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White blood cell count to mean platelet volume ratio as a novel non-invasive marker predicting long-term outcomes in patients with non-ST elevation acute coronary syndrome

Mohammad Reza Dehghani[1], Yousef Rezaei[2], Leila Taghipour-Sani[1]

[1]Department of Cardiology, Seyyed-al-Shohada Heart Center, Urmia University of Medical Sciences, Urmia, Iran
[2]Seyyed-al-Shohada Heart Center, Urmia University of Medical Sciences, Urmia, Iran

Abstract

Background: *Total white blood cell (WBC) count and mean platelet volume have previously been shown to predict outcomes in acute coronary syndrome (ACS) patients. In this prospective study, we sought to determine the prognostic value of baseline WBC count to mean platelet volume ratio (WMR) in patients with non-ST elevation acute coronary syndrome (NSTE-ACS).*

Methods: *A total of 490 patients with NSTE-ACS were prospectively enrolled. The relationship between baseline WMR and major adverse cardiovascular events (MACE) incidence was assessed during a mean follow-up of 330.8 ± 38 days.*

Results: *The patients' mean age was 60.4 ± 12.9 year, 59% of them were male. The patients were categorized into two groups based on WMR values, high- and low-WMR groups (< 755 vs. ≥ 755). The incidence of MACE was significantly higher in high-WMR compared with that of low-WMR group (22.4% vs. 10.7%, p < 0.001). Total WBC counts (median 7.9 vs. 6.9 $\times 10^3/\mu L$, p = 0.004), neutrophil count (median 4.6 vs. 4.2 $\times 10^3/\mu L$, p = 0.021), and WMR (median 863.2 vs. 731.5, p = 0.001) were significantly higher in the MACE-positive than MACE-negative group. The high-WMR was found to be significantly associated with the MACE-free survival rate (p < 0.001). In an adjusted cox regression model, the elevated WMR was independently predicted the incidence of MACE (hazard ratio 2.419, 95% CI 1.515–3.862, p < 0.001).*

Conclusions: *The elevated baseline WMR independently predicted the MACE incidence in patients with NSTE-ACS during long-term follow-up.* (Cardiol J 2015; 22, 4: 437–445)

Key words: white blood cell to mean platelet volume ratio, non-ST elevation acute coronary syndrome, major adverse cardiovascular events

Introduction

Atherosclerosis has been postulated to be an inflammatory disease [1]. Given previous studies, acute coronary events are not only attributable to the progressive narrowing of coronary artery lumen, but also to other pathophysiological factors involved in the development of such events. Atherosclerotic plaques ruptured and contribute to thrombus formation by inflammatory mechanisms,

Address for correspondence: Yousef Rezaei, MD, Seyyed-al-Shohada Heart Center, Urmia University of Medical Sciences, Urmia 5718749441, Iran, tel: +98-912-623-1864, fax: +98-441-237-5907, e-mail: yousefrezaei1986@gmail.com

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through which it can lead to the development of acute coronary syndrome (ACS) [2].

Leukocytes have been shown to be involved in the inflammatory processes, which have potential roles in the development of cardiovascular events [3]. T-cells and macrophages located in the lipid core of an atherosclerotic plaque are activated after endothelial injury, and those promote the thrombus formation as a result of producing cytokines and procoagulants. Therefore, all these processes enhance the thrombogenicity and the development of ACS [2]. Besides leukocytes, platelets have been reported to participate in the development of acute coronary events through inflammatory pathways [4]. Activated and inactivated platelets promote platelet-leukocytes adhesion, including adhesion molecules and cytokines, which result in the progression of atherogenesis [5]. The interaction between platelets and leukocytes can be attributed to the enhancement of leukocyte recruiting at the site of plaque rupture, and this may be of great importance in the development of ACS or its prognosis [5]. The interactions between these cells may be a pathogenic mechanism involved in the occlusion of coronary arteries during an ACS event [6].

