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Original Article

Relationship Between Baseline the WBC Count and the Neutrophil-to-Lymphocyte Ratio and the 6-Month Outcome in Patients With Non–ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention

Mohsen Maadani[1], MD; Alireza Ziaee[*2], MD; Mohammadali Sadr-Ameli[1], MD; Seyedeh Samaneh Ahmadi[2], MD; Yasaman Khalili[2], MD; Mostafa Miri[1], MD; Reza Ravanparsa[1], MD

ABSTRACT

Background: We sought to assess the relationship between the baseline white blood cell (WBC) count and the neutrophil-to-lymphocyte ratio (NLR) and the 6-month outcome in patients with non–ST-segment elevation myocardial infarction (NSTEMI) undergoing percutaneous coronary intervention (PCI).

Methods: Between April 2016 and April 2017, consecutive NSTEMI patients who underwent PCI were prospectively enrolled in a PCI registry. The patients' demographics, initial WBC count, NLR, and 6-month major adverse cardiac events (MACE) were assessed. The patients were divided into 3 groups based on their WBC count: WBC < 10000, WBC = 10000–12000, and WBC > 12000. According to the NLR, there were 3 groups: NLR < 2.5, NLR = 2.5–4.5, and NLR > 4.5. Finally, the association between these values and 6 months' MACE was assessed.

Results: The study was conducted on 161 patients with NSTEMI who underwent PCI. The mean age of the participants was 58.9 ± 11 years, and 135 (83.9%) of the patients were male. The results showed that 81.9% of the patients had WBC < 10000, 13.1% had WBC = 10000–12000, and 5% had WBC > 12000; additionally, 87 patients had NLR < 2.5, 57 patients had NLR = 2.5–4.5, and 20 patients had NLR > 4.5. There was no significant association between the time of admission, the WBC count, the number of involved coronary vessels, the reoccurrence of myocardial infarction, unstable angina, atrial fibrillation, cardiogenic shock, and death; nonetheless, there was a significant relationship between the admission NLR and the reoccurrence of myocardial infarction (P = 0.008) and unstable angina (P = 0.02).

Conclusions: The NLR can be considered a predictive parameter for long-term outcomes in NSTEMI patients undergoing PCI. ***(Iranian Heart Journal 2019; 20(4): 92-102)***

KEYWORDS: Non–ST-segment elevation myocardial infarction, Baseline WBC count, Neutrophil-to-lymphocyte ratio, Six-month outcomes

[1]Cardiovascular Intervention Research Center, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.
[2] Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.

***Corresponding Author:** Alireza Ziaee, MD
Email: ziaee.b.alireza@gmail.com **Tel:** 09394428699

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Over the last decade, cardiovascular diseases have become the single largest cause of death worldwide. In 2004, cardiovascular diseases caused an estimated 17 million deaths and led to 151 million disability-adjusted life years (DALYs) lost (about 30% of all deaths) and 14% of all DALYs lost that year.

Like many high-income countries during the last century, low- and middle-income countries have seen an alarming increase in the rates of cardiovascular diseases. In 2001, 75% of global deaths and 82% of total DALYs lost caused by coronary heart disease occurred in low- and middle-income countries.

Ischemic heart disease may be manifested clinically as chronic stable angina or acute coronary syndrome. The latter, in turn, can be subdivided into ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA).

Acute total occlusion of a coronary artery usually causes STEMI, whereas UA/NSTEMI most commonly results from the severe obstruction, but not total occlusion, of the culprit coronary artery.

Approximately two-thirds of patients with UA have evidence of myocardial necrosis on the basis of elevated cardiac serum markers such as cardiac-specific troponin T or I and creatine kinase isoenzyme (CK)–MB, and thus have a diagnosis of NSTEMI.

Among patients with acute coronary syndrome, women present more often with UA, representing 30%–45% of patients with this condition, compared with 25%–30% of patients with NSTEMI and only 20% of patients with STEMI. In comparison with the latter, patients with UA/NSTEMI are old and have high rates of previous myocardial infarction, stable angina, diabetes, previous coronary revascularization, and extracardiac vascular disease. Indeed, approximately 80% of patients with UA/NSTEMI have a history of coronary artery disease before the acute event.

