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Role of simple inflammatory parameters in predicting the severity of coronary artery disease

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SUMMARY

OBJECTIVE: In our study, we aimed to find simple, useful biomarkers in patients with non-ST elevation myocardial infarction to predict coronary artery severity.

METHODS: Between May 2022 and December 2022, patients diagnosed with non-ST elevation myocardial infarction according to the European cardiology guidelines were included in our study. The Synergy between PCI with Taxus and Cardiac Surgery score was calculated to determine the severity of coronary artery disease. These patients were classified into two groups according to Synergy between PCI with Taxus and Cardiac Surgery≥23 and Synergy between PCI with Taxus and Cardiac Surgery<23 scores. Biochemical markers such as platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were studied in blood tests taken before coronary angiography in patients diagnosed with non-ST elevation myocardial infarction according to current guidelines. These two groups were compared in terms of the data obtained.

RESULTS: There were 281 patients in group 1 and 67 patients in group 2. There was no significant difference between the two groups in terms of demographic data such as age and gender. Platelet-to-lymphocyte ratio [group 1=125 (26–134) and group 2=156 (73–293); p=0.001] and neutrophil-to-lymphocyte ratio [group 1=2.71 (1.3–30.2) and group 2=3.2 (2.1–32.1); p=0.002] were higher in the group of patients with a Synergy between PCI with Taxus and Cardiac Surgery score of <23, while lymphocyte-to-monocyte ratio [group 1=3.6 (0.56–11) and group 2=3.4 (0.64–5.75); p=0.017] was lower in group 2.

CONCLUSION: We observed that elevated platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios showed coronary artery severity. Multivessel disease and chronic total occlusion rates were observed to be higher in patients with high platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios.

KEYWORDS: Non-ST elevated myocardial infarction. Coronary artery disease. Inflammation. Blood platelets.

INTRODUCTION

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score is an indicator of the complexity of coronary artery disease. Various clinical outcomes in non-ST elevation myocardial infarction (NSTEMI) patients have been extensively studied using the SYNTAX score II, and this score is a reliable indicator of mortality in patients with acute coronary syndrome (ACS) who underwent PCI[1]. However, the SYNTAX score is an angiographic scoring system. Coronary angiography may be delayed in patients presenting with NSTEMI. Easy, practical, noninvasive, and faster markers are needed to predict the complexity of coronary artery disease. For complicated lesions, arterial sclerosis is in an advanced state. Atherosclerosis is recognized as a continuous, dynamic, and inflammatory process in the circulatory system, in addition to being a cholesterol problem that builds up on the arterial walls in the subintimal region[2]. The immune system and coagulation cells have important roles in the development and complications of atherosclerotic plaque. Many illnesses, including chronic heart failure, cancer, metabolic problems, and cardiovascular disease, have been related to inflammation[3]. For individuals with coronary artery disease, the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) have both offered valuable data for predicting future outcomes. Inflammation that is linked to adverse outcomes in individuals with ACS is shown by low lymphocyte numbers[4]. In the study of Kurtul et al., in patients with ACS, the platelet-lymphocyte ratio was significantly higher in patients with a high SYNTAX score; these patients also had significantly higher in-hospital mortality[5]. Cardiovascular diseases such as stable coronary heart disease, ACS, and non-ST elevation MI are associated with inflammation[6]. NLR is a novel marker of inflammation in various conditions including inflammatory bowel disease, diabetes mellitus, gastrointestinal conditions, thyroiditis, and

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SARS-CoV-2 infection[7]. In addition, it is associated with cardiac conditions[8]. On the contrary, elevated PLR has been reported in thyroid conditions, gastrointestinal diseases, thyroiditis, cancer, diabetes mellitus, irritable bowel disease, and COVID-19 infection[9,10]. Therefore, studying PLR and NLR as predictors of heart disease makes sense. By evaluating these biochemical values in NSTEMI, we may predict the high SYNTAX score, and these biochemical values may guide us in the classification of high-risk patients.

METHODS

Study population

Patients diagnosed with NSTEMI according to the European cardiology guidelines were included in our study. Patients who were referred to the emergency department with chest pain and had a change in electrocardiography and a significant increase in high-sensitive Troponin T levels between May 2022 and December 2022 were included. Patients with severe renal failure (creatinine>2 mg/dL), active infection, age <18 years, and patients with active inflammatory disease and malignancy were excluded from the study. We were able to ascertain the essential clinical characteristics of the patients by looking through the hospital's database. Blood samples were collected at the first arrival. An automated device was used to measure biochemical values and perform a complete blood count from the blood. Being treated for high cholesterol or having a total cholesterol level over 220 mg/dL were defined as signs of hyperlipidemia. Hypertension was defined as blood pressure exceeding 140/90 mmHg or the use of an antihypertensive medication. Glycated hemoglobin A1c values of 6.5%, usage of antidiabetic medicines, or fasting plasma glucose levels of 7.0 mmol/L (126 mg/dL) were all regarded as signs of diabetes mellitus. The study, which was conducted in compliance with the Declaration of Helsinki, was approved by the local ethics committee.

