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ORIGINAL RESEARCH

Predictive Value of Hematological Parameters in Non-ST Segment Elevation Myocardial Infarction and Their Relationship with the TIMI Risk Score

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ABSTRACT

Background: Hematological parameters, such as white blood cell count (WBC), mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and WBC to MPV ratio (WMR), could provide data in prognosis, risk stratification, and optimal management in patients with acute coronary syndromes. **Aim:** We aimed to investigate the prognostic value of hematological parameters and their relationship with the TIMI risk score in non-ST elevation myocardial infarction (NSTEMI) patients. **Material and Methods:** A total of 259 adult patients with NSTEMI were included in this retrospective and observational cohort study. During a 1-year follow-up period, the efficacy of the main hematological parameters in predicting major adverse cardiovascular events (MACE) and their correlation with the TIMI risk score was analyzed. Results: Among the 259 patients, 188 (72.6%) were male, and the mean age was 60.4 ± 11.9 years. MACE was observed in 60 patients (23.2%). Elevated baseline levels of WBC, neutrophils, NLR, PLR, and WMR were associated with MACE development throughout the 1-year follow-up. Moreover, WBC, WMR, and NLR were correlated with the TIMI risk score. When the predictive power of these parameters for MACE was evaluated by ROC analysis, the AUC values for WBC, WMR, and NLR were 0.670 (95% CI 0.590–0.750), 0.666 (95% CI 0.582–0.746), and 0.689 (95% CI 0.610–0.767), respectively. **Conclusion:** WBC, NLR, and WMR predicted MACE in NSTEMI patients and were consistent with the TIMI risk score. On this basis, they could provide supportive data for early risk stratification and optimized therapeutic approach, particularly in high-risk patients.

Keywords: hematological parameters, neutrophil to lymphocyte ratio (NLR), non-ST-segment elevation myocardial infarction (NSTEMI), TIMI risk score, WBC/MPV ratio (WMR)

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INTRODUCTION

Coronary artery disease (CAD), most commonly caused by atherosclerosis, is the leading cause of death worldwide.[1,2] Acute coronary syndrome (ACS), which may sometimes result in death, is a clinical condition that generally requires immediate intervention.[3,4] Inflammation plays a pivotal role in the pathogenesis of atherosclerosis and prognosis of CAD.[5] In this base, in recent years, evidence has been available concerning hematological parameters, key markers in both inflammation and CAD, given that they may provide data in prognosis, risk stratification, and optimal management in patients with CAD, specifically ACS.[6,7] Well-established parameters, in this sense, are mean platelet volume (MPV), white blood count (WBC), neutrophil count, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR).[8-13] However, very few data is available regarding WBC to MPV ratio (WMR).[6]

The thrombolysis in myocardial infarction (TIMI) risk score is a risk stratification model that has been shown to predict post-percutaneous coronary intervention (post-PCI) major adverse cardiovascular events (MACE) in patients with ACS.[14] Studies have revealed that the TIMI risk score is far better in providing diagnostic evidence for ACS than history, physical examination, ECGs, or biomolecular cardiac markers alone.[15,16]

Prediction of prognosis in patients with non-ST elevation myocardial infarction (NSTEMI), a variety of ACS, may be crucial for early risk stratification and optimal management.[7,14,17,18] A limited number of studies are available in the literature reporting the relationship between hematological parameters and the TIMI risk score in NSTEMI patients. Thefore, in this study, we aimed to describe the prognostic value of main hematological indices and their correlation with the TIMI risk score in NSTEMI patients.

MATERIAL AND METHODS

STUDY POPULATION

A total of 259 adult patients (>18 years old), who presented with NSTEMI and underwent coronary angiography between January 16, 2013 and December 15, 2016, were included in this retrospective, observational cohort study. The clinical, demographical, laboratory characteristics on admission and 1-year follow-up data were collected from hospital records. The patients were divided into two groups, MACE(+) and MACE(−), and the findings were compared accordingly. Exclusion criteria were as follows: 1) the main exclusion criteria consisted in other types of acute coronary syndromes than NSTEMI; 2) abscence of follow-up data; 3) the presence of an active infection; 4) immunosupressive treatment; 5) the presence of a hematological disorder; 6) malignancy. The complete blood count was analyzed using Sysmex XT 2000iV (Sysmex Corporation, Kobe, Japan). The ethical review board of the Medipol University approved the study protocol.

