

## **Evaluation of white blood cell and neutrophil/lymphocyte ratio in acute coronary syndrome patients admitted to emergency department.**

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### **Abstract**

**Objective:** Inflammatory reaction, which causes tissue damage in Acute Coronary Syndrome (ACS), leads to deterioration. White Blood Cell (WBC), Neutrophil (N), Lymphocyte (L) and Neutrophil/Lymphocyte (N/L) ratios were used to refer to the inflammation. High neutrophil levels show us acute inflammatory situation and low lymphocyte levels show us physiological stress. That is why N/L ratio is a valuable parameter which enables us to guess patient prognosis in Emergency Department (ED). In this study, white cell and NLR relations with ACS in patients with chest pain is evaluated.

**Material and method:** Patients referring to ED with chest pain within 3 months were investigated retrospectively. 100 patients were included in the study. Patients' WBC count, NLR and WBC values, gender, Troponin-I and CK-MB positivity, history of Coronary Heart Disease (CHD) and additional diseases were examined according to the final diagnoses. All the patients were divided into three groups according to ACS: Unstable Angina Pectoris (USAP), Non-ST Elevated Myocardial Infarction (NSTEMI), and ST-Elevated Myocardial Infarction (STEMI). Mortality and morbidity levels in hospital and after discharge were also examined in the study.

**Findings:** WBC values in patients with positive Troponin-I were found statistically higher than patients with negative Troponin-I ( $p<0.05$ ). In STEMI group, WBC values were statistically higher than USAP group ( $p<0.0083$ ). When patients' N/L ratio average distribution was examined; Troponin-I and CK-MB positive patients' NLR was found to be statistically higher than Troponin-I and CK-MB negative ones ( $p<0.05$ ).

**Conclusion:** N/L ratio, which is a marker of inflammatory process in the myocardial vascular bed, may be considered as a risk marker. For this reason, N/L ratio at admission can be used as an auxiliary parameter for predicting the diagnosis of ACS.

**Keywords:** Chest pain, Neutrophil/lymphocyte ratio, Emergency medicine.

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### **Introduction**

Coronary Artery Disease (CAD) is one of the main causes of premature death among adults. Cardiovascular diseases are responsible for 49% of all deaths in Europe [1].

Acute Coronary Syndrome (ACS) is associated with many hereditary and acquired risk factors. White blood cell, neutrophil, and lymphocyte counts and Neutrophil-Lymphocyte Count Ratio (NLR) are markers of systemic inflammation. White blood cell and its subtypes, which are major inflammatory cells, are responsible for adverse events in cardiovascular diseases and are used as a marker of inflammatory conditions. Leukocytes play a crucial role in the inflammatory process. In patients with or without CAD, white blood cell and its subtypes were studied as an inflammatory biomarker in predicting cardiovascular outcomes [2-4].

Today, N/L ratio is accepted as a parameter that combined shows the adverse effects of both high neutrophil levels, which reflect acute inflammation, and low lymphocyte levels, which reflect physiological stress [5]. The inflammatory reaction does not only show a response to tissue damage in ACS, but also leads to a poor clinical course [6,7].

In this study, the relationship between N/L ratio, WBC and ACS was evaluated in patients referring to emergency department with chest pain.

### **Materials and Methods**

This study included 100 patients aged 18 y and over who were admitted to emergency department with chest pain between July 2015 and November 2015 and who were followed with the preliminary diagnosis of ACS and who did not have

exclusion criteria. Due to the retrospective design of the study, approval from the local ethics committee was not obtained; however principles outlined by the Declaration of Helsinki were strictly followed. Patients who had clinically active infection, who had active malignancy, who had various hematologic proliferative disorders, who had an active or chronic autoimmune disease, who received steroids or chemotherapy, and who had a history of trauma or surgery within 10 days prior to admission were not included in the study. Non-Cardiac Chest Pain (NCCP) is defined by recurrent episodes of sub sternal chest pain in patients lacking a cardiac cause after a comprehensive evaluation. The data were obtained from the patients' files and the hospital computer registry system.

