ⓘ **Atakan Savrun**[1]
ⓘ **Seyda Tuba Savrun**[1]

[1] Department of Emergency Medicine, Ordu University Faculty of Medicine, Ordu, Turkey

Corresponding Author:
Atakan Savrun
Department of Emergency Medicine, Ordu University Faculty of Medicine, Ordu, Turkey
Phone: +90 544 264 70 70
mail: atakan4601@hotmail.com

The Use of Neutrophil Lymphocyte Ratio in Patients Presenting to the Emergency Department with Chest Pain

ABSTRACT

Objective: Objective: In this study, we aimed to determine the roles of neutrophil, MPV, and NLR, in the diagnosis of ACS and the differentiation of ACS subtypes (ST-elevation myocardial infarction and non-ST elevation myocardial infarction), in patients presented to the emergency department with chest pain and were diagnosed with ACS (acute coronary syndrome).

Methods: This study was designed as a single-center, cross-sectional, and retrospective. 402 patients who were applied to University Hospital Emergency Department between January 2020 and November 2020; and registered to hospital automation system with chest pain; and underwent further examinations and treatments were included in the study. Ethical approval was obtained from the Local Clinical Research Ethics Committee before the study. Patients who were hospitalized after further examination, who received medical treatment, and did not undergo PCI (Percutaneous coronary intervention) were accepted as NSTMI (n = 202). Patients who were hospitalized after further examination and underwent PCI were accepted as STMI (n = 200).

Results: 36.3% of the patients were female (n = 146) and 63.7% (n = 256) were male. The mean age of the cases was detected to be 61.46 ± 14.06. The number of hospitalized ACS patients for NSTMI suspicion and received medical treatment was 202. The number of patients who underwent PCI and accepted as STMI was 200. Mean neutrophils, MPV, NLR, and Troponin values were also significantly higher than those who are not hospitalized ($p < 0.001$). The mean WBC, Neutrophil, NLR, and Troponin values of the patients underwent PCI were also significantly higher than those without PCI ($p < 0.001$).

Conclusions: We believe that NLR is a diagnostic valuable that can be used as a biomarker in diagnosing ACS and determining the PCI.

Keywords: Emergency Department, Chest Pain, Acute Coronary Syndrome, Percutaneous Coronary Intervention, Neutrophil Lymphocyte Ratio.

Acil Servise Göğüs Ağrısı ile Başvuran Hastalarda Nötrofil Lenfosit Oranının Kullanımı

ÖZET

Amaç: Biz çalışmamızda acil servise göğüs ağrısı şikayeti ile başvuran ve AKS(Akut koroner sendrom) öntanısı alan olgularda; Nötrofil, MPV, NLR, nin AKS tanısı koymada ve AKS subtip ayrımını (ST elevasyonlu myokard enfarktüsüve non St elevasyonlu myokard enfarktüsü) yapabilme durumunu saptamayı amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma tek merkezli, kesitsel ve retrospektif olarak yapıldı. Çalışmaya Üniversite hastanesi acil servisinin 2020-Ocak, 2020-Kasım tarihleri arasında hastane otomasyon sistemine göğüs ağrısı tanısı girilip ileri tetkik ve tedavi yapılan 402 hasta dahil edilmiştir. Çalışma için öncesinde Lokal Klinik Araştırmalar Etik Kurulu'ndan etik onay alındı. İleri tetkik sonrasında hastaneye yatışı yapılan, medikal tedavi alan ve PCI (Perkütan koroner girişim) yapılmayan olgular NSTMI olarak (n=202) kabul edilmiştir. İleri tetkik sonrasında hastaneye yatan ve PCI yapılan olgular STMI (n=200) olarak kabul edilmiştir.