The mean platelet volume, a platelet activation marker [7], and leukocyte differentials [8–10] have been reported to be associated with cardiovascular morbidity and mortality. The components of complete blood count test have been increasingly used in cardiovascular setting and correlated with clinical outcomes. Hence, in this prospective study, we sought to determine whether the baseline white blood cell (WBC) count to mean platelet volume ratio (WMR) can predict the long-term outcomes in patients with non-ST elevation ACS (NSTE-ACS).

Methods

Study design and population

The present study was conducted in the Seyyed-al-Shohada Heart Center of Urmia University of Medical Sciences, Urmia, West-Azerbaijan province, Iran, to investigate the prognostic role of complete blood count components in the setting of ACS. Therefore, 862 consecutive patients who had been admitted to the Emergency Department with chief complaint of new onset chest discomfort were assessed from August 2012 to March 2013. A total of 490 patients with a diagnosis of NSTE-ACS were enrolled. This study was approved by both the local Ethics Committee of Urmia University of Medical Sciences and our institutional Review Board; and informed consents were obtained from all the participants.

All patients complaining of chest discomfort were evaluated using full examination, cardiac ischemia markers (creatine kinase MB isoenzyme [CK-MB] and troponin I), routine biochemical markers, and a 12-lead electrocardiogram (ECG). Unstable angina was defined as ischemic changes in ECG without increasing in cardiac enzymes. Non-ST segment elevation myocardial infarction (NSTEMI) was defined as patients without ST-segment elevation in their ECG but with an increase in the cardiac ischemia markers. The diagnosis of ST-segment elevation myocardial infarction (STEMI) was regarded as patients with typical ischemic chest pain lasting more than 20 min associated with one of the features, including at least 1 mm ST-segment elevation, a new Q wave, a new onset left bundle branch block in ≥ 2 contiguous leads, and/or the elevation of cardiac markers at least 2-fold of the maximum normal values. A non-ACS patient was considered a case whose chest pain was atypical without ischemic changes in ECG and/or an increase in cardiac markers. Exclusion criteria included non-ACS patients, STEMI, cancer history, inflammatory diseases, autoimmune diseases, infectious diseases, and being immunosuppressed. Additionally, due to small numbers of NSTE-ACS patients undergoing revascularization at the time of study conduction, we excluded such cases. To identify the incidence of major adverse cardiovascular events (MACE), all the patients were followed up to December 2013. The patients who had unstable angina were given anticoagulants (aspirin plus clopidogrel), beta-blocker, angiotensin converting enzyme inhibitors, nitrate, and statin. The NSTEMI patients were also treated as unstable angina ones. Furthermore, none of the patients underwent revascularization therapy. All blood samples were provided at admission and analyzed within 30 min of sampling by an automated blood cell counter (Sysmex, Kobe, Japan).

Clinical outcomes

All patients were followed for a mean of 330.8 ± ± 38 days. The measured clinical outcomes were as follows: (1) rehospitalization due to unstable angina; (2) any kind of cardiac arrhythmias required invasive therapies, including long-term consumption of anti-arrhythmic drugs and/or implementing implantable cardioverter defibrillator, which were continued up to end of follow-up time; (3) non-fatal MI; (4) and cardiac death. These endpoints were considered a composite MACE (n = 81).

Statistical analysis

WBC count, mean platelet volume, and WMR levels were divided into two groups according to their median values as follows: (1) WBC count $< 7.1 \times 10^3/\mu L$ or $\geq 7.1 \times 10^3/\mu L$; (2) mean platelet volume < 9.5 fL or ≥ 9.5 fL; and (3) WMR < 755 or ≥ 755. All continuous variables were reported as either median (25^{th} and 75^{th} percentiles) or mean ± standard deviation and those were analyzed using the Mann-Whitney U test or t-test, respectively. Categorical variables were reported as number (percentage) and compared by the χ^2 test. The receiver operating characteristics (ROC) curve analysis was conducted for the detection of diagnostic accuracy of biochemical markers. The Kaplan-Meier analysis was used to detect the MACE-free survival rate, and log-rank test was applied to calculate its significance. In addition, a multivariate Cox regression analysis, backward stepwise model, was used to identify the independent predictors of composite MACE at follow-up period. In this model, all baseline characteristics, drug histories, conventional cardiovascular risk factors, biomarkers, the status of diagnosis consisting of unstable angina or NSTEMI, and having multi-vessel disease were considered covariates, and MACE incidence was entered as a dependent variable. In the backward stepwise model, p value > 0.1 was applied for removing the covariates. The values of WBC, mean platelet volume, and WMR were entered as categorical variables based on their medians, high- vs. low-value. Moreover, in an adjusted Cox regression model, all variables whose p values were less than 0.05 were entered into another model. All statistical analyses were performed using SPSS, version 18.0 (SPSS Inc., Chicago, IL, USA). A 2-tailed p value less than 0.05 was considered statistically significant.