Five pathophysiologic processes may contribute to the development of UA/NSTEMI:

1 plaque rupture or erosion with superimposed nonocclusive thrombi (this causes by far the most UA/NSTEMI);

2 dynamic obstruction due to

- **a** spasm of an epicardial coronary artery, as in the Prinzmetal variant angina;
- **b** constriction of the small, intramural muscular coronary arteries (ie, the coronary resistance vessels);
- **c** local vasoconstrictors, such as thromboxane A_2, released from platelets;
- **d** dysfunction of the coronary endothelium; and
- **e** adrenergic stimuli including cold and cocaine;

3 severe coronary luminal narrowing caused by progressive coronary atherosclerosis or post–percutaneous coronary intervention (PCI) restenosis;

4 inflammation; and

5 secondary UA, which is severe myocardial ischemia related to an increased myocardial oxygen demand or a decreased oxygen supply (eg, tachycardia, fever, hypotension, or anemia)

Several serum markers can serve as effective tools for identifying pathophysiologic processes. Inflammatory factors increase following acute coronary syndrome, but most inflammatory biomarkers are too expensive and not easily available.

White blood cells (WBCs) have the most important role in the inflammatory process. The WBC count is an available test, and many different studies have shown that an increase in the WBC count and its subtypes is correlated with the prediction of coronary artery disease. [1] the WBC count is a strong independent predictor of mortality in patients with acute coronary syndrome and has a positive

correlation with coronary risk factors, cardiac biomarkers, and C-reactive protein.

The WBC count is a simple test that is available universally and is considered to be one of the most commonly obtained tests in the emergency department.

Recent studies have shown that WBCs destabilize coronary artery plaques at the onset of acute coronary syndrome and an elevated WBC count is considered to be an independent predictor of long-term cardiac mortality, especially following acute myocardial infarction. [2] Furthermore, the admission neutrophil-to-lymphocyte ratio (NLR) is a strong and independent predictor of short- and long-term mortalities in patients with NSTEMI. [3,4] The NLR is an indicator of baseline inflammatory response and is independently associated with the severity of coronary artery disease in patients with NSTEMI. [5]

Given the lack of research on this topic in Iran, we sought to evaluate the relationship between the WBC count and the NLR and the severity and number of affected coronary arteries and other sequences.

METHODS

The present single-center prospective cross-sectional study was conducted on NSTEMI patients undergoing PCI. Between April 2016 and April 2017, a total of 161 patients were initially evaluated.

Clinical, laboratory, and procedural characteristics of the study patients were collected and entered in a questionnaire.

Coronary angiography and PCI procedures were performed according to standard routines. The intention to treat was for the culprit artery.

A complete echocardiographic study was performed on the patients the day after PCI. The left ventricular ejection fraction was estimated using the Simpson equation in the 4-chamber view. All the echocardiograms were performed by a single attending physician to avoid inter-observer variability.

The patients were divided into 3 groups based on their WBC count: WBC < 10000, WBC = 10000–12000, and WBC > 12000. In terms of the NLR, there were 3 groups: NLR < 2.5, NLR = 2.5–4.5, and NLR > 4.5.

The patients were observed during their hospitalization and over a 6-month period and thereafter the association between these values and 6-month major adverse cardiac events (MACE) was assessed.

The Ethics Committee of Rajaei Cardiovascular, Medical, and Research Center approved the trial design.

Primary and Secondary Endpoints

The primary endpoint of this study was to determine whether there is a relationship between the initial WBC count and the NLR and in-hospital and 6-month follow-up outcomes (eg, reoccurrence of myocardial infarction, UA, cardiogenic shock, and death) in NSTEMI patients.

The secondary endpoints were an evaluation of the relationship between the WBC count and the NLR and the number of affected coronary arteries, the ejection fraction, the amount of CK-MB, the occurrence of atrial fibrillation, and other complications.

RESULTS

A total of 161 patients with NSTEMI undergoing PCI were enrolled in the present study. The mean age of the participants was 58.9 ± 11 years, and 135 (83.9%) patients were male.