The primary objective was adequate prediction of MACE by hematological parameters, while correlation of TIMI with MACE for prediction of MACE was accepted as the secondary objective.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

In the 1-year follow-up, rehospitalization due to unstable angina pectoris, need for an interventional procedure, or long-term medication-needing arrhythmia, non-fatal myocardial infarction, or death from cardiac reasons, were defined as MACE.[19,20]

TIMI RISK SCORE

We calculated the TIMI risk score for each subject, and patients were classified according to TIMI scores as follows: 0–2 points – low risk, 3–4 points – moderate risk, 5–7 points – high risk.[14]

The TIMI risk score consists of 7 factors: 1) age ≥65 years; 2) the presence of at least three risk factors for CAD (i.e., diabetes mellitus, hypertension, hyperlipidemia, smoking, family history); 3) previous history of coronary stenosis of 50% or more; 4) the presence of ≥2 episodes of angina 24 hours before the presentation; 5) aspirin use in the past seven days; 6) ST-segment deviations ≥0.05 mV on initial ECG at admission; 7) elevated serum cardiac markers of necrosis. Each factor contributes a value of one score point. The probability of MACE for score points are listed as follows: 4.7% for a score of 0/1, 8.3% for a score of 2, 13.2% for a score of 3, 19.9% for a score of 4, 26.2% for a score of 5, and 40.9% for a score of 6/7.

STATISTICS

Data obtained from this study was evaluated using the SPSS 20 (SPSS Inc., Chicago, IL, USA) program. Continuous data were expressed as the mean ± standard deviation; categorical data were exhibited as percent (%). When viewed with the Kolmogorov-Smirnov and Shapiro-Wilk tests, data were normally distributed. We used an independent T-test for the analysis of data in MACE groups and one-way ANOVA to analyze TIMI risk groups. Addi-

tionally, the Scheffe test was utilized to identify which significant difference was found between the groups in one-way ANOVA. A Chi-square test was applied to determine the relation between MACE and TIMI risk groups. Evaluation of the diagnostic performance of hematological parameters regarding MACE development was done using the ROC curve. The Youden Index was also employed to identify a cut-off value for maximization of sensitivity and specificity of variables. The statistical significance level was accepted as p <0.05.

RESULTS

Of the 259 patients, 188 (72.6%) were male and 71 (27.4%) were female. The average age of the study population was 60.4 ± 11.9 years. During the 1-year follow up, 60 (23.2%) patients developed MACE.

Demographic characteristics according to MACE are summarized in Table 1. Demographic characteristics and risk factors including age, gender, hypertension, diabetes mellitus, hyperlipidemia, family history, and smoking showed no significant difference between the MACE(+) and MACE(−) groups (all p values >0.05) (Table 1). However, a significant difference was found regarding particular laboratory findings and hematological parameters (Table 2). The lymphocyte count was significantly higher in MACE(−) compared to MACE(+) (2.212 ± 0.821 vs. 1.962 ± 0.854, p <0.05), whereas WBC, neutrophils, WMR, NLR, and PLR demonstrated the opposite, significantly higher in the MACE(+) group (8.11 ± 2.03 vs. 9.52 ± 2.51, 4.96 ± 1.63 vs. 6.58 ± 2.42, 789.89 ± 209.19 vs. 926.21 ± 243.43, 2.60 ± 1.57 vs. 4.44 ± 4.20, and 117.25 ± 53.73 vs. 150.82 ± 101.82, respectively, all p values <0.05).

When assessed with a ROC curve, the use of WBC, WMR, and NLR as predictors for MACE development showed a remarkable performance, while the use of MPV, RDW, and PLT was of no standing in this respect (Figure 1). Area under Curve (AUC) for WBC, WMR and NLR were 0.67 (95% CI 0.59–0.75), 0.664 (95% CI 0.582–0.746), and 0.689 (95% CI 0.610–0.767), respectively (Table 3). The cut-off value for WBC, WMR, and NLR were 8.94 (sensitivity 65%, specificity 68.7%), 863.9 (sensitivity 65%, specificity 67.7%), and 3.04 (sensitivity 53.3%, specificity 74.7%), respectively.