Results

Characteristics, clinical features, and biomarkers

The patients' mean age was 60.4 ± 12.9 year, and no significant difference was observed between the high- and low-WMR groups ($p = 0.052$); 59% of the patients were male ($p = 0.069$). Heart rate at presentation was significantly greater in the high- compared with that in low-WMR group (median of 80 vs. 78 bpm, $p = 0.021$). The frequency of patients who had NSTEMI was higher in the high-WMR group than low-WMR group (9% vs. 18.7%, $p = 0.002$). The more proportion of patients in the low-WMR group had consumed beta-blockers, nitrates, and dual anti-platelet therapy in comparison with those in the high-WMR group (Table 1). Among laboratories, mean platelet volume was significantly lower in the high-WMR compared with that in low-WMR group (median of 9.3 vs. 9.8 fL, $p < 0.001$), in contrast, the WBC count was greater in high-WMR compared with that in low-WMR group (median of 8.8 vs. 6 $\times 10^3/\mu L$, $p < 0.001$). Other characteristics and laboratories were summarized in the Table 1.

When comparing study variables between groups, MACE-positive vs. MACE-negative groups, the frequency of hypertension was significantly higher in the MACE-positive compared with that in the MACE-negative group (66.7% vs. 54.5%, $p = 0.044$). Amongst the biomarkers, WBC count (median of 7.9 vs. 6.9 $\times 10^3/\mu L$, $p = 0.004$), neutrophil count (median of 4.6 vs. 4.2 $\times 10^3/\mu L$, $p = 0.021$), and WMR (median of 863.2 vs. 731.5, $p = 0.001$) were significantly higher in the MACE--positive compared with those of MACE-negative group (Table 2).

In subgroup analysis, patients who were younger than 65 years, male, smoker, and diagnosed with NSTEMI, had higher WMR values compared with patients who were not (Fig. 1).

Diagnostic and survival analysis

According to the ROC curve analysis, the area under curve (AUC) for WMR was 0.595 (95% confidence interval [CI] 0.519–0.671, $p = 0.018$), and it was found to be higher than those of CK-MB and troponin I tests (Fig. 2).

The Kaplan-Meier analysis showed that the WMR subgroups (< 755 vs. ≥ 755) were significantly associated with the MACE-free survival rate (log-rank test p value < 0.001; Fig. 3).

Multivariate analysis

Based on the last step of backward stepwise multivariate analysis, male sex (hazard ratio [HR] 2.689, 95% CI 1.277–5.662, $p = 0.009$), having hypertension (HR 3.780, 95% CI 1.860–7.861, $p < < 0.001$), and a previous use of nitrates (HR 1.954, 95% CI 1.073–3.558, $p = 0.029$) were found to be the predictors of MACE. Moreover, CK-MB (HR 1.013, 95% CI 1.001–1.025, $p = 0.038$), platelet count (HR 1.005, 95% CI 1.001–1.009, $p = 0.014$), and hematocrit (HR 0.906, 95% CI 0.839–0.978, $p = 0.012$) were associated with the incidence of MACE. Furthermore, the high WMR (HR 2.406, 95% CI 1.257–4.607, $p = 0.008$) was found to be the strongest marker predicting MACE during follow-up (Table 3). In an adjusted model, entering

Table 1. Baseline characteristics, laboratories, and long-term outcomes according to white blood cell count to mean platelet volume ratio (WMR).