Bulgular: Hastaların %36.3'ü kadın (n=146), %63.7'si (n=256) erkek olarak saptandı. Olguların yaş ortalaması 61.46±14.06 olarak tespit edildi. Hastaneye yatan AKS düşünülen olgulardan NSTMI düşünülen ve medikal tedavi ile alan hasta sayısı 202 iken, PCI tedavisi uygulanan ve STMI kabul edilen olgu sayısı 200 olarak saptanmıştır. Nötrofil, MPV, NLR ve Troponin ortalamaları da yatış yapmayanlardan anlamlı derecede yüksekti (p<0.001). PCI yapılan hastaların WBC, Nötrofil, NLR ve Troponin ortalamaları da PCI yapılmayanlardan anlamlı derecede yüksekti (p<0.001).

Sonuç: AKS tanısı konmasında ve PCI tedavi yönteminin belirlenmesinde NLR' nin tanı değeri olan bir biyobelirteç olarak kullanılabileceği kanaatindeyiz.

Anahtar Kelimeler: Acil Servis, Göğüs Ağrısı, Akut Koroner Sendrom, Perkütan Koroner Girişim, Nötrofil Lenfozit Oranı.

INTRODUCTION

Acute coronary syndrome (ACS) is a clinical picture that occurs due to acute myocardial ischemia. In patients with ACS are divided into 2 subgroups. The pathology at the myocardial level in patients with non-ST elevation myocardial infarction (NSTMI) is cardiomyocyte necrosis that can be measured by troponin release, or less commonly, myocardial ischemia without cell damage. Generally, the risk of death is significantly lower in this group and they benefit less from aggressive pharmacological and interventional approaches (1). The other subgroup is ST-elevation myocardial infarction (STMI). STEMI is a clinical picture that often manifests itself with chest pain and damage to the heart muscles due to ischemia. ACS in this group is the clinical picture recommended to be hospitalized and treated by applying percutaneous coronary intervention (PCI) as soon as possible (2). In cases with STMI, PCI is a fast and effective method. By improving myocardial blood flow by PCI, the infarct area can be reduced, and mortality can be prevented. Incorrect or late diagnosis of ACS, even late or non-performing PCI in cases with ACS diagnosis, increases the rate of mortality and morbidity (3).

Nowadays, despite many diagnostic and treatment options, acute coronary syndrome continues to be the most important cause of morbidity and mortality in the world. Quick and accurate diagnosis of patients with the acute coronary syndrome in emergency services is very important. However, it may not always be possible to diagnose acute coronary syndrome (ACS) in patients presenting with chest pain and to make the percutaneous coronary intervention (PCI) indication for every diagnosed patient (4). In addition to routine diagnostic options (anamnesis, physical examination, ECG, cardiac markers), the ratio of neutrophil count to lymphocyte count (N/L ratio) has shown itself as a predictor used to show the diagnosis and prognosis of many cardiovascular diseases such as ACS (5). Clinical studies have shown the correlations between NLR and arterial stiffness, the progression of atherosclerosis, high coronary calcium scores, and increase in first diagnosed AF. In addition, complete blood count (CBC) is important, inexpensive, easily accessible, and can be performed easily in many laboratories (6).

In our study, in cases presented to the emergency department with chest pain and diagnosed as a pre- ACS; We aimed to determine the importance of neutrophil, MPV, and NLR in the diagnosis of ACS and the ability to distinguish the ACS subtype (STMI and NSTMI).

MATERIAL AND METHODS

Study Design and Groups: This is a retrospective study conducted in an emergency department of a University Hospital. The Emergency Service of the University Hospital, with approximately 150,000 applications per year to the emergency department. The patients who were registered to the automation system with chest pain between 01/01/2020 and 31/12/2020 were retrospectively scanned and a study group was formed. All cases over the age of 18 and who were stated that they had chest pain to the health personnel in triage and registered to the automation system were examined (n = 879).

The patients (n = 477) who were pre-diagnosed with chest pain and discharged without blood examination were considered as non-cardiac chest pain and were excluded from the study. All patients who were registered to the hospital automation system with chest pain and underwent further examination and treatment were accepted as cardiac chest pain (n = 402).

Patients who were hospitalized after further examination, who received medical treatment, and PCI did not apply were accepted as NSTMI (n = 202). Patients who were hospitalized after further examination and underwent PCI were accepted as STMI (n = 200). The preliminary diagnosis in the hospital system was accepted as anamnesis. In addition, laboratory values could be examined ECG of the patients could not be recorded in the hospital information system, so they could not be evaluated. This was considered among the limitations of the study.

