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Evaluation of the Relationship Between Eosinophil to Monocyte Ratio and left Ventricle Ejection Fraction in Patients With Acute Coronary Syndrome

Akut Koroner Sendrom Hastalarında Sol Ventrikül Ejeksiyon Fraksiyonu ile Eozinofil Monosit Oranı Arası İlişkinin Değerlendirilmesi

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Abstract

Introduction: Biomarkers have an important role in risk stratification of acute coronary syndromes.Various inflammatory markers,especially neutrophil to lymphocyte ratio,have been used to determine mortality in acute coronary syndrome.Eosinophil to monocyte ratio,which is also an inflammatory marker,has been evaluated in acute ischemic stroke,ST elevated myocardial infarction,and in many cardiovascular diseases,thus,its prognostic impact has been validated.In this study,our purpose was to investigate the relationship between eosinophil to monocyte ratio and left ventricle ejection fraction in acute coronary syndrome.

Method: 210 patients who underwent coronary revascularization with the diagnosis of acute coronary syndrome were enrolled.Complete blood count and fasting blood glucose,creatinine, Troponin I,total cholesterol,low-density lipoprotein,and triglyceride measurements were done with an autoanalyzer.Transthoracic echocardiography and coronary angiography were performed.The patients with at least one ≥ 70% coronary stenosis were included.

Results: 149(70.9 %) Non-ST elevated and 61(29.1 %) ST elevated myocardial infarction patients were enrolled.In ST elevated group,while eosinophil to monocyte ratio,hemoglobin, and left ventricle ejection fraction were lower;low-density lipoprotein,C-reactive protein,and Troponin were higher. Eosinophil to monocyte ratio was significantly higher in Non-ST elevated group than in ST elevated group, and we found, increased eosinophil to monocyte ratio was correlated with an increase in left ventricle ejection fraction in the multiple linear regression analysis. The partial effect plot showed an association between eosinophil to monocyte ratio and left ventricle ejection fraction in multiple linear regression model. Until eosinophil to monocyte ratio increases 0.2,left ventricle ejection fraction increases;upper than 0.2 no effect of eosinophil to monocyte ratio on left ventricle ejection fraction was detected.The correlation between eosinophil to monocyte ratio and Troponin was significant.

Conclusion: Eosinophil to monocyte ratio might predict left ventricle ejection fraction on admission and because of the prognostic role of left ventricle ejection fraction,eosinophil to monocyte ratio also may be a predictor of worse outcomes in patients with acute coronary syndrome.

Keywords: Eosinophil to monocyte ratio; acute coronary syndrome; left ventricle ejection fraction.

Özet

Amaç: Biyobelirteçler, akut koroner sendromda önemli yere sahiptir. Akut koroner sendromda çeşitli inflamatuar belirteçler; özellikle nötrofil/lenfosit oranı kullanılmıştır. İnflamatuar bir belirteç olan eozinofil monosit oranı, ST elevasyonlu miyokard infarktüsünde ve birçok kardiyovasküler hastalıkta değerlendirilmiş, prognostik etkisi doğrulanmıştır. Bu çalışmada amacımız; akut koroner sendrom hastalarında eozinofil monosit oranı ile sol ventrikül ejeksiyon fraksiyonu arasındaki ilişkiyi araştırmaktı.

Gereç ve Yöntem: Akut koroner sendrom tanısıyla koroner revaskülarizasyon uygulanan 210 hasta çalışmaya alındı. Tam kan sayımı analizi ve açlık kan şekeri, kreatinin, Troponin I, total kolesterol, düşük dansiteli lipoprotein, yüksek dansiteli lipoprotein ve trigliserid ölçümleri yapıldı. Transtorasik ekokardiyografi ve koroner anjiyografi yapıldı. %70 ve üzeri en az bir koroner darlığı olan hastalar dahil edildi