	Total (n = 490)	Low-WMR[a] (n = 232)	High-WMR[a] (n = 254)	P
Age [years]	60.4 ± 12.9	61.5 ± 12	59.3 ± 13.7	0.052
Male	289 (59%)	134 (54.9%)	155 (63%)	0.069
Body mass index [kg/m^2]	27.7 (24.6, 30.8)	27.7 (24.6, 30.1)	27.7 (24.7, 31.5)	0.593
Heart rate [bpm]	80 (75, 85)	78 (72, 83)	80 (74, 90)	0.021
Systolic BP [mm Hg]	137 (125, 150)	136 (125, 150)	137 (125, 150)	0.870
Diastolic BP [mm Hg]	80 (78, 90)	81.5 (76, 90)	80 (80, 90)	0.917
NYHA:				0.594
Class 1	122 (24.9%)	55 (22.5%)	67 (27.2%)	
Class 2	74 (15.1%)	36 (14.8%)	38 (15.4%)	
Class 3	265 (54.1%)	139 (57%)	126 (51.2%)	
Class 4	29 (5.9%)	14 (5.7%)	15 (6.1%)	
Diabetes mellitus	145 (29.6%)	67 (27.5%)	78 (31.7%)	0.303
Hypertension	277 (56.5%)	142 (58.2%)	135 (54.9%)	0.459
Dyslipidemia	87 (17.8%)	40 (16.4%)	47 (19.1%)	0.432
Current smoking	129 (26.3%)	55 (22.5%)	74 (30.1%)	0.058
Familial history	142 (29%)	67 (27.5%)	75 (30.5%)	0.460
Diagnosis:				0.002
Non-ST elevation MI	68 (13.9%)	22 (9%)	46 (18.7%)	
Unstable angina	422 (86.1%)	222 (91%)	200 (81.3%)	
Multivessel disease[b]	124 (25.3%)	70 (28.7%)	54 (22%)	0.086
Drug histories:				
Beta-blockers	226 (46.1%)	130 (53.3%)	96 (39%)	0.002
ACE-I	76 (15.6%)	41 (16.9%)	35 (14.3%)	0.442
Statins	209 (42.7%)	107 (43.9%)	102 (41.5%)	0.593
Nitrates	184 (37.9%)	104 (56.5%)	80 (43.5%)	0.025
Dual anti-platelet	112 (22.9%)	65 (26.6%)	47 (19.1%)	0.047
Biochemical markers:				
CK-MB [IU/L]	25 (20, 33)	24 (19, 31)	27 (20, 36)	0.003
Troponin I [ng/μL]	0.01 (0.01, 0.2)	0.01 (0.01, 0.08)	0.01 (0.01, 0.3)	0.005
HDL [mg/dL]	38 (33, 44)	38 (33, 44)	39 (34, 45)	0.202
LDL [mg/dL]	86 (70, 104)	84 (67, 100)	88 (72, 105)	0.051
Blood urea nitrogen [mg/dL]	17.5 (14, 22)	17 (14, 21)	18 (14, 23)	0.158
Creatinine [mg/dL]	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.103
Blood sugar [mg/dL]	107.5 (93, 142)	103 (89, 134.5)	110.5 (95, 146)	0.041
White blood cell count [$\times 10^3/\mu$L]	7.1 (6, 8.8)	6 (5.3, 6.7)	8.8 (7.8, 10)	< 0.001
Neutrophil [$\times 10^3/\mu$L]	4.3 (3.4, 5.6)	3.5 (3, 4.2)	5.4 (4.3, 7.6)	< 0.001
Lymphocyte [$\times 10^3/\mu$L]	2 (1.5, 2.6)	1.8 (1.5, 2.3)	2.4 (1.7, 2.9)	< 0.001
Red blood cell count [$\times 10^6/\mu$L]	473 (440, 506)	470 (433.5, 499.5)	478.5 (447, 517)	0.017
Hematocrit [%]	41.7 (38.8, 44.9)	41.6 (38.2, 44.3)	41.8 (39.4, 45.6)	0.058
Platelet count [$\times 10^3$/L]	212 (182, 255)	197 (169.5, 228.5)	232 (198, 284)	< 0.001
Mean platelet volume [fL]	9.5 (8.9, 10.2)	9.8 (9.2, 10.4)	9.3 (8.7, 9.8)	< 0.001
Follow-up features:				
Follow-up duration [day]	336 (309, 360)	336 (309, 366)	333 (300, 360)	0.197
MACE incidence	81 (16.5%)	26 (10.7%)	55 (22.4%)	< 0.001

