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White blood cell count to mean platelet volume ratio: A novel and promising prognostic marker for ST-segment elevation myocardial infarction

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Abstract

Background: *Increased white blood cell (WBC) count is associated with increased mortality in patients with ST-segment elevation myocardial infarction (STEMI). We aimed to evaluate predictive value of admission WBC to mean platelet volume (MPV) ratio (WMR) on prognosis in patients undergoing primary percutaneous coronary intervention (pPCI) for STEMI.*

Methods: *A total of 2,603 consecutive patients with STEMI who underwent pPCI were recruited for the study. Follow-up data were obtained from digital records, patient files or by telephone interview with patients, family members, or primary care physicians.*

Results: *WMR has the highest area under receiver operating characteristic (ROC) curve and pairwise comparisons of the ROC curves revealed that WMR has the higher discriminative ability for long-term mortality than WBC, MPV, red blood cell distribution with (RDW), WBC-MPV combination, and platelet to lymphocyte ratio and neutrophil to lymphocyte ratio (PLR-NLR) combination in patients undergoing pPCI for STEMI (a WMR value of 1,653.47 was also found as threshold value for mortality with 75.4% sensitivity and 87.3% specificity by ROC curve analysis).*

Conclusions: *Higher WMR value on admission was associated with worse outcomes in patients with STEMI and independently better predicted the long-term mortality than other complete blood count components, such as MPV, RDW, PLR-NLR and WBC-MPV combinations.* (Cardiol J 2016; 23, 3: 225–235)

Key words: mean platelet volume, ST-segment elevation myocardial infarction, white blood cell

Introduction

The role of inflammation in coronary artery disease (CAD) has been widely recognized [1]. White blood cells (WBCs) and platelets have potential roles in the pathogenesis of ST-segment elevation myocardial infarction (STEMI) [2, 3]. Increased WBC count is associated with increased mortality in patients with STEMI [4]. Mean platelet volume (MPV) is a potentially useful biomarker of platelet activity [5]. Apart from WBC count, other blood count parameters such as neutrophil count, red blood cell distribution with (RDW), mean platelet volume (MPV), high neutrophil to lymphocyte ratio (NLR) and high platelet to lymphocyte ratio (PLR) also seem to have prognostic value in STEMI [6–10]. As a combination of both WBC and mean platelet volume, WBC count to mean

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platelet volume ratio (WMR) has been recently found as a novel non-invasive marker predicting long-term outcomes in patients with non-ST elevation myocardial infarction (NSTEMI) [11]. Until now, the use of this marker for cardiovascular (CV) prognosis has not been investigated in patients undergoing primary percutaneous coronary intervention (pPCI) for STEMI. Therefore, we evaluated whether admission WMR obtains considerable prognostic information in patients undergoing pPCI for STEMI in a large population. We also assessed if this novel marker can provide further information in addition to other blood cell count parameters.

Methods

Study design

A total of 2,603 consecutive patients with STEMI who presented within 12 h from the onset of symptoms and underwent pPCI were recruited for the study. The study was approved by the Local Ethics Committee and all subjects gave their written informed consent. Patients with active infection, autoimmune diseases, hematologic proliferative disease, malignant neoplasia, and other chronic systemic disease were excluded from the study. Symptoms of myocardial ischemia and ST-segment elevation ≥ 1 mm in two contiguous electrocardiographic leads or new onset of complete left bundle-branch block were defined as ST elevation myocardial infarction. A previous diagnosis of diabetes mellitus (DM), use of antidiabetic medicines, or a fasting venous blood glucose level of 126 mg/dL on two occasions in previously untreated patients were required for a diagnosis of DM. Hypertension (HT) was defined as a previous use of antihypertensive medications, a systolic pressure higher than 140 mm Hg, or a diastolic pressure higher than 90 mm Hg on at least two separate measurements. Hypercholesterolemia was defined as total cholesterol of at least 200 mg/dL. The glomerular filtration rate (GFR) was estimated by using the Modification of Diet in Renal Disease (MDRD) equation at admission. Left ventricular ejection fraction was assessed by modified biplane Simpson's method in two-dimensional (2D) echocardiography.

Definition of re-infarction was formed according to the Third Universal Definition of Myocardial Infarction [12]. Target vessel revascularization (TVR) was defined as the need for PCI or coronary surgery because of restenosis or re-occlusion of the infarct-related artery (IRA). Major adverse cardiac events (MACE) were defined as CV death, re-infarction, or TVR.