Laboratory Methods: CBC, biochemistry and Troponin parameters were obtained from the results of venous blood samples taken during admission to the emergency department and analyzed retrospectively. CBC analysis was performed via LH 780 Analyzer (Beckman Coulter, Miami, USA). Blood for biochemical analysis such as urea, creatinine, AST (aspartate aminotransferase), ALT (alanine aminotransferase), LDH (lactate dehydrogenase), and troponin was taken during admission to the emergency department and was performed via ADVIA 2400 (Siemens, NY, USA). Among CBC parameters, red blood cell (Rbc), hemoglobin (Hb), hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), RDW, platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), white blood cell (WBC), neutrophil count, lymphocyte count, and neutrophil/lymphocyte ratio (NLR) were examined. The relationships of these parameters with the hospitalization decision of patients with chest pain and the decision of PCI in hospitalized patients was examined.

Ethics Consideration: Ethics approval was obtained from the Ordu University Clinical Research Ethics Committee before the study (24/12/2020 No: 2020/268). Since the study was designed retrospectively, the informed consent forms of the patients were waived. The study was carried out following the Helsinki Declaration.

Data Analysis: The parametric test assumptions were analyzed with the Levene test

and the Kolmogorov Smirnov test. When appropriate, independent samples t-test was used. When the assumptions were not provided, Welch's t-test was used. ROC analysis was used to evaluate the diagnostic performances of the study variables. Youden's index was used as a criterion for choosing an optimal cut-off value. All statistical tests were performed using SPSS v26 (IBM SPSS, IBM Corp) at the significance level of p < 0 .05.

RESULTS

In this study, data of 879 cases registered to hospital automation system with chest pain between January 2020 and November 2020 in a university hospital emergency department were analyzed. From these cases, 402 patients who were thought to have cardiac chest pain and needed further examination were included in the study. 36.3% of the included cases were female (n = 146) and 63.7% (n = 256) were male. The mean age of the cases was 61.46 ± 14.06. The demographic characteristics of the included patients are shown in Table 1.

The number of hospitalized patients after further examinations was 402. Among the inpatients with ACS pre-diagnosis, the number of cases which thought to be NSTMI and ACS treatment was administered with medical treatment was 202. The number of patients underwent PCI after hospitalization and accepted as STMI was determined as 200.

Table 1. Demographic characteristics of the included cases.

		n	%
Gender	Female	146	36.3
	Male	256	63.7
DM	Yes	97	24.1
	No	305	75.9
HT	Yes	119	29.6
	No	283	70.4
PCI	Yes	69	17.2
	No	333	82.8
COPD	Yes	30	7.5
	No	372	92.5
ASTHMA	Yes	10	2.5
	No	392	97.5
	Yes	161	40.0

DM; Diabetes mellitus, HT; Hypertension, PCI; Percutaneous Coronary Intervention, COPD; chronic obstructive pulmonary disease

The comparison of study variables according to hospitalization is given in Table 2. According to the t-test, there was no significant difference between hospitalization status in terms of Lymphocyte, Hemoglobin, and PLT (p> 0.05). The mean age of hospitalized patients (64.07 ± 12.87) was significantly higher than the non-hospitalized patients (58.87 ± 14.74) (p <0.001). Similarly, the mean WBC, Neutrophil, MPV, NLR, LDH, AST, ALT, and Troponin values of the hospitalized patients were significantly higher than the non-hospitalized patients (p <0.001). Mean Creatine value was also significantly higher in hospitalized patients than non-hospitalized patients (p <0.05).

Table 2. Comparison of study variables according to hospitalization.