All values are presented as mean ± standard deviation, median (interquartile range), or number (percentage); [a]WMR value is categorized according to its median, low-WMR < 755 and high-WMR ≥ 755; [b]Multivessel disease was defined as coronary artery disease ≥ 2 vessels. This parameter was available in 360 of patients; ACE-I — angiotensin-converting enzyme inhibitors; BP — blood pressure; CK-MB — creatine kinase MB isoenzyme; HDL — high density lipoprotein; LDL — low density lipoprotein; MACE — major adverse cardiovascular events; MI — myocardial infarction; NYHA — New York Heart Association

Table 2. Baseline characteristics and laboratories in groups according to major adverse cardiovascular events (MACE) incidence.

	MACE-positive (n = 81)	MACE-negative (n = 409)	P
Age [years]	60.6 ± 13.1	60.3 ± 12.9	0.875
Male	49 (60.5%)	240 (58.7%)	0.762
Body mass index [kg/m^2]	28.3 (25, 30.8)	27.7 (24.6, 30.7)	0.602
Heart rate [bpm]	80 (75, 86)	80 (75, 85)	0.753
Systolic BP [mm Hg]	140 (123, 155)	135 (125, 150)	0.071
Diastolic BP [mm Hg]	82 (80, 90)	80 (77, 90)	0.310
NYHA:			0.479
Class 1	15 (18.5%)	107 (26.2%)	
Class 2	15 (18.5%)	59 (14.4%)	
Class 3	46 (56.8%)	219 (53.5%)	
Class 4	5 (6.2%)	24 (5.9%)	
Diabetes mellitus	31 (38.3%)	114 (27.9%)	0.061
Hypertension	54 (66.7%)	223 (54.5%)	0.044
Dyslipidemia	13 (16%)	74 (18.1%)	0.660
Current smoking	24 (29.6%)	105 (25.7%)	0.460
Familial history	23 (28.4%)	119 (29.1%)	0.899
Diagnosis:			0.254
Non-ST elevation MI	8 (11.8%)	60 (17.3%)	
Unstable angina	73 (90.1%)	349 (82.7%)	
Multivessel disease	21 (25.9%)	103 (25.2%)	0.888
Drug histories:			
Beta-blockers	39 (48.1%)	187 (45.7%)	0.689
ACE-I	17 (21%)	59 (14.5%)	0.144
Statins	36 (44.4%)	173 (42.3%)	0.721
Nitrates	35 (43.2%)	149 (36.8%)	0.277
Dual anti-platelet	20 (24.7%)	92 (22.5%)	0.667
Biochemical markers:			
CK-MB [IU/L]	27 (20, 33)	24 (20, 33)	0.536
Troponin I [ng/μL]	0.01 (0.01, 0.3)	0.01 (0.01, 0.2)	0.814
HDL [mg/dL]	38.5 (33, 44)	38 (33, 44)	0.792
LDL [mg/dL]	86 (71, 105)	86.5 (68, 96)	0.491
Blood urea nitrogen [mg/dL]	17.5 (14, 22)	18.5 (13.5, 22.5)	0.938
Creatinine [mg/dL]	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.495
Blood sugar [mg/dL]	119 (94, 171)	106 (93, 134)	0.051
White blood cell count [$\times 10^3/\mu$L]	7.9 (6.7, 9.8)	6.9 (5.9, 8.7)	0.004
Neutrophil [$\times 10^3/\mu$L]	4.6 (3.9, 6.9)	4.2 (3.4, 5.5)	0.021
Lymphocyte [$\times 10^3/\mu$L]	2.2 (1.6, 2.7)	2 (1.5, 2.5)	0.308
Red blood cell count [$\times 10^6/\mu$L]	470 (441, 504)	474 (440, 507)	0.663
Hematocrit [%]	41.4 (38.2, 44.4)	41.8 (38.9, 44.9)	0.105
Platelet count [$\times 10^3$/L]	220 (185, 274)	211 (181, 250)	0.239
Mean platelet volume [fL]	9.5 (8.9, 10)	9.5 (8.9, 10.2)	0.413
WMR	863.2 (687.5, 1012.5)	731.5 (616.8, 924.5)	0.001
Follow-up duration [day]	330 (300, 360)	348 (315, 372)	0.197

