ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Platelet-Lymphocyte Ratio As a Novel Predictor of Severity in Patients With Unstable Angina Pectoris: Randomized Control Double-Blind Study

Kararsız Angina Pektorisli Hastalarda Ciddiyetin Yeni Bir Belirteci Olarak Trombosit Lenfosit Oranı: Randomize Kontrollü Çift Kör Çalışma

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ABSTRACT

Aim: Acute Coronary Syndrome (ACS); covers a wide spectrum of clinical conditions ranging from Non-ST and ST-Elevation Myocardial Infarction to unstable angina pectoris (UAP). UAP does not show detectable with any biomarkers in the Emergency Department (ED). Platelet-lymphocyte ratio (PLR) has been introduced as a potential marker to determine excess thrombotic activity and inflammation in cardiac disorders. Syntax score (SXscore) is an anatomic scoring system based on coronary angiography that quantifies lesion severity and complexity and predicts poor cardiovascular outcomes, including mortality, in patients with ACS. This study aimed to investigate the predictive value of PLR compared with SXscore in patients with UAP in the ED.

Material and Method: The study group consisted of patients diagnosed with UAP who presented in ED and adult patients who experienced UAP in ED. The control group was comprised of healthy adults with no chronic disease. We performed CA to the patients suspected ACS in the study group, and the Syntax Score was calculated for each patient. The levels of PLR were compared between the study and control group, and PLR levels of the study group were compared with Syntax scores of the former group.

Results: The mean levels of PLR were 122.89±52.44 in the UAP group and 104.21±22.85 in the control group (p: 0.005). The PLR level of 113.98 had a sensitivity of 55.8%, specificity of 66.7% and was negatively correlated with SXscore (r=-0.325; p: 0.004).

Conclusion: PLR levels significantly increase in patients presenting with UAP. PLR may be considered a novel marker in predicting the severity of UAP. However, it was found to be ineffective in evaluating coronary vascular damage.

Key words: syntax score; platelet-lymphocyte ratio; unstable angina pectoris

ÖZET

Amaç: Akut Koroner Sendrom (AKS), ST segment yükselmeli miyokard enfarktüsünden kararsız angina pektorise (UAP) kadar geniş bir klinik durum yelpazesini kapsar. UAP, Acil Servis kliniğinde herhangi bir biyobelirteçle tespit edilemez. Trombosit lenfosit oranı (PLR), kardiyak bozukluklarda aşırı trombotik aktiviteyi ve enflamasyonu belirlemek için potansiyel bir işaret olarak gösterilmiştir. Syntax skoru (SXscore), sadece lezyon şiddetini ve kompleksitesini ölçmekle kalmayan, aynı zamanda AKS'li hastalarda mortalite dahil olmak üzere ağır kardiyovasküler sonuçları öngören koroner anjiyografiye dayalı anatomik bir skorlama sistemidir. Bu çalışmanın amacı, UAP'lı hastalarda trombosit lenfosit oranı ile SXscore karşılaştırılarak bu hastalarda PLR'nin prediktif değerini ortaya koymaktır.

Materyal ve Metot: Çalışma grubu, acil servise başvuran UAP tanısı alan hastalar ve acil servise'de UAP tanıs alan yetişkin hastalardan oluşturuldu. Kontrol grubu, kronik hastalığı olmayan sağlıklı yetişkinlerden oluşmuştur. Çalışma grubunda AKS şüphesi olan hastalara koroner anjiyografi uyguladık ve her hasta için Syntax Skoru hesaplandı. Çalışma ve kontrol grubu arasında PLR seviyeleri karşılaştırıldı ve çalışma grubunun PLR seviyeleri ile Syntax skorları karşılaştırıldı.

Bulgular: Ortalama PLR düzeyleri UAP grubunda 122,89±52,44 ve kontrol grubunda 104,21±22,85 idi (p: 0,005). PLR düzeyi 113,98 olduğunda %55,8 duyarlılığa, %66,7 özgülüğe sahip olarak bulundu ve SXscore ile negatif korelasyon gösterdiği görülüldü (r=-0,325; p: 0,004).