The most common cardiovascular risk factor was hyperlipidemia, which was observed in 91 (56.5%) patients, followed by hypertension in 90 (55.9%) patients and diabetes in 61 (37.9%). Fifty-six (34.8%) patients were smokers, and 35 (21.7%) had a positive family history of cardiovascular diseases.

Table 1. Demographic data of the patients

		Number	Percent
DM	no	100	62.1
	yes	61	37.9
HTN	no	71	44.1
	yes	90	55.9
DLP	no	70	43.5
	yes	91	56.5
HF	no	154	95.7
	yes	7	4.3
CS	no	105	65.2
	yes	56	34.8
FH	no	126	78.3
	yes	35	21.7
PH-MI	no	146	90.7
	yes	15	9.3
PH_PCI	no	140	87.0
	yes	21	13.0
PH_CABG	no	152	94.4
	yes	9	5.6
PH_CVA	no	160	99.4
	yes	1	0.6
PH_peripheral disease vascular	no	159	98.8
	yes	2	1.2

DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; HF, Heart failure; CS, Cigarette smoking; FH, Family history; PH-MI, Past history of myocardial infarction; PH_PCI, Past history of percutaneous coronary intervention; PH_CABG, Past history of coronary artery bypass grafting; PH_CVA, Past history of cerebrovascular attack

Moreover, 9.3% of the patients had a past history of myocardial infarction, 13% had a history of PCI, and 5.6% of the patients had undergone coronary artery bypass graft surgery before.

Table 2. Admission CK-MB (unite/mL)

		Frequency	Percent	Valid Percent	Cumulative Percent
CK-MB	≤50	134	83.2	83.2	83.2
	>50	27	16.8	16.8	100.0
	Total	161	100.0	100.0	

On admission, 83.2% of the patients had CK-MB < 50.

Table 3. Ejection fraction (%) of the patients after percutaneous coronary intervention

		Frequency	Percent	Valid Percent	Cumulative Percent
Ejection Fraction	≥45-55	131	81.4	81.4	81.4
	≥35-<45	24	14.9	14.9	96.3
	<35	6	3.7	3.7	100.0
	Total	161	100.0	100.0	

A total of 81.4% of the patients had an ejection fraction = 45%–55%.

Table 4. WBC count (cells/mm^3)

WBC					
		Frequency	Percent	Valid Percent	Cumulative Percent
WBC Count	>10000	131	81.4	81.9	81.9
	≥10000-12000	21	13.0	13.1	95.0
	≥12000	8	5.0	5.0	100.0

WBC, White blood cells

Additionally, 81.9% of the patients had WBC < 10000, 13.1% had WBC = 10000–12000, and 5% had WBC > 12000.

In terms of the NLR, the patients were divided into to 3 groups: NLR < 2.5, NLR = 2.5–4.5, and NLR > 4.5. Eighty-seven patients had NLR < 2.5, 57 patients had NLR = 2.5–4.5, and 20 patients had NLR > 4.5.

Table 5. Relationship between the NLR and the number of involved coronary vessels

		Vessel_ Involvement			*P* value
		SVD	2VD	3VD	
PMN_L	N/L<2.5	47	32	8	0.467
	2.5≤N/L<4.5	36	15	6	
	N/L≥4.5	9	9	2	

NLR, Neutrophil-to-lymphocyte ratio

Table 6. Relationship between the WBC count and the NLR and the reoccurrence of myocardial infarction

		Reoccurrence of Myocardial Infarction		Total	*P* value
		No	Yes		
WBC Count (cells/mm^3)	<10000	117	14	131	0.9
		81.8%	82.4%	81.9%	
	≥10000-12000	19	2	21	
		13.3%	11.8%	13.1%	
	≥12000	7	1	8	
		4.9%	5.9%	5.0%	
PMN_L Ratio	<2.5	74	5	79	**0.008**
		51.4%	29.4%	49.1%	
	2.5≤N/L<4.5	56	6	62	
		38.9%	35.3%	38.5%	
	≥4.5	14	6	20	
		9.7%	35.3%	12.4%	

WBC, White blood cells; NLR, Neutrophil-to-lymphocyte ratio

There was no significant relationship between the NLR and the number of involved coronary vessels (P = 0.467)

The results also demonstrated that there was no significant relationship between the WBC count and the reoccurrence of myocardial infarction (P = 0.9); nevertheless, the relationship between the NLR and the reoccurrence of myocardial infarction was significant (P = 0.008).