Variables	Hospitalization	n	Mean	SD	p
Age	No	202	58.87	14.74	**<0.001***
	Yes	200	64.07	12.87	
WBC	No	202	8.05	2.68	**<0.001***
	Yes	200	9.68	3.52	
Neutrophil	No	202	4.86	2.19	**<0.001***
	Yes	200	6.53	3.27	
Lymphocyte	No	202	2.34	1.12	0,976
	Yes	200	2.34	1.78	
Hb	No	202	13.48	1.93	0,457
	Yes	200	13.96	8.95	
PLT	No	202	236.41	60.47	0,422
	Yes	200	231.56	60.33	
MPV	No	202	10.01	0.82	**<0.001***
	Yes	199	10.33	0.88	
NLR	No	202	2.58	2.21	**<0.001***
	Yes	166	3.91	2.94	
LDH	No	202	205.06	44.47	**<0.001***
	Yes	196	345.43	280.88	
AST	No	202	19.70	7.40	**<0.001***
	Yes	200	67.95	93.11	
ALT	No	202	19.51	11.47	**<0.001***
	Yes	200	29.58	30.53	
Troponin	No	202	0.10	0.00	**<0.001***
	Yes	193	12705.01	29447.19	
Creatinine	No	202	0.92	0.34	**0,037***
	Yes	200	1.04	0.71	

WBC; White Blood Cell, Hb; Hemoglobin, PLT; Platelet, MPV; Mean platelet volume, NLR; Neutrophil lymphocyte ratio, LDH; lactate dehydrogenase, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase;
Ki-kare testi *<0.05 ** <0.01 ***<0.001

The comparison of study variables according to hospitalization status is given in Table 2. According to the t-test, Lymphocyte, Hemoglobin, and PLT did not differ significantly according to hospitalization status (p> 0.05). The mean age of the hospitalized patients (64.07 ± 12.87) was significantly higher than the non-hospitalized patients (58.87 ± 14.74) (p <0.001). Similarly, the mean WBC, Neutrophil, MPV, NLR, LDH, AST, ALT, and Troponin values of the inpatients were significantly higher than the outpatients (p <0.001). The mean creatine value was also significantly higher in inpatients than non-hospitalized patients (p <0.05).

The comparison of study variables according to the PCI status is given in Table 3. The mean age of the inpatients (62.78 ± 12.55) was higher than the outpatients (60.57 ± 14.95), but it was not statistically significant according to the t-test (p> 0.05). Similar situation was valid for Lymphocyte, Hb, and creatine (p> 0.05). In addition, also the mean PLT values did not change according to hospitalization (p> 0.05). In inpatients, the mean WBC, Neutrophil, NLR, LDH, AST, ALT, and Troponin values were also significantly higher than the outpatients (p <0.001). MPV values of inpatients (10.32 ± 0.83) was lower than non-hospitalized patients (10.07 ± 0.88) and this was statistically significant (p <0.01).

Table 3. Comparison of study variables according to PCI status.

Variables	PCI	n	Mean	SD	p
Age	No	241	60.57	14.95	0.110
	Yes	161	62.78	12.55	
WBC	No	241	8.10	2.73	**<0.001*****
	Yes	161	10.01	3.57	
Neutrophil	No	241	4.97	2.28	**<0.001*****
	Yes	161	6.76	3.37	
Lymphocyte	No	241	2.28	1.11	0.338
	Yes	161	2.44	1.92	
Hb	No	241	13.40	1.92	0.214
	Yes	161	14.21	9.93	
PLT	No	241	234.59	59.97	0.811
	Yes	161	233.11	61.16	
MPV	No	241	10.07	0.88	**<0.01****
	Yes	160	10.32	0.83	
NLR	No	241	2.78	2.43	**<0.001*****
	Yes	127	3.95	2.87	
LDH	No	241	206.87	46.50	**<0.001*****
	Yes	157	377.52	304.40	
AST	No	241	20.18	8.21	**<0.001*****
	Yes	161	78.92	100.65	
ALT	No	241	19.34	11.28	**<0.001*****
	Yes	161	32.28	33.11	
Troponin	No	241	0.1004	0.0036	**<0.001*****
	Yes	154	12705.0072	29447.1869	
Creatinine	No	241	0.95	0.41	0.182
	Yes	161	1.03	0.73	

PCI; Percutaneous Coronary Intervention, WBC; White Blood Cell, Hb; Hemoglobin, PLT; Platelet, MPV; Mean platelet volume, NLR; Neutrophil lymphocyte ratio, LDH; lactate dehydrogenase, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase
Ki-kare testi *<0.05 ** <0.01 ***<0.001