Coronary angiography

Antiplatelet and anticoagulant therapy was started in all patients as soon as the diagnosis of NSTEMI was made in the emergency department. The analysis of coronary angiograms was performed by two independent cardiologists who were unaware of the patient's information. A major coronary artery with a stenosis of 50% or more was considered to be significant. SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) scores II were calculated for all patients after the angiography procedure[11]. Patients were classified into two groups with a SYNTAX score of ≥23 and a SYNTAX score of <23.

Statistical analysis

The statistical analysis was carried out using the statistical software SPSS 22.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean±standard deviation (SD) or median (minimum-maximum). Categorical variables were expressed as percentages and compared using chi-square or Fischer's exact tests. The normality of data distributions was evaluated using the Kolmogorov-Smirnov test. An independent samples t-test was used for continuously distributed data with a normal distribution. Non-normally distributed data were examined using the Mann-Whitney U test. The PLR, LMR, and NLR ratio cutoff values were determined using receiver-operating characteristic analyses (ROC) to predict the degree and complexity of coronary artery disease in individuals with NSTEMI. We used Youden's J statistic for finding the best cutoff values. Univariate and multivariate regression analyses were performed for independent parameters in predicting the severity and complexity of coronary artery disease in patients with NSTEMI. The relationship between the PLR, LMR, and NLR ratios and the severity of the coronary arteries was examined using the Spearman correlation test. For $p<0.05$, statistics were deemed significant.

RESULTS

In total, the data of 432 patients were analyzed. Two groups were formed in which basic clinical and biochemical parameters were similar. Notably, 84 patients were excluded from the study. As a result, 348 patients were included in the study. Group I includes patients with a SYNTAX score of <23, and group II includes patients with a SYNTAX score of ≥23. Table 1 shows the basic characteristics and laboratory findings. There was no difference between the two groups in terms of demographic characteristics. Multi-vessel disease and chronic total occlusion rates were higher in group I. Left ventricular ejection fraction rates were lower in group II. Regarding the medical treatment given to the study's participants, there was no difference between the two groups. The NLR, PLR, and Troponin T levels were statistically high in Group II [NLR 3.2 (2.1–32.1) and 2.71 (1.3–30.2), p=0.002; PLR 156 (73–293) and 125 (26–134), p=0.001; Troponin T 424 (9–2836) and 265 (6–3501), p=0.003]. LMR and lymphocyte counts were statistically lower in Group II. [LMR 3.6 (0.56–11) and 3.4 (0.64–5.75), p=0.017; lymphocyte count 2.4±1 and 2±1.2, p=0.008].

The ROC analysis of PLR, NLR, and LMR values for predicting the severity and complexity of coronary artery disease in patients with NSTEMI were as follows: PLR cutoff value of ≥117, AUC: 0.634; 95%CI (0.558–0.710) with 64.2% sensitivity and 63.3% specificity, p=0.001, NLR cutoff value of

≥3.5, AUC: 0.407; 95%CI (0.332–0.482) with 44.8% sensitivity and 45.2% specificity, p=0.018, LMR cutoff value of ≤2.8, AUC: 0.622; 95%CI (0.544–0.701) with 62.7% sensitivity and 61.9% specificity, p=0.002 (Figure 1). A moderately positive correlation between PLR, NLR, and SYNTAX score II was found using Spearman correlation analysis, respectively (PLR r=0.55, p<0.001, and NLR r=0.51, p=0.002). A moderately negative correlation was found between LMR and

Table 1. Baseline clinical and angiographic characteristics of the study population according to the Synergy between PCI with Taxus and Cardiac Surgery score II.