Table 7. Relationship between the WBC count and the NLR and the reoccurrence of unstable angina

		Unstable Angina		Total	*P* value
		No	Yes		
WBC Count (cells/mm^3)	<10000	109	22	131	0.6
		80.7%	88.0%	81.9%	
	≥10000-12000	19	2	21	
		14.1%	8.0%	13.1%	
	≥12000	7	1	8	
		5.2%	4.0%	5.0%	
PMN_L Ratio	<2.5	71	8	79	**0.02**
		52.2%	32.0%	49.1%	
	2.5≤N/L<4.5	52	10	62	
		38.2%	40.0%	38.5%	
	≥4.5	13	7	20	
		9.6%	28.0%	12.4%	

WBC, White blood cells; NLR, Neutrophil-to-lymphocyte ratio

The results revealed no significant relationship between the WBC count and the occurrence of UA ($P = 0.6$), whereas there was a significant relationship between the NLR and the occurrence of UA ($P = 0.02$).

Table 8. Relationship between the WBC count and the NLR and the occurrence of atrial fibrillation

		Atrial Fibrillation		Total	*P* value
		No	Yes		
WBC	<10000	129	2	131	0.7
		81.6%	100.0%	81.9%	
	≥10000-12000	21	0	21	
		13.3%	0.0%	13.1%	
	≥12000	8	0	8	
		5.1%	0.0%	5.0%	
PMN_L Ratio	<2.5	78	1	79	0.8
		49.1%	50.0%	49.1%	
	2.5≤N/L<4.5	61	1	62	
		38.4%	50.0%	38.5%	
	≥4.5	20	0	20	
		12.6%	0.0%	12.4%	

WBC, White blood cells; NLR, Neutrophil-to-lymphocyte ratio

According to our results, there was no significant relationship between the WBC count and the NLR and the occurrence of atrial fibrillation ($P = 0.7$ and $P = 0.8$, respectively).

Table 9. Relationship between the WBC count and the NLR and the occurrence of cardiogenic shock

		Cardiogenic Shock		Total	*P* value
		No	Yes		
WBC	<10000	129	2	131	0.799
		81.6%	100.0%	81.9%	
	≥10000-12000	21	0	21	
		13.3%	0.0%	13.1%	
	≥12000	8	0	8	
		5.1%	0.0%	5.0%	
PMN_L	<2.5	78	1	79	0.214
		49.1%	50.0%	49.1%	
	2.5≤N/L<4.5	62	0	62	
		39.0%	0.0%	38.5%	
	≥4.5	19	1	20	
		11.9%	50.0%	12.4%	

WBC, White blood cells; NLR, Neutrophil-to-lymphocyte ratio

There was no significant relationship between the WBC count and the NLR and the occurrence of cardiogenic shock (P = 0.799 and P = 0.214, respectively).

Table 10. Relationship between the WBC count and the NLR and the occurrence of death

		Death		Total	*P* value
		No	Yes		
WBC	<10000	128	3	131	0.146
		82.1%	75.0%	81.9%	
	≥10000-12000	21	0	21	
		13.5%	0.0%	13.1%	
	≥12000	7	1	8	
		4.5%	25.0%	5.0%	
PMN_L	<2.5	78	1	79	0.069
		49.7%	25.0%	49.1%	
	≥2.5N/L-4.5	61	1	62	
		38.9%	25.0%	38.5%	
	≥4.5	18	2	20	
		11.5%	50.0%	12.4%	

WBC, White blood cells; NLR, Neutrophil-to-lymphocyte ratio

The results demonstrated no significant relationship between the WBC count and the NLR and the occurrence of death (P = 0.146 and P = 0.069, respectively).

The area under the curve (AUC) is indicative of accuracy.

According to these curves, the AUC for the evaluation of the relationship between the WBC count and atrial fibrillation, reoccurrence of myocardial infarction, and UA was 0.428, 0.633, and 0.528, which means that this diagnostic power was weak.