The age, gender, WBC count, N/L ratio, and presence of additional diseases (Hypertension (HT), Diabetes Mellitus (DM), dyslipidemia (HL), Congestive Heart Failure (CHF), Chronic Renal Failure (CRF), Chronic Obstructive Pulmonary Disease, asthma, and history of CAD (MI, CAG, CABG)) were recorded for all patients included in the study. HT cases were defined as those who had been previously diagnosed and were taking antihypertensive agents. DM cases were defined as those who were taking oral anti-diabetic drugs and insulin. HL cases were defined as those who were taking lipid-lowering therapy. CRF cases were defined as those who were on chronic dialysis program or who were taking anti-acidosis agents and medications affecting potassium homeostasis due to low clearance. All the patients were divided into three groups according to ACS: Unstable Angina Pectoris (USAP), Non-ST Elevated Myocardial Infarction (NSTEMI), and ST-Elevated Myocardial Infarction (STEMI). ACS was defined as having ECG (electrocardiogram) changes and/or elevated cardiac enzyme levels together with a chest pain associated with myocardial ischemia. When patients with STEMI apply to emergency department with chest pain or equivalents, ECG findings may be observed as follows in accordance with ACC/ESC criteria:

- New ST elevation at the J point in two contiguous leads of  $>0.1$  mV in all leads other than leads V2-V3.
- In leads V2-V3:
  - (i)  $>0.2$  mV in men  $>40$  y,
  - (ii)  $>0.25$  mV in men  $<40$  y (or)
  - (iii)  $>0.15$  mV in women
- Patients are considered as STEMI if they have high levels of troponin and CK-MB, which are biochemical markers of cardiac necrosis, with new left bundle branch block.

White blood cell, neutrophil, and lymphocyte counts and levels of cardiac markers (troponin/CKMB) obtained from the first venous blood sample on admission to emergency department were recorded as laboratory findings. Differential white blood cell counts were obtained with the Automatic Coulter Counter Method (Coulter LH 780 Hematology Analyzer, Beckman Coulter Corp., Hialeah, Florida).

The N/L ratios were classified into 3 groups: low ( $<3.0$ ), moderate ( $3.0-4.7$ ), and high ( $>4.7$ ).

The average distribution of N/L ratios and WBC counts was examined according to gender, troponin-I and CK-MB positivity, history of CAD, presence of additional diseases, and definitive diagnosis.

### Statistical analysis

Statistical analysis was performed using the IBM SPSS Statics Version 22 package program. The Independent Samples t-test was used to compare the ages of male and female subjects. The Chi-Square and Fisher's exact tests were used to compare categorical data between groups. The Mann-Whitney U-test was used for comparing two groups because continuous data did not show a normal distribution. The Kruskal-Wallis test (a Bonferroni-corrected Mann-Whitney U-test) was used for comparing more than two groups.  $p < 0.05$  was considered statistically significant.

### Results

100 patients who were admitted to emergency department within the last 3 months were included in this cross-sectional retrospective study. Of the patients included in the study, 70% ( $n=70$ ) were male and 30% ( $n=30$ ) were female. There was no statistically significant difference between the male and female subjects in terms of mean age ( $p > 0.05$ ). The mean age was  $57.8 \pm 12.8$  (mean-max: 29-84) y; men  $56.2 \pm 11.7$  (mean-max: 29-81) y, women  $61.5 \pm 14.7$  (mean-max: 33-84) ( $p > 0.05$ ).

Of the 100 patients, 66% ( $n=66$ ) had ACS (USAP, NSTEMI, STEMI), 44% ( $n=44$ ) had NCCP.

When the average distribution of WBC counts in the patients was examined, WBC count was found to be higher in the patients with positive troponin-I than in the patients with negative troponin-I ( $p < 0.05$ ) (Table 1).

**Table 1.** The average distribution of WBC counts according to gender, troponin-I and CK-MB positivity, history of CAD, presence of additional disease, and definitive diagnosis.