Bulgular: 149 (% 70.9) Non-ST elevasyonlu ve 61 (% 29.1) ST elevasyonlu miyokard infarktüsü hastasında; ST elevasyonlu miyokard infarktüsü grubunda eozinofil monosit oranı, hemoglobin ve sol ventrikül ejeksiyon fraksiyonu daha düşük iken; düşük dansiteli lipoprotein, C-reaktif protein ve Troponin daha yüksekti. Eozinofil monosit oranı, Non-ST elevasyonlu miyokard infarktüsü grubunda, ST elevasyonlu miyokard infarktüsü grubuna göre anlamlı olarak daha yüksekti. Çoklu lineer regresyon analizinde artan eozinofil monosit oranı, sol ventrikül ejeksiyon fraksiyonu artışıyla korele idi. Çoklu lineer regresyon modelinde eozinofil monosit oranı ile sol ventrikül ejeksiyon fraksiyonu arasında bir ilişki olduğu gösterildi. Eozinofil monosit oranı için 0,2 seviyesine kadar sol ventrikül ejeksiyon fraksiyonu artmakta, ancak 0,2'nin üzerinde eozinofil monosit oranının sol ventrikül ejeksiyon fraksiyonu ile korelasyonu bulunmamaktaydı. Eozinofil monosit oranı ve Troponin arasındaki korelasyon anlamlıydı.

Sonuç: Eozinofil monosit oranının başvurudaki sol ventrikül ejeksiyon fraksiyonunu öngörebileceğini ve sol ventrikül ejeksiyon fraksiyonunun akut koroner sendromdaki prognostik rolü nedeniyle, eozinofil monosit oranının akut koroner sendromlu hastalarda kötü sonlanımın bir göstergesi olabileceğini belirledik. Eozinofil monosit oranının akut koroner sendromdaki etkisini belirlemek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Eozinofil monosit oranı; akut koroner sendrom; sol ventrikül ejeksiyon fraksiyonu.

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Introduction

Acute coronary syndromes (ACS), which include unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), remain one of the most important cause of death worldwide (1). Coronary artery disease, in particular ACS, is the foremost cause of heart failure (HF). Nonetheless, not only HF is a frequent complication of ACS, but also its presence in ACS significantly worsens the prognosis (2,3). Impairment of left ventricle ejection fraction (LVEF) may be a result of ACS and some patients may remain asymptomatic despite reduced systolic function. LVEF is a crucial predictor of mortality following ACS (4). In addition to LVEF, biomarkers have been an important aspect in risk stratification and management of ACS (5). In patients with ACS, modifiable cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia, and smoking are crucial; however, myocardial infarction in the absence of these is not uncommon. The outcomes of individuals without these risk factors are not well known, as a consequence; additional risk predictors are needed (6). Various inflammatory markers, especially neutrophil to lymphocyte ratio (NLR), have been used to determine mortality in patients with ACS (7). Eosinophil to monocyte ratio (EMR), which is also applied as an inflammatory marker, has been evaluated in acute ischemic stroke, STEMI, and in many cardiovascular diseases, thus, its prognostic impact has been validated (8,9). However, to the best of our knowledge, there is no study evaluating the relationship between EMR and LVEF in patients presenting with ACS. In this study, our purpose was to investigate the relationship between EMR and LVEF in patients presented to our emergency department and diagnosed with ACS.

Materials and Method

395 patients were retrospectively analysed and 210 patients who underwent coronary revascularization with the diagnosis of ACS were enrolled in the study. 49 of them were female (23.3 %) and 19 patients (9 %) had a history of coronary artery bypass surgery. According to electrocardiogram (ECG) findings, Troponin levels and ischemic symptoms (typical chest pain or less typically dyspnea, palpitations, nausea/vomiting or rarely syncope), the patients were diagnosed with UAP, NSTEMI, or STEMI based on current ESC guidelines (1) regardless of revascularization option (either percutaneous coronary intervention or coronary artery bypass surgery). The exclusion criteria were the presence of moderate or severe valvular heart disease, pre-procedural resuscitation, and previous HF diagnosis. Complete blood count analysis and fasting blood glucose, creatinine, blood urea nitrogen, Troponin I, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride measurements were done with an autoanalyzer. Transthoracic echocardiography (TTE) was performed using the Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway) unit with a 2.5 MHz FPA probe. The LVEF was assessed by visual estimation and confirmed with Teicholtz's method. The coronary angiography was performed via the femoral artery or left radial artery according to operator discretion. The patients with at least one $\geq$ 70% coronary stenosis were included. All patients provided written informed consent, and the study protocol was approved by the local ethics committee in accordance with the principles of the Helsinki Declaration and the medical records were evaluated retrospectively.