The association between MACE and the TIMI score is presented in Table 4. In the MACE(−) group, TIMI score points 1, 2, 3, 4, and 5 accounted for 22.6%, 31.7%, 28.1%, 14.6%, and 3% of the patients, respectively, while in the MACE(+) group the same score points accounted for 6.8%, 18.6%, 25.4%, 32.2%, and 16.9%, respectively.

According to the one-way ANOVA analysis, while WMR and NLR means showed significant differences between TIMI score points (p <0.05), RDW and PLR presented similar values. For WMR and NLR, to determine which TIMI score points the differences are, the Tukey test was used, and the findings were as follows: the mean WMR in TIMI score 4 and 5 groups were found to be significantly higher than TIMI score 1, 2, and 3 groups. On the other hand, it was similar in TIMI score 4 and 5 groups. Also, NLR showed a significantly higher mean in TIMI score group

TABLE 1. Demographic characteristics according to MACE

		MACE (-)	MACE (+)	p value
		n (%)	n (%)	
Age (years), mean ± SD		60.0 ± 11.8	61.7 ±12.4	0.3
Gender	Male	145 (72.9)	43 (71.7)	0.4
	Female	54 (27.1)	17 (28.3)	
Hypertension	No	42 (21.1)	10 (16.7)	0.2
	Yes	157 (78.9)	50 (83.3)	
Diabetes mellitus	No	124 (62.3)	33 (55.0)	0.1
	Yes	75 (37.7)	27 (45.0)	
Hyperlipidemia	No	118 (59.3)	32 (53.3)	0.2
	Yes	81 (40.7)	28 (46.7)	
Family history	No	170 (85.4)	48 (80.0)	0.2
	Yes	29 (14.6)	12 (20.0)	
Smoking	No	138 (69.3)	46 (76.7)	0.1
	Yes	61 (30.7)	14 (23.3)	

MACE, major adverse cardiovascular events

TABLE 2. Laboratory findigns according to MACE

	MACE (-)	MACE (+)	p value
	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	
CK-MB (IU/L)	22.0 ± 37.4	37.4 ± 94.9	0.1
Troponin I (ng/L)	0.26 (0.06–0.82)	0.3 (0.05–2.3)	0.9
High-density lipoprotein (mg/dL)	40.3 ± 10.4	43.4 ± 10.3	0.3
Low-density lpoprotein (mg/dL)	120.7 ± 40.9	117.4 ± 43.9	0.6
Urea (mg/dL)	37.11 ± 16.80	38.48 ± 19.80	0.6
Creatinine (mg/dL)	1.02 ± 0.55	1.05 ± 0.51	0.7
Glucose (mg/dL)	146.7 ± 73.0	162.6 ± 77.9	0.1
WBC ($\times 10^3$/µL)	8.11 ± 2.03	9.52 ± 2.51	<0.001
RBC ($\times 10^6$/µL)	4.78 ± 0.67	4.77 ± 0.67	0.9
Hematocrit (%)	40.9 ± 5.5	40.2 ± 5.2	0.4
Thrombocyte ($\times 10^3$/µL)	230.8 ± 65.0	236.2 ± 78.1	0.6
MPV (fL)	10.3 ± 0.8	10.3 ± 0.8	0.8
Neutrophil ($\times 10^3$/µL)	4.96 ± 1.63	6.58 ± 2.42	<0.001
Lymphocyte ($\times 10^3$/µL)	2.212 ± 0.821	1.962 ± 0.854	0.04
RDW (%)	14.2 ± 1.6	14.3 ± 1.5	0.7
WMR	789.89 ± 209.19	926.21 ± 243.43	<0.001
NLR	2.60 ± 1.57	4.44 ± 4.20	<0.001
PLR	117.25 ± 53.73	150.82 ± 101.82	0.001

CK-MB, creatine kinase-MB; WBC, white blood cell count; RBC, red blood cells; MPV, mean platelet volume; RDW, red cell distribution width; WMR, WBC to MPV ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio

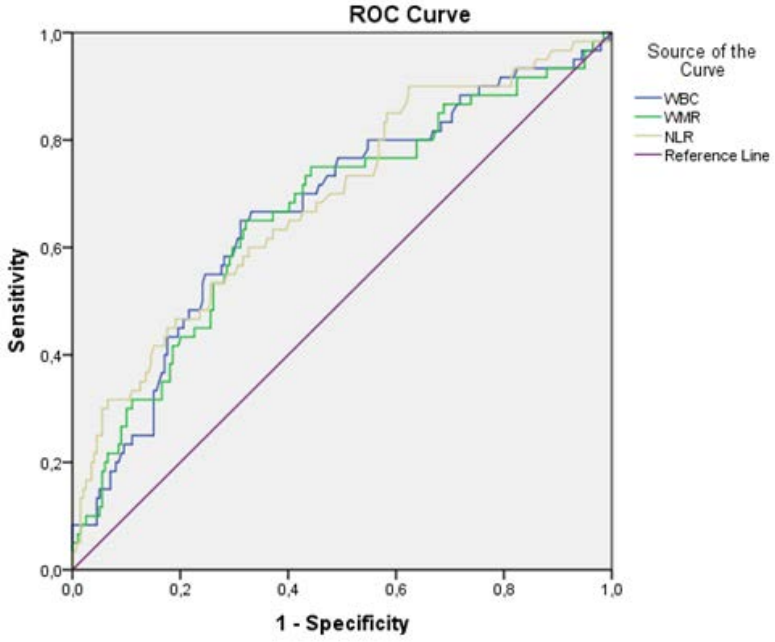

FIGURE 1. Diagnostic performance of WBC, WMR and NLR by ROC curve. WBC, white blood cell count; MPV, mean platelet volume; WMR, WBC to MPV ratio; NLR, neutrophyl to lymphocyte ratio; ROC, reciever operating characteristic

TABLE 3. Diagnostic performance of hematological parameters

	AUC	SD	95% CI	p value
WBC	0.670	0.041	0.590–0.750	<0.001
MPV	0.504	0.043	0.420–0.588	0.9
RDW	0.539	0.041	0.458–0.621	0.3
WMR	0.664	0.042	0.582–0.746	<0.001
NLR	0.689	0.040	0.610–0.767	<0.001
PLR	0.581	0.046	0.491–0.670	0.05

WBC, white blood cell count; MPV, mean platelet volume; RDW, red cell distribution width; WMR, WBC to MPV ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; AUC, area under curve; SD, standart deviation; CI, confidence interval

4 than TIMI score 1 and 2 groups. It was also significantly higher in the TIMI score 5 group compared to TIMI score 1. Moreover, a Scheffe test was used to evaluate the correlation between hematological parameters and TIMI risk groups (low, moderate, and high); the higher the risk, the higher the WBC and WMR values. However, for NLR, there was no significant difference in all TIMI risk groups. Only the moderate-risk group showed higher NLR compared to the low-risk group.

A significant relationship ($p < 0.05$) was found between the 1-year MACE development status and the TIMI risk group when examined by Chi-square analysis. In the MACE(−) group, 54.3%, 42.7%, and 3% of the patients accounted for low, moderate, and high TIMI risk. In the MACE(+) group, proportions of low, moderate, and high TIMI risk were 25%, 56.7%, and 18.3%, respectively.

DISCUSSIONS

In recent years, few studies have examined the relationship between WMR and ACS.[6,8] Our study investigated the one-year prognostic value of hematological parameters, including WMR, and its correlation with the TIMI risk score in NSTEMI patients.

The average age of our study population (60.4 ± 11.9) was similar to prior reports. Moreover, age among MACE(−) and MACE(+) groups showed similarity.

According to Dehghani *et al.*,[6] when followed-up 336 days, 81 (16.5%) of 490 NSTEMI patients developed MACE. Çiçek *et al.* followed-up 2,603 STEMI patients for 12 months, and 565 (21.7%) of them developed MACE.[8] In our study, MACE was observed in 23.2% of patients through a 1-year follow-up. Although our study population consisted of NSTEMI patients, the results are similar to a report that examined STEMI populations,[8] and the MACE ratio was higher than in the study that included a matching population (NSTEMI patients).[6]

In a meta-analysis consisting of 16 studies, including 2,809 patients with acute MI, MPV was associated with post-MI mortality and restenosis following coronary angioplasty.[9] On the other hand, Shah *et al.* analyzed 1,512 patients who underwent percutaneous intervention.[10] Basal MPV value was not associated with long-term outcomes; however, an increase in MPV throughout an 8.7-year follow-up was associated with increased mortality. Furthermore, Dehghani *et al.*[6] assessed MPV between MACE(−) and MACE(+) groups and found no notable difference. MPV showed similarities in MACE(−) and MACE(+) groups in our study. Thus, the disparity amongst findings underlines that the prognostic value of MPV among ACS patients is unclear and should be explored in more depth.