Sonuç: UAP ile başvuran hastalarda PLR seviyelerinin önemli ölçüde arttığı görüldü. PLR, UAP'ın ciddiyetinin tahmininde yeni bir belirteç olarak düşünülebilir. Ancak koroner vasküler hasarın değerlendirilmesinde etkisiz olduğu görülmüştür.

Anahtar kelimeler: syntax score; platelet-lymphocyte oranı; unstable angina pektoris

Introduction

Acute Coronary Syndrome (ACS) is the primary cause of death in the world[1]. The chest pain covers almost 6.3% of the Emergency Department (ED)[2]. ACS; covers a wide spectrum of clinical conditions ranging from unstable angina pectoris (UAP) to Non-ST Elevation Myocardial Infarction (N-STEMI) and ST-Elevation Myocardial Infarction (STEMI). UAP is thought to be an ACS in which there are no detectable cardiac biomarkers of myocardial necrosis such as creatine-kinase MB isozyme, troponin, myoglobin in the circulation[3].

Missed UAP patients are challenging because of various clinical manifestations[4]. Missed Myocardial Infarction is still one of the most common reasons behind malpractice lawsuits against emergency physicians, almost 20% of all claims[5]. All chest pain patients <25% will have an ACS[6]. If patients at high risk for ACS could be recognized promptly, it has the potential to reduce mortality, morbidity, and adverse effects of delayed treatment[7]. Therefore, accurate and fast risk stratification is paramount in the acute management of these patients, mainly to identify those patients with immediate risk of complications, as those with an ACS.

The Syntax score (SXscore) is an anatomic scoring system based on coronary angiography (CA) designed to be performed by the cardiologist that not only quantifies lesion severity and complexity but also predicts poor cardiovascular outcomes, including mortality, in patients with ACS[8,9]. The SXscore can predict mortality and morbidity at early and late follow-up in patients irrespective of disease severity in different clinical situations, including ACS. In the PCI study, Capodanno et al.[9] reported, Patients were divided into tertiles based on SYNTAX scores: low (≤18), intermediate (>18 to 27), and high (>27). At 1 year, patients in the highest tertile showed a significantly higher mortality (13.1% vs. 2.5%, P<0.001) and MACE rate (21.4% vs. 7.4%, P<0.001) than patients in the lowest tertile[10].

Early diagnosis and the initiation of appropriate treatment within 24 hours are essential to reduce UAP-related mortality and morbidity[11]. Despite the investigated use of various diagnostic, prognostic and predictive factors, there is currently no biomarker, such as troponin, etc., in patients with UAP. There is still a need for a sensitive, specific, simple, and predictive marker in patients with UAP to reduce mortality and provide a good outcome with cost-effective treatments.

The platelet-lymphocyte ratio (PLR) has been claimed to have the potential as a marker to help identify thrombotic activity and inflammation in cardiac diseases[12]. Inflammatory mediators and endothelial dysfunction play a fundamental role in the pathophysiology of ACS and widespread coronary inflammation found during UAP[13]. It has recently been observed that there is a close relation between cardiovascular mortality and the number of platelets or their ability to aggregate. Platelets play a key role in the pathophysiology of ACS. Compounded with fibrin, platelets form a coronary thrombus[14]. The PLR, which is calculated by dividing absolute platelet count by absolute lymphocyte count, is a new indicator of the inflammatory response. However, recent studies have shown that PLR, which is evaluated as a prognostic marker of ACS, may also increase in patients with N-STEMI and STEMI[15–17].

However, there are no studies in the literature regarding PLR levels in patients with UAP. No studies in the literature have examined PLR levels compared with SXscore in patients with UAP in the ED. The present study aimed to investigate the predictive value of PLR levels compared with SXscore in patients with UAP in the ED.

Methods

Medipol University Clinical Research Ethics Committee approved this prospective randomized controlled study. The study was conducted in Medipol University Hospital Adult ED and Cardiology Department within 12 months of approval. (20.01.2016/E.1049-30)

Study and Control Groups

The study group consisted of patients diagnosed with UAP who presented in ED and adult patients who experienced UAP in ED. UAP was defined according to Thygesen K et al.'s Third universal definition of myocardial infarction[3]. The control group was comprised of healthy adults with no chronic disease. Patients who agreed to participate in the study provided a written informed consent form. All patients in both groups were ≥18 years old. The groups were named 'UAP' and 'Control.' Gender, Age, hemograms, and PLR levels were recorded for both groups. The study group examined the following: Blood Urea Nitrogen (BUN), creatinine, CK-MB, 0. and 3. Hour cTnI and Syntax score. We performed CA to the patients suspected ACS in the

study group, and the Syntax Score was calculated for each patient. The levels of PLR were compared between the study and control group, and PLR levels of the study group were compared with Syntax scores of the former group. The cardiologist performed coronary angiography cardiologists interpreted degrees of coronary artery stenosis are separated to make the study double-blinded.