All values are presented as mean ± standard deviation, median (interquartile range), or number (percentage); abbreviations as in Table 1

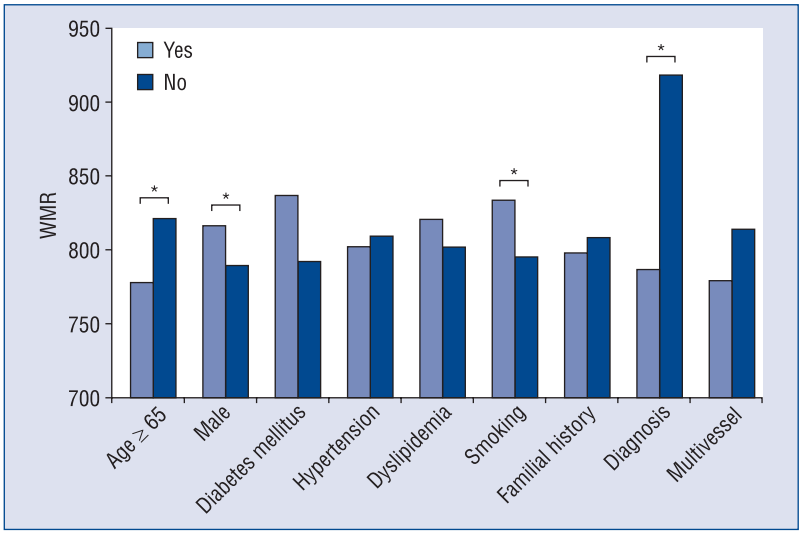

Figure 1. Comparison of white blood cell count to mean platelet volume ratio (WMR) values in the subgroups. Yes — being positive for mentioned variable; No — being negative for mentioned variable. Asterisk showing significant differences between paired groups.

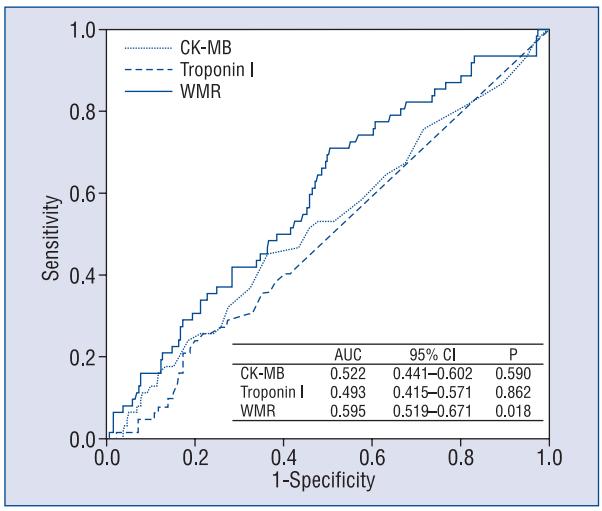

Figure 2. Receiver operating characteristics curve identifying the long-term clinical outcomes; AUC — area under curve; CI — confidence interval; rest abbreviations as in Table 1.