Ethical committee: Clinical Trials Local Ethics Committee approved this trial, at 24/8/2021 with 523 article number, and 2021/10/523 reference number.

Statistical analysis: The continuous predictors were displayed with median, interquartile-range (IQR) (25th-75th). Discrete predictors were displayed in percentages and absolute value, to compare categorical variables between groups, the Chi-square test was utilized. The Mann-Whitney U tests were used to compare continuous variables.

Response variable*:* Admission LVEF.

Candidate predictors and statistical modeling: LVEF and potential predictors were investigated using linear regression, individual predictor's effects were reported with the use of Beta-coefficients and 95 percent confidence interval (95%). The regression coefficient of continuous variables was summarized using their interquartile range (25th-75th). Variable's age, sex, hypertension (HT), diabetes mellitus (DM), C-reactive protein (CRP), hemoglobin, Troponin, STEMI, and our focused variable EMR were used in multiple linear regression analysis. Besides, a partial effect plot was used to describe the relative effect of EMR in the model. Also, an association between variables was assessed with the Spearman correlation coefficient.

Table 1: The demographic, clinical characteristics, laboratory findings, and outcomes of the study population

	NSTEACS (N:149)	STEMI (N:61)	p-value
Eosinophil (10^3/μL)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.001
Monocyte (10^3/μL)	0.7 (0.6-0.9)	0.7 (0.5-1.0)	0.72
EMR	0.2 (0.1-0.3)	0.1 (0.0-0.2)	0.001
Hemoglobin (g/dL)	14.2 (12.4-15.4)	13.1 (12.4-14.3)	0.03
Platelet (10^3/μL)	250.0 (200-307.0)	259.0 (224-294.7)	0.36
Neutrophil (10^3/μL)	5.8 (4.2-6.9)	8.2 (6.8-10.4)	0.001
Lymphocyte (10^3/μL)	2.4(1.7-3.1)	1.9 (1.3-2.5)	0.001
Creatinine (mg/dL)	0.9 (0.8-1.1)	0.8 (0.7-1.0)	0.03
Troponin (ng/ml)	0.1 (0.0-0.2)	0.5 (0.2-2.4)	0.01
CRP (mg/L)	4.0 (2.4-8.9)	8.0 (3.0-20.0)	0.01
Total Cholesterol (mg/dL)	188.0 (144.0-218.3)	186.0(159.3-208.3)	0.85
LDL (mg/dL)	109.0 (87.0-139.7)	113.0 (98.3-129.3)	0.56
Triglyceride (mg/dL)	146.0 (114.3-194.3)	130.0 (100.0-181.7)	0.19
HDL (mg/dL)	38.0 (32.7-44.0)	37.0 (33.0-43.0)	0.78
LVEF (%)	60.0 (45.7-65.0)	44.0(40.0-47.0)	0.001
HT Presence	76 (51%)	54 (88%)	0.001
DM Presence	40 (26%)	39 (63%)	0.83
CKD Presence	10 (6.7%)	7(11.4%)	0.42
COPD Presence	26 (17.4%)	13 (21.3%)	0.52
Age, years	64.0 (56.0-71.0)	60.0(50.0-70.3)	0.13
Gender (Female)	35 (23.4%)	14 (23%)	0.93

Abbreviations: NSTEACS: non-ST segment elevation Acute coronary syndromes, EMR: Eosinophil to monocyte ratio, CRP: C-reactive protein, LDL: low-density lipoprotein, HDL: High-density lipoprotein, LVEF: Left ventricle ejection fraction, HT: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease

Table 2: Multiple linear regression analysis of some variables

Variables	B-coefficients (95% Confidence Interval)	p-Value
EMR	30.37 (1.41;19.32)	0.023
Gender (Female refenrence)	2.07 (-1.47;5.62)	0.250
Age (Per age increasing)	-0.15 (-0.29;-0.01)	0.028
Hemoglobin (g/dL)	0.29 (-0.14;0.73)	0.183
Troponin (ng/ml)	-0.45 (-0.70;0.79)	0.472
CRP (mg/L)	-0.007(-0.061;0.046)	0.786
STEMI presence	-11.68 (-15.27;-8.09)	0.001
HT presence	-0.59 (-4.19;2.99)	0.743
DM presence	-0.14 (-3.06;2.78)	0.925

Abbreviations: EMR: Eosinophil to monocyte ratio, CRP: C-reactive protein, STEMI: ST-segment elevation myocardial infarction, HT: Hypertension, DM: Diabetes mellitus

Lower than 0.05 were accepted to be statistically significant for the p-value. All statistical analyzes were performed with R v-4.01 (Vienna, Austria).