Inclusion and Exclusion Criteria

Inclusion Criteria

UAP group: Patients presented with suggestive of UAP above the age of 18 without known previous history of CAD were enrolled in the study.

Control group: The control group consists of healthy adults above 18 with no chronic disease.

Exclusion Criteria

Patients were also excluded if they had a previously known disease to explain the chest pain other than angina and did not agree to participate in the study.

Biochemical Analysis

All blood samples were taken from the brachial veins. BUN and creatinine were measured with an auto-analyzer (Cobas6000, Roche, Tokyo, Japan). Blood samples for hemograms were collected in 2 ml EDTA tubes and analyzed on an automated hematology analyzer (XT-2000I; Symex, Osaka, Japan). The PLR was calculated as the ratio of platelet count to lymphocyte count. Blood samples were centrifuged within 30 minutes, and CK-MB, 0th and 3rd hour cardiac troponin-I (cTnI) were determined with AQT90 FLEX analyzer device (Radiometer, Copenhagen, Denmark) by immunoassay method. Cut-off values for CK-MB and cTnI were 7.2μg/L and 0.023μg/L, respectively.

Coronary Angiography and Syntax Score

The cardiologist performed coronary angiography through right femoral catheterization on patients with exertional dyspnea symptoms, chest pain, and without ST-segment and T wave changes (ECG). Blinded experienced interventional cardiologists interpreted degrees of coronary artery stenosis. A syntax scoring system was used to assess angiographic vessel-specific disease severity[18].

Statistical Analysis

Statistical analyses were made using commercial statistical software (SPSS Ver. 23.0, IBM Inc., Chicago, IL, USA). Variables were stated as mean and standard deviation. Frequencies were compared with the Chi-square and Fisher's exact tests. Spearman's correlation tests were applied for correlation analyses. Simple correlation analyses were performed to investigate the association of serum PLR levels with SX scores. To determine a cut-off value of PLR level for UAP, receiver operating characteristic (ROC) analysis was performed in sensitivity and specificity calculations. A value of $p < .05$ was considered statistically significant.

Results

The study included 77 patients admitted with UAP and 75 control subjects. The mean age was 64.23±11.02 years in the study group and 65.36±10.35 years in the control group (p=0.51). The study group comprised 28 (36%) females and 49 (64%) males and the control group, 28 (37%) females and 47 (63%) males (p=. 90). In the UAP group, all troponin and CK-MB values were negative. The mean levels of platelet were 241.30±53.68 10^3/μL and lymphocyte were 2.22±0.81 10^3/μL in the study group. The mean levels of platelet were 220.44±40.13 10^3/μL, and lymphocyte was 2.18±0.48 10^3/μL in the control group. The mean levels of PLR of the UAP group (122.89±52.44) were higher than those of the control group (104.21±22.85) (Fig. 1, p: 0.005). The area under the ROC curve for the PLR level was 0.597 (95% confidence interval [CI], 0.503–0.690), the PLR level had a sensitivity of 55.8% and specificity of 66.7% at 113.98 (Fig. 2). PLR levels were found negatively correlated with SXscore in the study (r=-0.325; p: 0.004) (Fig. 3).

Discussion

Several factors in cardiac diseases that could lead to predicting in previous studies have been analyzed. However, no studies in the literature have examined PLR levels compared with SXscore to predict the severity of coronary pathology in patients with UAP in the ED.