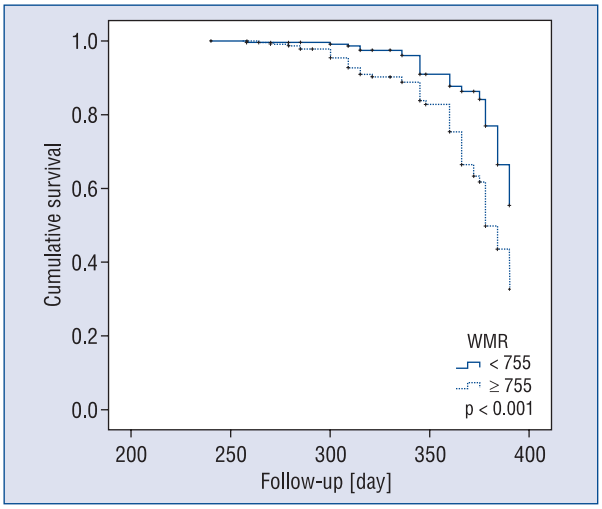

Figure 3. Kaplan–Meier curve showing difference between groups by white blood cell count to mean platelet volume ratio (WMR) for major adverse cardiovascular events (MACE)-free survival rate.

variables with a p value of < 0.05, including hypertension, WBC count, neutrophil count, and WMR, the elevated WMR was the strongest independent predictor of MACE, as well (HR 2.419, 95% CI 1.515–3.862, p < 0.001) (Table 3).

Discussion

In this prospective study, we showed, for the first time that the elevated baseline WMR was associated with MACE incidence during long-term follow-up in the patients with NSTE-ACS. Being male and having hypertension were the independent predictors of MACE. Moreover, the high-WMR was associated with a significant increase in the risk of MACE incidence, and it was the strongest marker among complete blood count components predicting the long-term clinical outcomes.

Traditionally, it has been increasingly reported that atherosclerosis develops during the decades

Table 3. Multivariate Cox regression analysis identifying the predictors of composite major adverse cardiovascular events (MACE).

	HR	95% CI	P[a]
Unadjusted model:			
Male	2.689	1.277–5.662	0.009
Diabetes mellitus	1.913	0.978–3.738	0.058
Hypertension	3.780	1.860–7.681	< 0.001
Beta-blockers	0.581	0.319–1.056	0.075
Nitrates	1.954	1.073–3.558	0.029
CK-MB	1.013	1.001–1.025	0.038
Blood urea nitrogen	0.951	0.920–0.982	0.002
High density lipoprotein	0.976	0.939–1.014	0.210
Platelet	1.005	1.001–1.009	0.014
Hematocrit	0.906	0.839–0.978	0.012
Mean platelet volume	1.915	0.987–3.714	0.055
WMR	2.406	1.257–4.607	0.008
Adjusted model:[b]			
Hypertension	2.005	1.257–3.198	0.003
WMR	2.419	1.515–3.862	< 0.001

[a]All p values of variables in the last step of backward stepwise regression model are listed; [b]All variables whose p values were < 0.05 in the Table 2 were entered into the second model, adjusted Cox regression model; CI — confidence interval; CK-MB — creatine kinase MB isoenzyme; HR — hazard ratio; WMR — white blood cell count to mean platelet volume ratio

of our life. The main factors involved in the development of NSTE-ACS include inflammation and thrombus formation resulting in the reduction of coronary artery flow and resultant ischemia [11]. During the rupture of an atherosclerotic plaque, platelets adhere to the injured endothelial cells and then are activated [4]. The activated ones release the inflammatory mediators, express some selectin molecules, and secrete cytokines and chemokines as well as proinflammatory lipids [4, 5, 12]. The adhesion molecules and mediators activate the leukocytes [5, 13] and promote the atherothrombotic events [5, 14].