WBC was statistically higher in the MACE(+) group than in the MACE(−) group in our study, similarly to the study reported by Dehghani *et al.*[6] In a similar vein, Ruggiero *et*

TABLE 4. Number of the patients in various TIMI scores according to MACE

	TIMI Score					Total (n)
	1	2	3	4	5	
MACE(−)	45 (22.6%)	63 (31.7%)	56 (28.1%)	29 (14.6%)	6 (3.0%)	199
MACE(+)	4 (6.8%)	11 (18.6%)	15 (25.4%)	19 (32.2%)	10 (16.9%)	59
Total	49 (19.0%)	74 (28.7%)	71 (27.5%)	48 (18.6%)	16 (6.2%)	258

TIMI, thrombolysis in myocardial infarction; MACE, major adverse cardiovascular events

al. showed in 2,803 patients that elevated WBC was correlated with both increased mortality and cardiovascular disease risk.[11] In another study, WBC was connected with impaired myocardial perfusion and increased risk of 6-month mortality.[21]

Parallel to our report, in a study including 692 MI patients, He *et al*.[12] concluded that the mean NLR value was a powerful indicator of mortality and adverse outcomes over a mean follow-up period of 9.4 years. NLR (AUC 0.726) showed better performance than WBC (AUC 0.600) in predicting the long-term prognosis. However, the optimal cut-off value they estimated was higher than ours (4.22, sensitivity 69.3%, specificity 68.8% vs. 3.04, sensitivity 53.3, specificity 74.4%).[12] We estimated that the difference in both cut-off value and sensitivity might be due to the difference in follow-up time or the fact that we included only NSTEMI patients and did not include higher-risk STEMI patients. Notably, in our study, the predictive performance of NLR was better than that of WBC and WMR considering the AUC value.

Reports by Li *et al*. and Azab *et al*. evidenced that PLR was significantly associated with mortality and poor outcome in patients with ACS and NSTEMI, respectively.[13,22] In our study, the mean PLR in the MACE(+) group was significantly higher than in the MACE(−) group. This result supports the reports published before.

As in our study, Dehghani *et al*.[6] showed that mean WMR was statistically different between the MACE(+) and the MACE(−) groups in a 1-year follow-up. They found AUC for WMR 0.595 (95% CI 0.519–0.671). Of note, in our study AUC for WMR was higher, 0.664 (95% CI 0.582–0.746, p <0.001). To our knowledge, the study of Dehghani *et al*.[6] is the only published report investigating WMR in NSTEMI patients in the literature. The similarities between the results of these two studies, which were conducted in similar patient groups, for similar follow-up periods (average one year) in different centers, is essential in confirming the prognostic effectiveness of WMR, a newly defined prognostic marker in NSTEMI patients.

While the TIMI score was developed for risk stratification in unstable angina pectoris/NSTEMI patients, its success in predicting 14-day outcomes was demonstrated in the original study.[14] However, subsequently, other researchers concentrated on investigating its long-term impact.[23–25] Weisenthal *et al*. investigated the 1-year prognostic value of the TIMI score in 2,819 patients presented to the prognostic cohort study's emergency ward, in which 253 (9%) patients developed MACE.[23] It was demonstrated that as the TIMI score increased, the frequency of MACE increased proportionally. The higher the TIMI score, the higher the likelihood of development of MACE. Similarly, in our study, MACE rates increased significantly with the increasing TIMI score.

In our study, cardiovascular risk factors, including age, gender, hypertension, diabetes mellitus, hyperlipidemia, family history, and smoking, showed no significant differences between the MACE(+) and MACE(−) groups. However, the hematological parameters seemed to provide prognostic data independently of these clinical factors.

LIMITATIONS

Our study's limitations are as follows: 1) The main limitation of our study is that it is a retrospective and single-center study. 2) Since we were lacking detailed data about pharmacological therapy for CAD risk factors, we could not calculate how treatment affected the development of MACE.

CONCLUSION

Simple, rapid, and widely available hematological parameters, WBC, NLR, and WMR, were predictors of MACE in patients with NSTEMI and were consistent with the TIMI risk score. On this basis, they could provide supportive data for early risk stratification and optimized therapeutic approach, particularly in high-risk patients.

CONFLICT OF INTEREST

Nothing to declare.

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