Results

A total of 210 patients, including 149 (70.9%) NSTEMI and 61 (29.1%) STEMI patients, were enrolled in the study. The median age in the NSTEMI population was 64 years (56-71 IQR), and 23 (15.4%) of the patients were female. 76 (51.0 %) patients had HT and 40 (26.8 %) patients had DM. In the STEMI group, while EMR, hemoglobin, and LVEF were lower; LDL, CRP, and Troponin were higher than the NSTEMI

group. The demographic, clinical characteristics, laboratory findings, and outcomes of the study population are presented in Table 1. EMR was significantly higher in the NSTEMI group than in the STEMI group, and we found that, increased EMR was correlated with an increase in LVEF in the multiple linear regression analysis (Beta Coefficient = 10.37 CI 95%1.41-19.32 p = 0.023). Besides, age and STEMI were associated with decrease in LVEF in multiple regression analysis (Beta Coefficient = -0.15 CI 95% -0.29, -0.01 p = 0.028, Beta Coefficient = -11.68 CI 95% -15.27, -8.09 p <0.001). While other parameters in the model were not associated with admission LVEF (Table 2). The partial effect plot showed an association between EMR and LVEF in a multiple linear regression model, until EMR increases 0.2 level LVEF increases, upper than 0.2 no effect of EMR on LVEF was detected (Figure 1) The correlation between EMR and Troponin was significant r: 0.396 (Figure 2 and 3).

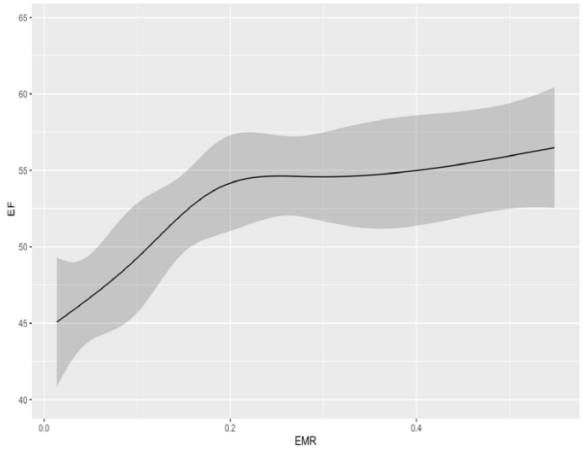

Figure 1. Partial Effect Plot between EMR and EF

Discussion

In this study, we demonstrated an association between EMR and LVEF. Moreover, EMR was also found to be correlated with admission Troponin levels. Systolic HF is widely considered as LVEF ≤ 40 %; with signs and symptoms of HF. The foremost cause of HF is coronary artery disease and the presence of previous MI (10). In a patient presenting with ACS; there are many predictors of prognosis both in diagnosis and follow-up period. Higher age, low LVEF, SYNTAX scores, etc. are associated with the prognosis of ACS (11). Furthermore, cardiac Troponins (especially high-sensitivity Troponin), natriuretic peptides (especially brain natriuretic peptide (BNP)), and NLR are well-known biomarkers for predicting HF and mortality in ACS (7,12,13).