Platelets are derived from megakaryocytes in the bone marrow, which have been increasingly shown to be involved in the hemostasis and maintenance of vascular endothelial integrity [12]. Although there are several laboratories to measure platelets' activity, none of them have been considered in daily clinical practice. The mean platelet volume, a platelet activation marker, is a widely available and easily measured hematologic test in a complete blood cell count test [7], and the elevated one has been demonstrated to be associated with diabetes mellitus, hypertension, hypercholesterolemia, and obesity [7]. In addition, it has been found to be a diagnostic and prognostic marker in patients with ACS or those undergoing percutaneous coronary intervention [15–17]. However, in a prospective study, no relationship was found between increased baseline mean platelet volume and the clinical outcomes of patients undergoing elective angioplasty, but increases in postoperative serial measurements were associated with higher mortality rate instead [18]. This study failed to find any relationship between elevated baseline mean platelet volume and MACE incidence or MACE-free survival rate. We think that this may be caused by either our population's feature, which only included NSTE-ACS patients rather than high risk ones (i.e. STEMI) or its short follow-up duration, which might be associated with lower number of adverse events. The findings of this study and those of Shah et al. [18] underscore the need for further investigations regarding the relationship between mean platelet volume and the prognosis of ACS patients, especially NSTE-ACS cases.

In a longitudinal study, elevated total WBC count was associated with high rate mortality [19] and the increased risk of cardiovascular diseases [20]. Moreover, Sabatine et al. [10] reported that an elevated baseline WBC count correlated with impaired myocardial perfusion and increased 6-month mortality in patients diagnosed with STEMI. In previous studies concerning the role of leukocytes in the prediction of ACS outcomes,

it has been increasingly shown that those can be used as prognostic and risk stratification tools in such cases, although there have been controversies in terms of the best leukocyte subtype [8–10, 21]. In this study, we found that WBC count was associated with MACE-free survival rate at long-term follow-up, but it did not predict outcomes. These findings are consistent with previous studies showing the prognostic role of leukocyte differentials, including total WBC count, neutrophil count, lymphocyte, or neutrophil to lymphocyte ratio in patients with STEMI [22–25], NSTE-ACS [8], or NSTEMI [26]. Although the prognostic value of total WBC count has been reported in previous literatures, the superiority of WMR over WBC count was demonstrated in the present study by both the stronger probability of MACE-free survival rate and the multivariate analysis. We think that the ongoing studies concerning the relationship between complete blood count components and cardiovascular diseases might better clarify this notion and identify the best prognostic marker for implementation in clinical practice.

The interactions between platelets and leukocytes and vascular endothelial cells at culprit lesion have been found to be the main pathophysiologic mechanisms involved in the development of atherothrombotic events in the setting of ACS [4, 6, 12, 27–29]. Platelet-leukocyte complex assessed by flow cytometry has been found as a pathophysiologic mechanism for the development of thrombogenesis [6], and monocyte-platelet aggregation was also shown as an early marker for acute MI [28] and NSTE-ASC patients [30]. Rinder et al. [5] showed that this cellular interaction is a dynamic process, in which platelet activation status and the ability of leukocytes to adhere result in different bindings. We should submit that although the elevated mean platelet volume is a marker of activated platelets, and its increase can contribute to decrease in the WMR values, if we consider that the both activated and inactivated platelets are involved in the platelet-leukocyte adhesion, WMR may not differ between patients with or without elevated baseline mean platelet volume.

Limitations of the study

The main limitation of the study was that we did not measure the markers of platelet-leukocyte interactions, including selectin molecules [31], adhesion ligands, and receptors [13, 32], which can be used as indicative of the platelet-leukocyte interactions. Thus, the evaluation of these biomarkers along with WMR may confirm causality. In addition, the small sample size of our study is another limitation; further large scale studies among STEMI patients and those undergoing angioplasty will be useful in order to prove these preliminary findings. Furthermore, we did not consider revascularization procedures developed during follow-up a MACE; hence, it may be associated with outcomes and provides further information with respect to any relationship between the WMR values of patients being revascularized and their outcomes. On the other hand, this shortcoming cannot be interfered with our findings showing the WMR as a prognosticator of long-term outcomes.

Conclusions

An elevated baseline WMR value was associated with clinical outcomes in patients with NSTE--ACS, and independently predicted the MACE incidence even stronger than other complete blood count components, including leukocyte differentials, platelet indices, and red blood cell indices.

Conflict of interest: None declared

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