The AUC for the evaluation of the relationship between the NLR and atrial fibrillation, reoccurrence of myocardial infarction, and UA was 0.769, 0.799, and 0.692, which appear to be desirable by comparison with the AUC for the WBC count.

In the logistic regression analysis, the association between the NLR and the reoccurrence of myocardial infarction was significant and a 1-unit rise in the NLR amount increased the probability of the reoccurrence of myocardial infarction by 1.3 fold.

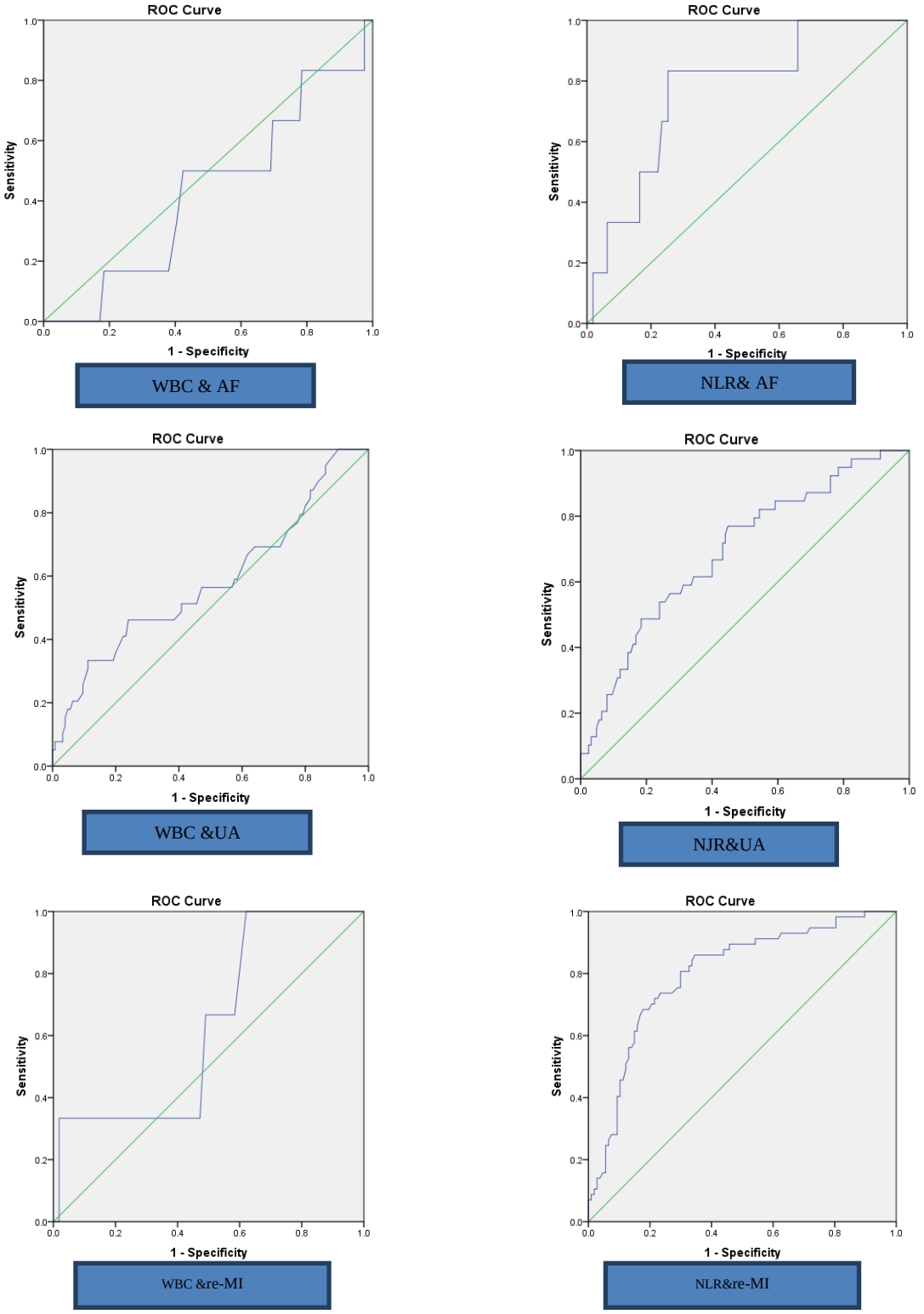

Figure 1. ROC curve of the WBC count and the NLR with major adverse cardiovascular events over a 6-month period after hospital discharge
ROC, Receiver operating characteristic; WBC, White blood cells; NLR, Neutrophil-to-lymphocyte ratio; MI, Myocardial infarction; UA, Unstable angina; AF, Atrial fibrillation

CONCLUSIONS

In the current prospective cross-sectional study, we evaluated 161 NSTEMI patients undergoing PCI.