Most commonly caused by atherosclerosis, ACS is the leading cause of death worldwide. Atherosclerosis is a systemic, lipid-driven immune inflammatory disease[14]. ACS is an inflammatory disease, and serum levels of inflammatory markers, such as interleukin (IL)-6, IL-18, and C-reactive protein, evaluate patients with
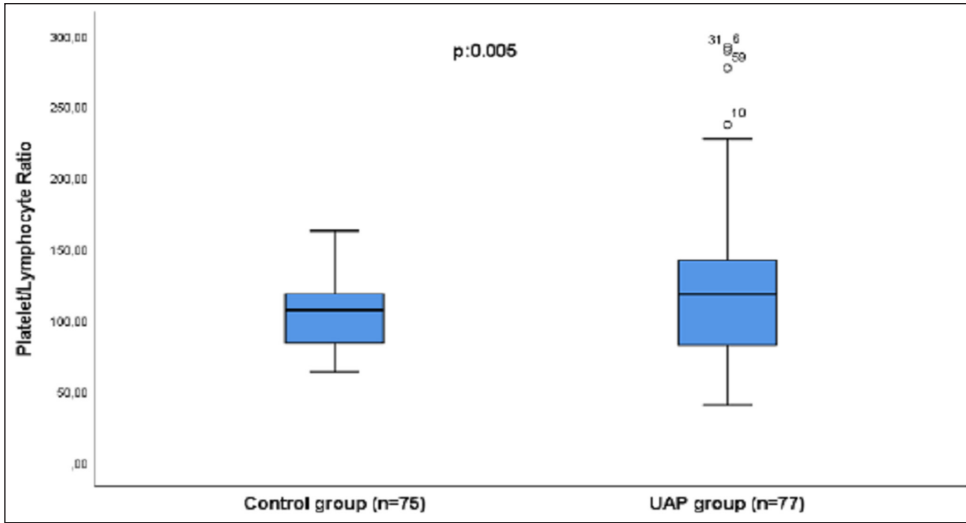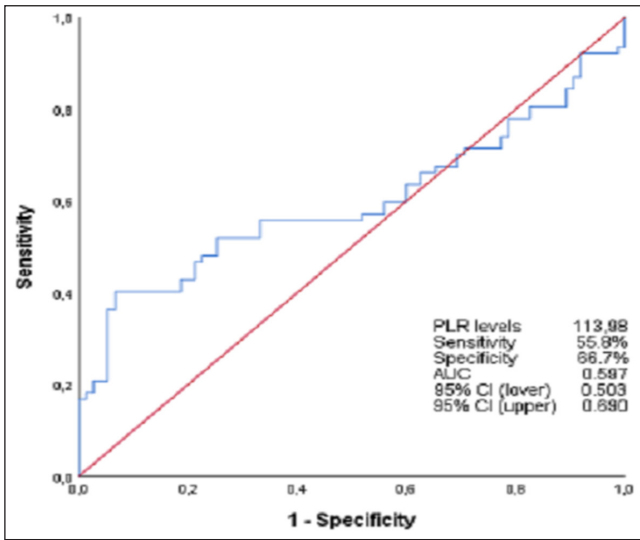
Figure 1. *Comparison of PLRs between groups.*

Figure 2. *Receiver-operating characteristic analysis of PLR levels for each group (AUC, area under the curve).*
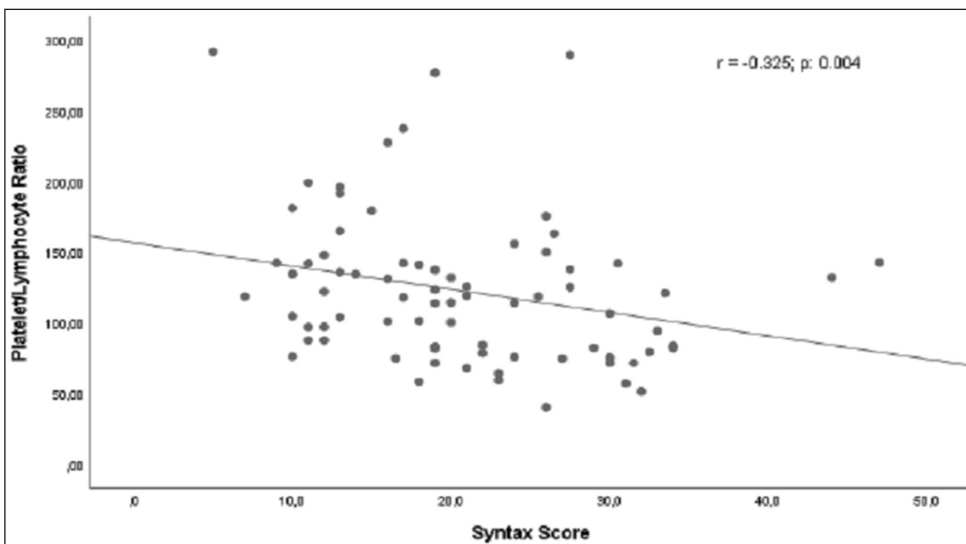