Coronary angiography

All pPCI procedures were performed after loading dose of 300 mg acetylsalicylic acid and 300 mg clopidogrel by experienced interventional cardiologists who were unaware of the study. Coronary angiography was performed using the percutaneous femoral route. Heparin (100 U/kg) was administered when the coronary anatomy was first assessed and the use of glycoprotein IIb/IIIa inhibitors was left to the preference of the operator. Follow-up data were obtained from digital records, patient files or by telephone interview with patients, family members, or primary care physicians.

Laboratory measurements

Venous blood samples were obtained from all patients for hematologic and biochemical measurements on admission. An automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland) was used to measure hematologic parameters. The PLR was calculated as the ratio of the platelets and lymphocytes, the NLR was calculated as the ratio of the neutrophils and lymphocytes, and WMR was calculated as the ratio of WBC count and MPV, all obtained from the same automated blood sample at admission of the study. The 12-h fasting serum lipid profile was measured by standard enzymatic methods.

Statistical analysis

Analyses were performed using SPSS Statistics, version 20.0 (IBM SPSS Inc., Chicago, IL) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium). Continuous variables were tested for normal distribution by Kolmogorov-Smirnov test and expressed as mean ± standard deviation or median (interquartile range [IQR]) values as appropriate. One way ANOVA was used to compare data with normal distribution and the Kruskal-Wallis H test was applied to compare the data without normal distribution and significance after Bonferroni correction for multiple comparisons. Categorical variables were expressed as numbers and percentiles and compared by χ^2 and Fisher's exact tests. Among parameters that are found to be univariable and associated with the outcome, but also in a strong relationship with some others; only the variables showing the strongest univariable association with the outcome ($p < 0.25$)

are included in the stepwise multivariable Cox regression analysis. Since there is a high correlation (Goodman and Kruskal's Gamma Correlation, G = = 0.976, $p < 0.001$) which can cause multicollinearity between WMR risk groups and WBC-MPV combination risk groups, WMR and WBC-MPV combinations were included in two distinct Cox-regression models. Kaplan-Meier survival curves and the log-rank test were used to compare all-cause mortality between the low, intermediate, and high-risk groups. A 2-sided p value < 0.05 was considered statistically significant.

Results

In total, 2,603 patients, 2,129 (81.8%) males and 474 (18.2%) females, were recruited for the study. Mean age of the participants was 57.6 ± ± 11.8. Among the participants, 625 (24.0%) had DM, 1,085 (41.7%) had HT and 834 (32.0%) had hyperlipidemia. Median follow-up time was 12 (1–54) months.

Cutoff values for PLR, NLR, WBC, MPV and WMR were calculated with receiver-operating characteristics (ROC) curves and risk stratification was made according to WBC-MPV combination and WMR values. A PLR of 162.30 (50.8% sensitivity, 69.9% specificity), a NLR of 6.32 (53.3% sensitivity, 75.5% specificity), a WBC of 14,400 (57.8% sensitivity, 90.3% specificity) and a MPV of 8.1 (73.2% sensitivity, 68.0% specificity) were found as threshold values for mortality by ROC curves. If both PLR and NLR were above the selected threshold values, patients were classified as "high-risk". If either PLR or NLR were above the threshold individually, patients were classified as "intermediate-risk". If both levels were under threshold values, patients were classified as "low-risk". In the second model, if both WBC and MPV were above the selected threshold values, patients were classified as "high-risk". If either WBC or MPV were above the threshold individually, patients were classified as "intermediate-risk". If both levels were under threshold values, patients were classified as "low-risk". A WMR value of 1,653.47 was also found as threshold value for mortality with 75.4% sensitivity and 87.3% specificity by ROC curve analysis. A second ROC curve analysis was conducted for patients with WMR > 1,653.47 and a WMR value of 1,824.18 was found to show mortality with 77% sensitivity and 100% specificity.

Mean age and rates of female gender, DM, HT, anterior myocardial infarction, and cardiogenic shock were higher in both high-risk groups compared to low and medium risk groups (Table 1).

Laboratory findings of the patients were summarized in Table 2. In both high-risk groups, creatinine, peak creatinine kinase-MB, glucose, RDW, WBC, PLR and NLR were higher and hemoglobin, MPV, triglyceride and GFR were lower.

Distribution of culprit vessels, number of diseased vessels, stent length, stent diameter and tirofiban use were similar among risk groups. However, stent use was less frequent in both high-risk groups compared to others. Patients with post-procedural Thrombolysis in Myocardial Infarction (TIMI) 3 flow were less frequent in high-risk groups (Table 3).

In-hospital and long-term CV events were shown in Table 4. Rates of in-hospital mortality, MACE, stroke, ventricular tachycardia-fibrillation, heart failure, cardiogenic shock, atrial fibrillation, temporary pacemaker use, gastrointestinal bleeding, need for hemodialysis and blood transfusion were significantly higher in both high-risk groups. Rate of in-hospital re-infarction was higher in WMR high-risk group but did not differ between WBC--MPV combination risk groups. Rates of long-term CV mortality, MACE, heart failure and re-infarction was significantly higher in both high risk groups compared to low and intermediate-risk groups. However, long-term stroke and TVR rates were similar among the groups.