The mean age of the participants was 58.9 ± 11 years, and men accounted for 135 (83.9%) of the study population.

Our objective was to determine whether there is a relationship between the admission WBC count and the NLR and the 6-month outcome in NSTEMI patients undergoing PCI. In our patients, we considered some variables as outcomes, including the number of involved coronary arteries, the reoccurrence of myocardial infarction, UA, atrial fibrillation, cardiogenic shock, and death.

Our results revealed no significant relationship between the admission WBC count and these variables; nevertheless, there was a significant relationship between the admission NLR and the reoccurrence of myocardial infarction and UA.

Sabatine et al [6] showed that higher baseline WBC counts were associated with lower flow grades of thrombolysis in myocardial infarction (TIMI) and myocardial perfusion grades as well as a greater extent of coronary artery disease. They also reported that a higher baseline WBC count was predictive of a higher 6-month mortality rate.

In our study, there was no relationship between the baseline WBC count and the number of involved coronary vessels and also between the WBC count and death.

Leukocytes may influence the development of coronary artery disease by causing infarct expansion. During the reperfusion of ischemia, neutrophils can plug capillaries in the coronary microcirculation, resulting in the no-reflow phenomena, ventricular arrhythmia, loss of vascular reserve, infarct expansion, and even organ dysfunction. [7] In contrast, in our study, we found no relationship between baseline the WBC count and the number of involved coronary vessels.

Munir and Afzal [2] showed that WBCs destabilize coronary artery plaques at the onset of acute coronary syndrome. They also reported that an elevated WBC count was an independent predictor of long-term cardiac mortality, especially following acute myocardial infarction. As was mentioned before, our study did not yield a similar result.

Misumida et al [8] evaluated the association between the NLR and the severity of coronary artery disease and reported that NLR > 2.8 was an independent predictor of left main/triple vessel disease in patients with NSTEMI. We, however, found no relationship between the baseline NLR and the number of involved coronary vessels.

Gul and colleagues [3] showed that the NLR was a strong and independent predictor of the 3-year cardiovascular mortality rate in patients with NSTEMI and UA. Elsewhere, Kurtul and coworkers [5] showed that the NLR was independently associated with the severity of coronary artery disease in patients with NSTEMI. We found only a significant association between the admission NLR and the reoccurrence of myocardial infarction and UA.

Azab et al [4] showed that the NLR was an independent predictor of short- and long-term mortality in patients with NSTEMI with an average NLR > 4.7. In our study there was no significant relationship between the NLR and the occurrence of death during our 6-month follow-up; nevertheless, in our patients with NLR > 4.7, there was a significant association with the reoccurrence of myocardial infarction and UA.

Khan et al [9] showed that in patients with NSTEMI, a high NLR was a good predictor of in-hospital mortality, atrial fibrillation, and ST-segment deviation. In contrast, we found no significant relationship between a high NLR and the occurrence of atrial fibrillation.

Finally, this was a single-center study with an observational nature; larger study populations could produce more accurate results. Additionally, we had some confounding variables that might have influenced the NLR. For instance, underlying diseases such as diabetes mellitus, hypertension, hyperlipidemia, and smoking can influence the NLR. Khandare and coworkers [10] showed that there was a significant relationship between the NLR and diabetic nephropathy. Moreover, Wang et al [11] showed that the NLR in patients with hypertension was higher than that in normotensive patients. What is more, a rise in the NLR in smokers was shown in a study by Tulgar and colleagues. [12] Therefore, in the interpretation of the results of the current study, the effects of confounding variables should be taken into consideration.

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