Figure 3. *Correlation between PLR and Syntax score.*

CAD[19]. The inflammation leading to ACS encourages research into the clinical usage of new inflammatory biomarkers. (17). Eight to 10 million individuals are evaluated annually in the EDs in the United States (US) for possible acute MI[20]. Many of these individuals are assessed with serial cardiac markers and held in observation units for stress testing or cardiac imaging, which is time-consuming and costly. In patients with UAP, the troponin values and repeats are negative, and no detectable blood test is available in the diagnosis of UAP in the ED[21].

Predicting coronary anatomy as early as possible will provide precious information about the major adverse cardiac events (MACE) and risk of cardiac death. The inflammatory processes play a key role in the development of atherosclerosis, destabilization of atherosclerotic plaques, and formation of clots on the plaque surface[22]. Increased platelet activity is closely associated with atherosclerosis and thromboembolic states; ACS increases inflammation in the atherosclerotic plaques within months[23]. It has been suggested that the PLR is a new indicator showing chronic inflammation. In particular, the PLR has been introduced as a potential marker to determine excess thrombotic activity and inflammation in cardiac disorders[24].

A previous study showed the relationship between PLR and coronary collateral development in patients with stable angina pectoris and chronic total occlusion[25]. In another study, the SXscore is an independent predictor of the 1-year rates of death, cardiac death, MI, and target vessel revascularization in patients with N-STEMI who undergo PCI[26], and high preprocedural PLR levels were found to be significant and independent predictors of no-reflow in patients with STEMI[27]. In addition, Kurtul et al. reported; the correlation of PLR with SXscore in patients with ACS, including NSTEMI and STEMI. There was a positive correlation between PLR levels and SXscore in patients with ACS[28]. However, there are no studies in the literature regarding PLR levels in patients with UAP. No studies in the literature have examined PLR levels compared with SXscore in patients with UAP in the ED. In the present study, although there is a significant increase in serum PLR levels in patients with UAP compared to healthy control subjects, PLR levels were negatively correlated to SXscore in patients with UAP, and PLR levels have a high negative link between SXscores in patients with UAP.

This early and simple prediction by a PLR of inflammation is important. It may improve our ability to risk stratify UAP patients and guide therapeutic decisions and preserve the patients from MACE and risk of sudden cardiac death. The study results have shown that PLR is sufficient to expose high values with poorly battered coronary arteries and has a high negative link between SXscores.

This study showed a significant increase in serum PLR levels in patients with UAP compared to healthy control subjects; recent research has already put this assumption forward[29]. What is novel about this study is that the Syntax score, most widely used to predict coronary artery lesion with CA, was negatively correlated to serum PLR levels in patients with UAP. The previous finding can be explained by the fact that the endothelial nitric oxide levels of coronary arteries in the UAP and the coronary anatomy could not be hardly damaged as can be found in non-ST elevation myocardial infarction and ST-elevation myocardial infarction[30].

Conclusion

There is currently no biomarker, such as troponin, etc., to diagnose and predict coronary pathology's severity in patients with UAP in the ED. The PLR may be an important, simple, and cost-effective tool predicting the severity but not the complexity of coronary atherosclerosis in patients with UAP. Thus, the PLR levels can be used for risk stratification in patients with UAP.

Study Limitations

PLR may be affected by several pathological variables. However, it was not possible in this study to control all the variables that could influence PLR levels. The contact time to the hospital was accepted as the initial hour for this study. The period that started after collecting the first blood samples was not standardized in every patient, and the number of subjects included in the study was limited. And also, patients with UAP were reluctant to undergo coronary angiography procedures; this also kept our list short.

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