of our study were as follows: the relatively low number of patients, not examining other inflammatory parameters (hs-CRP, etc.), evaluating only STEMI patients.

CONCLUSION

In our study, the NLR and PLR values in patients who had STEMI had significantly decreased after a CR program that was applied one month after the primary PCI. This suggests that CR has a positive effect on inflammation. Our study is the first in the literature to assess the effect of CR on the cardiac inflammatory process as a guideline for studies to be performed in larger patient populations.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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