Variables	Group I n=281	Group II n=67	p-value
Male, n (%)	185 (65.8%)	37 (55.2%)	0.104
Age (years)	61±12.7	62±11.2	0.212
Weight (kg)	78±14.6	77±15.8	0.582
Height (cm)	166±9.1	165±10.4	0.478
Body mass index (kg/m^2)	28.5±4.9	28.3±5.2	0.826
Hypertension, n (%)	142 (50.5%)	39 (58.2%)	0.258
Diabetes mellitus, n (%)	91 (32.4%)	30 (44.8%)	0.056
Hypercholesterolemia, n (%)	90 (32%)	21 (31.3%)	0.914
Smoking, n (%)	20 (7.1%)	5 (7.4%)	0.896
Stroke, n (%)	6 (2.1%)	2 (3%)	0.677
Prior CABG history, n (%)	10 (3.6%)	4 (6%)	0.367
Prior myocardial infarction, n (%)	21 (7.5%)	7 (10.4%)	0.421
Left ventricular ejection fraction	53±9	45±12	**<0.001**
Multi-vessel disease, n (%)	135 (48%)	65 (97%)	**<0.001**
Chronic total occlusion, n (%)	29 (10.3%)	27 (40.2%)	**<0.001**
Biochemical and hematological measurements of the study population			
Hemoglobin (g/dL)	14.1±1.9	14.3±1.9	0.798
WBC (×10^9/L)	9.8±3.2	9.7±3.3	0.784
Neutrophil (×10^9/L)	6.4±2.8	6.8±3	0.303
Lymphocyte (×10^9/L)	2.4±1	2±1.2	**0.008**
Monocyte (×10^9/L)	0.67±0.27	0.62±0.23	0.190
Platelet (×10^9/L)	246.3±78.3	244.3±73	0.850
NLR	2.71 (1.3–30.2)	3.2 (2.1–32.1)	**0.002**
PLR	125 (26–134)	156 (73–293)	**0.001**
LMR	3.6 (0.56–11)	3.4 (0.64–5.75)	**0.017**
Glucose (mg/dL)	156±18	159±72	0.241
Creatinine (mg/dL)	1±0.3	1.1±0.3	0.052
Total cholesterol (mg/dL)	209±63	201±44	0.541
Triglycerides (mg/dL)	156±87	159±71	0.802
LDL-C (mg/dL)	125±42	120±38	0.386
HDL-C (mg/dL)	42±11	43±9.4	0.406
Hs-CRP (mg/L)	7.2 (0.6–9.9)	8.1 (0.9–10.9)	0.081
Uric acid (mg/L)	5.7±1.5	5.9±1.5	0.494
High sensitivity Troponin T (ng/mL)	265 (6–3501)	424 (9–2836)	**0.003**
CK-MB (ng/mL)	14 (0.78–281)	20 (2.91–105)	0.059
GFR (mL/min/1.73 m^2)	70±24	68±20	0.320

CABG: coronary artery bypass graft; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio. Bold values indicate statistical significance at the p<0.05 level.

SYNTAX score II (r=-0.52, p<0.001). In univariate and multivariate logistic regression analysis, a high PLR ratio was an independent predictor of a high SYNTAX score II (OR: 1003; 95%CI (0.998–1.009), p=0.019) (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the association between composite inflammatory ratios and angiographic severity of coronary artery disease in patients presenting with NSTEMI. In this observational study, we found NLR, PLR, and LMR were associated with high SYNTAX scores. PLR, NLR, and LMR may be capable of predicting the severity and complexity of coronary artery disease. Moreover, a high PLR ratio was an independent predictor of a high SYNTAX score.

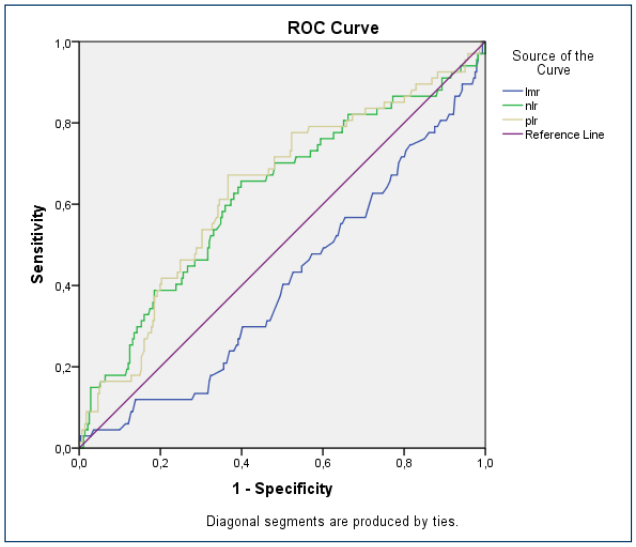

Figure 1. The receiver operating characteristic curve analysis for the cutoff values of platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio for predicting a high Synergy between PCI with Taxus and Cardiac Surgery score II. NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio.