		WBC/mm <sup>3</sup>	Mean-max	p
		Mean $\pm$ SD		
Gender	Male	9.11 $\pm$ 2.8	4.49-17.49	0.913*
	Female	9.06 $\pm$ 2.62	5.29-17.25	
Troponin-I	Negative	8.46 $\pm$ 2.49	4.49-17.49	0.006*
	Positive	10.01 $\pm$ 2.84	4.54-17.25	
CK-MB	Negative	8.93 $\pm$ 2.69	4.49-17.49	0.088*
	Positive	10.42 $\pm$ 2.86	6.25-16.3	
History of CAD	No	9.3 $\pm$ 3.04	4.49-17.49	0.657*
	Yes	8.88 $\pm$ 2.39	4.93-14.33	
Additional disease	No	8.71 $\pm$ 2.28	4.93-17.25	0.201*
	Yes	9.47 $\pm$ 3.09	4.49-17.49	

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Definitive diagnosis	Non-cardiac	8.84 ± 2.71	4.49-17.49	0.012**
	NSTEMI	9.29 ± 2.77	4.54-17.25	
	STEMI	10.53 ± 2.72	6.25-16.3	
	USAP	7.78 ± 2.13	4.93-12.82	

\*Mann-Whitney U test; \*\*Kruskal-Wallis test.

**Table 2.** The average distribution of N/L ratios according to gender, troponin-I and CK-MB positivity, history of CAD, presence of additional disease, and definitive diagnosis.

		WBC/ mm <sup>3</sup> Mean ± SD	Mean-max	p
Gender	Male	3.63 ± 4.53	0.69-31.06	0.532*
	Female	4.22 ± 3.86	0.99-15.16	
Troponin-I	Negative	3.06 ± 4.3	0.69-31.06	0.002*
	Positive	4.89 ± 4.19	0.9-19.35	
CK-MB	Negative	3.55 ± 4.31	0.69-31.06	0.010*
	Positive	5.86 ± 4.11	1.16-15.41	
History of CAD	No	3.73 ± 4.99	0.82-31.06	0.268*
	Yes	3.89 ± 3.56	0.69-15.41	
Additional disease	No	2.96 ± 2.09	0.82-10.69	0.542*
	Yes	4.63 ± 5.62	0.69-31.06	
Definitive diagnosis	Non-cardiac	3.84 ± 5.52	0.9-31.06	0.019**
	NSTEMI	4.1 ± 2.93	0.9-10.69	
	STEMI	5.13 ± 5.17	1.16-19.35	

**Table 5.** The distribution of rates of definitive diagnosis according to N/L ratios.

		Definitive diagnosis								Total	p	
		Non-cardiac		NSTEMI		STEMI		USAP		n	%	
		n	%	n	%	n	%	n	%			
N/L ratio	Low	23	36.5	14	22.2	10	15.9	16	25.4	63	63	0.034
	Moderate	6	40	3	20	3	20	3	20	15	15	
	High	5	22.7	10	45.5	7	31.8	0	0	22	22	
Total		34	34	27	27	20	20	19	19	100	100	

Fisher's Exact test.

There was a difference between WBC counts according to definitive diagnosis (p<0.05). The Bonferroni-corrected Mann-Whitney U-test was performed in order to detect which group created the difference; and WBC count was found to be higher at a statistically significant level in the patients with STEMI than in the patients with USAP (p<0.0083) (Table 1).

When the average distribution of N/L ratios in the patients was examined, it was observed that N/L ratio was found to be higher in the patients with positive troponin-I than in the

USAP	1.93 ± 0.96	0.69-4.05
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\*Mann-Whitney U test, \*\*Kruskal-Wallis test.

**Table 3.** The distribution of rates of troponin-I positivity according to N/L ratios.

	Troponin-I				Total		p
	Negative		Positive		n	%	
	n	%	n	%			
N/L ratio	Low (<3.0)	44	69.8	19	30.2	63	0.001
	Moderate (3.0-4.7)	11	73.3	4	26.7	15	
	High (>4.7)	4	18.2	18	81.8	22	
Total		59	59	41	41	100	100

Chi-square trend analysis.

**Table 4.** The distribution of rates of CK-MB positivity according to N/L ratios.

	CK-MB				Total		P
	Negative		Positive		n	%	
	n	%	n	%			
N/L ratio	Low (<3.0)	61	96.8	2	3.2	63	0.001
	Moderate (3.0-4.7)	13	86.7	2	13.3	15	
	High (>4.7)	15	68.2	7	31.8	22	
Total		89	89	11	11	100	100

Chi-square trend analysis.

patients with negative troponin-I (p<0.05). N/L ratio was also found to be higher in the patients with positive CK-MB than in the patients with negative CK-MB (p<0.05) (Table 2).