The comparison of study variables according to the PCI is given in Table 4. The mean age of the patients underwent PCI (62.78 ± 12.55) was higher than the non-hospitalized patients (60.57 ± 14.95), but it was not statistically significant according to the t-test (p> 0.05). Similar situation was valid for Lymphocyte, Hb, and Creatine (p> 0.05). Also, the mean PLT did not change according to the PCI (p> 0.05). The mean WBC, Neutrophil, NLR, LDH, AST, ALT, and Troponin values of the patients underwent PCI were also significantly higher than those did not (p <0.001). The MPV values (10.32 ± 0.83) of the patients underwent PCI were lower than those did not (10.07 ± 0.88), and this was statistically significant (p <0.01).

Table 4. Area Under the ROC Curve (AUC), sensitivity and specificity by optimized cut-off points for study variables in PCI.

Variables	AUC (95% CI)	Cut-off according to the Youden index	Sensitivity (%)	Specificity (%)	p
WBC	0.666 (0.608-0.724)	8.42	61.2	60.6	**<0.001**
NEU	0.687 (0.630-0.745)	5.20	65.3	65.6	**<0.001**
MPV	0.593 (0.533-0.654)	10.15	54.5	56.8	**<0.01**
NLR	0.691 (0.634-0.747)	2.53	65.3	66.4	**<0.001**
LDH	0.741 (0.680-0.802)	224.50	66.9	69.7	**<0.001**
AST	0.770 (0.709-0.830)	21.50	72.7	68.9	**<0.001**
ALT	0.695 (0.637-0.753)	19.50	64.5	61.4	**<0.001**
Troponin	0.968 (0.943-0.993)	2.43	90.9	99.6	**<0.001**

PCI; Percutaneous Coronary Intervention, WBC; White Blood Cell, NEU; Neutrophil, MPV; Mean platelet volume, NLR; Neutrophil lymphocyte ratio, LDH; lactate dehydrogenase, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase

ROC Curve Analysis: The diagnostic value of NLR, which was determined to show a significant change according to the PCI, was examined by ROC analysis. As a result of ROC curve analysis, there is no 0.5 value in the 95% confidence interval (CI) calculated for Area Under the ROC Curve (AUC) in both female and male patients (Table 4). NLR predicted the presence of PCI with 58.3% Sensitivity and 57.0% Specificity (with a positive likelihood ratio of 1.36) in women if it was> 2.215. NLR predicted the presence of PCI with 73.6% Sensitivity and 62.4% Specificity (with a positive likelihood ratio of 1.96) in men if it was> 2.345. Therefore, NLR may be a diagnostic biomarker for both men and women. However, it is more effective in males than females in terms of PCI decisions. For these reasons, while NRL can be used for PCI decisions in male patients, it needs additional biomarkers in female patients.

DISCUSSION

In this study, systemic inflammation biomarkers from CBC, routine emergency biochemistry, and troponin panel examinations of patients presenting with chest pain were examined. Neutrophil, MPV, and NLR values of the inpatients (ACS) were found to be significantly higher than the outpatients (for ACS diagnosis). In addition, the Neutrophil, MPV, and NLR values were significantly higher in STMI inpatients (underwent PCI), than NSTMI inpatients who did not undergo PCI. In the pathogenesis of ACS, it is known that there is a dysfunction in the inflammatory system. Dysfunction in this system makes the plaques more unstable and causes ACS (7). Neutrophil-lymphocyte ratio (NLR) shows the balance between regulatory factors and inflammation that occurs from various reasons. Therefore, it is considered as a new biomarker of thrombosis. Various studies about inflammatory response reported associations between NLR and many clinical conditions such as diabetes, malignant tumors, ACS, atherosclerosis, obesity, heart failure, and dyslipidemia (8,9). In a study conducted by Karagun, in inflammatory and infective events, an increase in neutrophil and thrombocyte count was observed, and a decrease in lymphocyte counts was reported. He also reported that NLR increases in many disease groups such as sepsis, cardiovascular diseases, neurovascular diseases, and malignancies, and it can be used in the prognostic follow-ups (10). Although mean platelet volume (MPV), which is another parameter in the CBC, is generally used to evaluate platelet functions in routine practice, it has been reported to show inflammatory load and disease activity. Also, MPV has been reported to be associated with disease activity in unstable angina, ulcerative colitis, myocardial infarction, pre-eclampsia, and Crohn's disease (11). In our study, we detected that neutrophil, MPV, and NLR values were significantly higher in patients diagnosed with the acute coronary syndrome in the emergency department (inpatients) than patients who were not diagnosed with ACS (outpatients).