It is not unexpected that individuals with coronary artery disease have elevated levels of inflammatory indicators such as neutrophil and platelet counts, red blood cell distribution width, NLR, and PLR. At the onset of atherosclerosis, platelets are crucial. They release inflammatory immunomodulatory molecules such as prostaglandin E2 and platelet-activating factor. Inflammation related to adverse outcomes in patients with ACS is demonstrated by low lymphocyte counts[12,13]. There is a complex relationship between innate immunity and adaptive immunity during the rupture of atherosclerotic plaque. Neutrophils that are attempting suicide may release pro-oxidant and pro-inflammatory mediators and form neutrophil extracellular traps. Neutrophil extracellular traps may cause the development of atherosclerotic plaque and increase thrombus stability[14]. NLR is regarded as a sign of subclinical inflammation. NLR is an independent predictor of cardiovascular events and mortality in ST-segment elevation myocardial infarction[15]. Blood components, such as platelets, neutrophils, and lymphocytes, are included in the systemic immune inflammation index, a novel inflammation marker. In previous studies, systemic immune inflammation index was related to an increased risk of cardiac death, nonfatal MI, nonfatal stroke, and heart failure[16].

In many previous studies and meta-analyses, high PLR rates were found in individuals with stable coronary artery disease as a prognostic marker[17]. In clinical practice, PLR, a systematic inflammatory maker, was used to predict the outcome of oncologic illnesses[18]. PLR has also been used as a prognostic marker in coronary slow flow, coronary collateral circulation, atrial fibrillation, and heart failure[19]. PLR was also a good indicator of atherosclerotic plaque burden. In patients with ACS before the primary percutaneous coronary intervention, Yayla et al., observed that a higher PLR was an independent predictor of the patency of the infarct-related artery[20]. In previous

Table 2. Univariate and multivariate regression analysis of independent variables in predicting a high Synergy between PCI with Taxus and Cardiac Surgery score.

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Gender (male)	0.640	0.373–1.099	0.106	–	–	–
Hypertension	1.363	0.795–2.337	0.260	–	–	–
Diabetes mellitus	1.693	0.984–2.912	0.057	–	–	–
PLR	1.006	1.002–1.010	**0.001**	1.003	0.998–1.009	**0.019**
LMR	0.847	0.709–1.011	0.065	–	–	–
NLR	1.100	1.026–1.180	**0.008**	1.020	0.927–1.124	0.680

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio. Bold values indicate statistical significance at the p<0.05 level.

studies, high PLR levels have been observed to be associated with in-stent restenosis, saphenous vein graft disease, slow coronary flow, and poor coronary collateral circulation[21].

Atherosclerosis can be slowed down and cardiovascular events can be decreased by reducing the inflammatory response through the management of hyperlipidemia and thrombosis. According to the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study, interleukin-1 beta-targeted anti-inflammatory medication may lower levels of high-sensitivity C-reactive protein and reduce the frequency of recurrent cardiovascular events[22].

The fact that the PLR, NLR, and Troponin T levels increased more in the group with NSTEMI and a high SYNTAX score in our study supports previous studies. Examining these biomarkers in patients diagnosed with ACS in the emergency department will help us both in predicting the prognosis of the patient and in diagnosing complex coronary artery disease. We found that patients with NSTEMI had higher PLR and NLR levels, which indicated the severity of their coronary arteries. Furthermore, it was found that the rates of multivessel disease and chronic complete occlusion were higher in these patients. As a result, coronary angiography is required to calculate the SYNTAX score. Coronary angiography may be delayed for many reasons. PLR and NLR may be used for risk stratification before an invasive angiography-based SYNTAX score. PLR and NLR, which are easily obtained from routine blood tests in clinical practice, may be calculated quickly in patients presenting with NSTEMI and may provide information about the SYNTAX score without coronary angiography.

Limitations

The main limitations are as follows. Our study included only a small number of patients, was conducted at a single center, and had a retrospective design. From the patients who participated in our study, more blood samples could be taken. The effect on long-term mortality is not fully understood, as changes in parameters in-hospital or after discharge are not followed. It was not questioned whether patients had previously taken aspirin, statins, beta-blockers, or anti-inflammatory agents that would affect the inflammatory process. To confirm the results of this investigation, larger, multi-center prospective investigations must be carried out.

CONCLUSION

Early risk stratification of NSTEMI is one of the important problems. New biomarkers are practical parameters that can help us in diagnosis and treatment. PLR, NLR, and LMR may be helpful for stratifying high-risk individuals with NSTEMI since they are practical and cost-effective biomarkers.

AUTHORS' CONTRIBUTIONS

CA: Formal Analysis, Supervision, Writing – review & editing. **UU:** Conceptualization, Resources. **MK:** Data curation, Investigation, Methodology. **AD:** Supervision, Visualization, Writing – original draft.

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