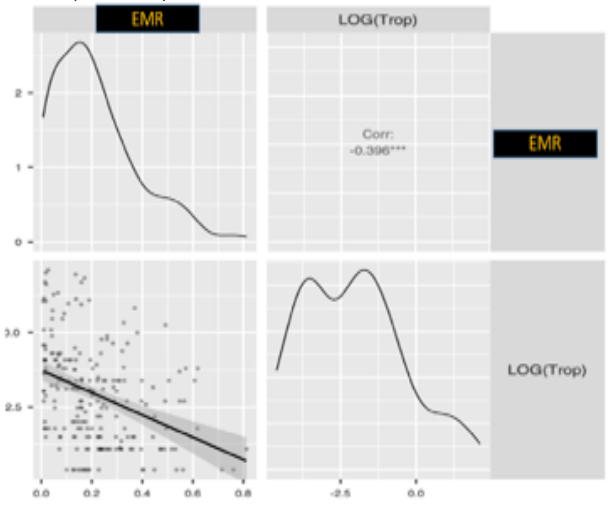

Figure 2. Spearman correlation between EMR and Troponin

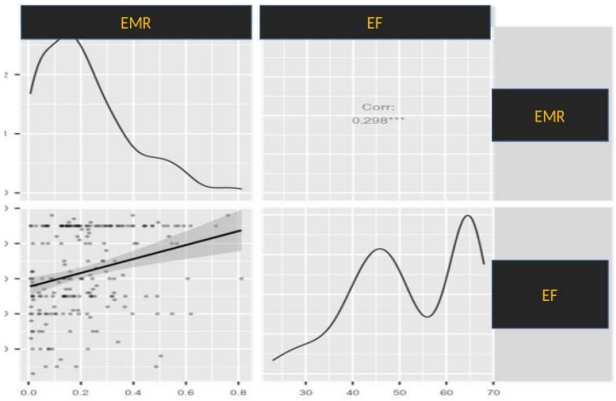

Figure 3. Spearman correlation between EMR and EF

The EMR, calculated as a simple ratio between eosinophil and monocyte, has previously been evaluated as an inflammatory biomarker in various cardiovascular diseases; but to best to our knowledge, this study is the first to investigate the relationship between EMR and LVEF in patients with ACS. The role of eosinophils in inflammation and thrombosis, and also eosinophil-related vascular toxicity have gained increased attention in recent years. Eosinophils, where activated by platelets, are gathered in human thrombi and in atherosclerotic plaques, and further promote thrombus formation by the release of eosinophil peroxidase, platelet activation factor, and some other proteins. More than that, eosinophils have procoagulant effects, and, it has been reported

that eosinophils are potent producers of tissue factors and are able to generate procoagulant phospholipids and activate factor XII (14,15). Riegger et al. have demonstrated that white blood cells especially neutrophils are present in thrombus samples, reflecting the important role of inflammation in-stent thrombosis, and eosinophils are observed both in bare metal and drug-eluting stent thrombus specimens. Notably, in patients with very late stent thrombosis, there was a significantly higher number of eosinophils detected in thrombus when compared to those detected in thrombus of first MI (16). In a case report, Lu Qiao et al. determined that myocardial involvement in Churg-Strauss syndrome, may be associated with a surge in eosinophils, which may clarify the pathogenesis. When intravascular eosinophil count increases up to 20% of white blood cell count; eosinophils start to infiltrate into the extravascular area (myocardium or other tissues). Eosinophil count increases distinctively in patients with myocarditis, and white blood cells also increase due to eosinophilia (17). The acute and markedly decrease in eosinophil counts and percentages in peripheral blood in patients with ACS, and abundant eosinophil percentage in thrombus specimens extracted from occluded coronary arteries or as mentioned above from myocardial specimens, seem to be due to activation, accumulation, and capture of these cells into the fresh clot or myocardial tissue resulting in a possible "consumptive eosinopenia" (18). And these mechanisms might be the cause of the reduction in LVEF and its correlation with EMR, in our study population. Current therapy of patients with a related declining LVEF with ACS mostly depends on the treatment of modifiable risks, HT, dyslipidemia, smoking, and DM. While this was targeted, there is a large percentage of ACS patients without them, leading to considerable improvements in the survival following the ACS. Nearly 15% of individuals with STEMI did not have a classical risk factor in a recent study (19). This underlines the importance of occult, non-traditional risk factors not typically evaluated, and those new biomarkers are needed. For patients without typical risk factors, evidence-based medical therapy was recommended less frequently. Therefore, the evaluation of EMR for assessment LVEF might help the patient who is at risk of declining LVEF also for prognosis and guideline-based therapy.

Study limitations: This is a retrospective study with a low patient number. Due to the nature of the regression model we might not include some important confounders, also this is a single-center study. We used retrospective design, even if consecutively admitted patients were included.

Conclusion

We showed that EMR might predict LVEF on admission and because of the prognostic role of LVEF in ACS, EMR also may be a predictor of worse outcomes in patients with ACS. Further studies are needed to determine the impact of EMR in ACS.

Ethical Committee: Clinical Trials Local Ethics Committee approved this trial, at 24/8/2021 with 523 article number, and 2021/10/523 reference number.

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