NSTMI is the ACS subgroup that has less myocardial damage. Generally, the mortality rate in this group is lower than STMI, medical treatment sare recommended rather than invasive treatments. Therefore, patients in this group are hospitalized and generally, the medical treatment protocol is preferred (1). High sensitivity troponin (hs-Tn) measurement is recommended in the diagnoses of ACS. The second cTn test time interval can be shortened with the use of hs-cTn kits, due to their higher sensitivity and diagnostic accuracy in MI detection at the time of admission. It is recommended to use 0 hour/1-hour (best option) or 0 hour/2-hour (second-best option) algorithms (1).

Another subgroup of ACS is ST-elevation myocardial infarction (STMI). STMI is a clinical picture that usually manifests itself with chest pain and heart muscle damage due to ischemia. Among the ACS subgroups, this clinical picture has the highest mortality. This group is recommended to be hospitalized and treated with PCI as soon as possible. If ischemia is not resolved in the first 4 hours following coronary occlusion, myocardial damage increases, and heart contraction deteriorates. If reperfusion can be achieved during this period, it will prevent infarction. Therefore, (early) opening of the occluded vessel without expanding the area of ischemic necrosis; decreases mortality, decreases the risk of complications, and

contributes positively to the life expectancy of the patient (2). Therefore, opening of the occluded vessel before ischemic necrosis expands (early) decreases mortality and the risk of complications thus prolongs the life expectancy (2). In a study, it was emphasized that even minutes are very important in emergency reperfusion treatment, and PCI should be performed as quickly as possible because it reduces mortality and complications in ACS (12). For this reason, ACS patients should be diagnosed and underwent PCI quickly. Rapid diagnosis protocol with anamnesis, physical examination, and high-precision cardiac troponin test is recommended for ACS (13). Besides, there are publications reporting that Neutrophil, MPV, and NLR values can be used in the diagnosis of ACS subtypes (8). In addition, the relative lymphopenia observed in STMI patients compared to NSTMI patients causes a higher rate of NLR. In this direction, NLR can be used in the differentiation of STMI patients and NSTMI patients (14). In another study, it was reported that neutrophil, MPV, and NLR values can be used in the diagnosis of ACS and in determining the poor prognosis (15). Similarly, to the study of Tamhane et al., Azab et al. also found troponin levels of ACS patients with higher NLR levels significantly higher

(16,17). In their study, Aydın et al. reported that neutrophil, MPV, and NLR values can be used in the diagnosis of STMI (8). Similar to the literature, in our study, MPV, Neutrophil, and Troponin values of patients with ACS (STMI) who underwent PCI were found to be higher than ACS without PCI patients (NSTMI). It is thought that the unavailability of troponin tests, especially in peripheral hospitals, and long intervals needed for control tests such as 2 hours at the earliest may cause delays in the decision of PCI. CBC parameters such as WBC, Neutrophil, MPV, and NLR are inexpensive, common, and reproducible. Therefore, we believe that they can be used in the diagnosis of ACS and in making PCI decisions.

CONCLUSION

In conclusion, in our study, the diagnostic specificity and sensitivity of Troponin were found to be significantly high in diagnosing ACS and determining the PCI. In addition, diagnostic specificity and sensitivity of NLR were also found to be high. Although troponin is important for the diagnosis of ACS in emergency departments, we believe that NLR too can be used as a diagnostic biomarker, especially in male patients with suspected ACS.

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