There was difference between N/L ratios according to definitive diagnosis (p<0.05). In the Bonferroni-corrected Mann-Whitney U-test performed in order to detect which group created the difference, N/L ratio was found to be higher in the patients with STEMI than in the patients with USAP (p<0.0083) (Table 2).

When the distribution of rates of troponin-I positivity was examined according to N/L ratios, it was observed that there was a relationship between the groups ( $p<0.05$ ) (As N/L ratio increased, troponin-I positivity increased) (Table 3).

When the distribution of rates of CK-MB positivity was examined according to N/L ratios, it was observed that there was a relationship between the groups ( $p<0.05$ ) (As N/L ratio increased, CK-MB positivity increased as well) (Table 4).

When the distribution of rates of presence of additional disease and history of CAD was examined according to N/L ratios, it was observed that there was no relationship between the groups ( $p>0.05$ ).

When the distribution of rates of definitive diagnosis was examined according to N/L ratios, it was observed that there was a relationship between the groups ( $p<0.05$ ) (Table 5).

## Discussion

Risk factors for CAD were first identified in the Framingham heart study, which began in 1948. The incidence and prevalence of this disease increase with age. Therefore, age can be considered as the most important risk factor [8,9].

Studies have also shown that the age limit varies between 58 and 67 y [10-13]. The majority of the 100 patients included in our study were male (70%, n: 70). The mean age was  $57.87 \pm 12.85$  y. This was similar to previous studies. Patients were old like in these studies.

The primary cells involved in early inflammatory response are neutrophils. The relationship between ACS, atherosclerosis, and inflammation is known. In a study of Huang et al., they evaluated the role of WBC count and its subtypes at admission in predicting major cardiac events in ACS. It was reported that the number of neutrophils was an independent marker of multi-vessel disease [14-19]. It was shown that N/L ratio can be used in predicting adverse events in CAD [20,21].

In our study, the N/L ratios were classified into 3 groups: low ( $<3.0$ ), moderate (3.0-4.7), and high ( $>4.7$ ). These values were determined on the basis of the model established by comparing the average N/L ratios in the relevant literature [22-25]. So we used this classification.

Large and long-term studies found that the GRACE scores calculated at admission and discharge, the number of patients with TIMI 0-2 and TIMI 3-4 in the NSTEMI/USAP group, and the average TIMI scores calculated for STEMI patients were significantly different between the groups. The scores were found to be higher in groups with higher N/L ratio, and this increase was also statistically significant between the groups [26,27].

In our study, when the average distribution of N/L ratios in the patients was examined, N/L ratio was found to be higher in the patients with positive troponin-I than in the patients with negative troponin-I, and in the patients with positive CK-MB than in the patients with negative CK-MB. In conclusion, many studies have shown that N/L ratio, which is used for risk

classification in ACS, had enough accuracy and gave better results than clinical evaluation. When taking into account the fact that there is a significant relationship between these two risk scoring systems and N/L ratios and N/L ratio is higher in patients with higher troponin levels, this supports other literature information and considerations of important authors about N/L ratio can be used as a practical risk marker in ACS. In a study of Zhan et al., N/L ratio was found highest in the STEMI group among the ACS subgroups [28].

In a study of Tamhane et al., the number of patients with elevated cardiac markers was found to be significantly higher in the group with higher N/L ratio. In a study of Azab et al., troponin levels were found to be significantly higher among the patients in the group with higher N/L ratio [26,27].

In our study, it was seen that as N/L ratio increased, troponin positivity increased. N/L ratio was found to be higher in the patients with NSTEMI than in the patients with USAP. As a result, the detection of a statistically significant relationship between N/L ratio and CK-MB, troponin (which had been previously demonstrated for extent of myocardial injury and for cardiovascular events during follow-up) supports that N/L ratio can be used as a risk marker in ACS together with studies having similar findings in the literature.

## Conclusion

There was a positive correlation between N/L ratio and WBC count, which are markers of inflammatory response during ACS, and troponin and CK-MB, which are markers of myocardial damage. This finding suggests that N/L ratio, which is a marker of inflammatory process in the myocardial vascular bed, may be considered as a risk marker. For this reason, N/L ratio at admission can be used as an auxiliary parameter for predicting the diagnosis of ACS. Defining the role of inflammation in CHD will help us to develop new and effective ways to protect against this management of disease, which is the most important cause of death in our country as it is in the whole world.

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