Age > 70, male gender, HT, DM, Killip class > 1, heart rate > 100 bpm, admission anemia, RDW and PLR-NLR combination were found as independent predictors of long-term CV mortality in Cox regression models I and II. In addition, WBC-MPV combination was an independent predictor of mortality in model I and WBC/PLR was an independent predictor of mortality in model II. Strongest predictors of mortality were WBC-MPV combination high-risk group in model I and WMR high-risk group in model II. Since the –2 Log Likelihood (LL) value was lower in model II than model I (model I: –2 LL = 2,675.6, $\chi^2 = 635.7$, $p < 0.001$; model II: 2 LL = 2,564.8, $\chi^2 = 811.5$, $p < 0.001$), model II was found more appropriate for mortality prediction (Table 5).

Receiver operating characteristic curves of WBC-MPV combination, WMR, PLR-NLR combination and their components for long-term mortality is shown in Figure 1. WMR has the highest area under ROC curve and pairwise comparisons of the ROC curves revealed that WMR has the highest discriminative ability for long-term mortality (Fig. 1). A log-rank p value < 0.001 was obtained while comparing survival amongst three risk groups in both risk models (Fig. 2).

Table 1. Baseline characteristics of the patients.

Variables	Combined WBC-MPV			P	WMR			P
	Low risk (n = 1,209)	Intermediate risk (n = 1,266)	High risk (n = 128)		Low risk (n = 2,120)	Intermediate risk (n = 340)	High risk (n = 143)	
Age [years]	57.5 ± 11.4	57.2 ± 12	62.3 ± 12†‡	< 0.001*	57.6 ± 11.7	55.1 ± 11.7	63.9 ± 11.8†‡	< 0.001*
Male gender	978 (80.9)	1062 (83.9)	89 (69.5)	0.001*	1738 (82)	292 (85.9)	99(69.2)	< 0.001*
Smoking	730 (60.4)	757 (59.8)	70 (54.7)	0.458	1251 (59)	233 (68.5)	73 (51)	< 0.001*
Diabetes	294 (24.3)	274 (21.6)	57 (44.5)	< 0.001*	486 (22.9)	71 (20.9)	68 (47.6)	< 0.001*
Hypertension	507 (41.9)	511 (40.4)	67 (52.3)	0.033*	875 (41.3)	136 (40)	74 (51.7)	0.039*
Family history	237 (19.6)	258 (20.4)	12 (9.4)	0.007*	416 (19.6)	78 (22.9)	13 (9.1)	0.001*
Hyperlipidemia	393 (32.5)	410 (32.4)	31 (24.2)	0.147	693 (32.7)	109 (32.1)	32 (22.4)	0.138
Dialysis	0 (0)	4 (0.3)	1 (0.8)	0.082	2 (0.1)	2 (0.6)	1 (0.7)	0.065
Prior CABG	45 (3.7)	32 (2.5)	5 (3.9)	0.178	74 (3.5)	3 (0.9)	5 (3.5)	0.018*
PCI history	107 (8.9)	109 (8.6)	19 (14.8)	0.042*	181 (8.5)	29 (8.5)	25 (17.5)	0.003*
Prior MI	152 (12.6)	129 (10.2)	24 (18.8)	0.008*	241 (11.4)	32 (9.4)	32 (22.4)	0.001*
Anterior MI	527 (43.6)	608 (48)	75 (58.6)	0.002*	937 (44.2)	189 (55.6)	84 (58.7)	< 0.001*
Admission CS	15 (1.2)	32 (2.5)	30 (23.4)	< 0.001*	29 (1.4)	15 (4.4)	33 (23.1)	< 0.001*
Angina-to-perfusion time [h]	4 ± 118	4 ± 58	4.5 ± 10	0.462	4 ± 88	3.5 ± 58	4 ± 8	0.977
Killip class > 1	47 (3.9)	60 (4.7)	50 (39.1)	< 0.001*	74 (3.5)	29 (8.5)	54 (37.8)	< 0.001*
SBP < 100 mm Hg	89 (7.4)	102 (8.1)	44 (34.4)	< 0.001*	149 (7)	34 (10)	52 (36.4)	< 0.001*
Heart rate > 100 bpm	34 (2.8)	52 (4.1)	37 (28.9)	< 0.001*	56 (2.6)	26 (7.6)	41 (28.7)	< 0.001*
Admission anemia	289 (23.9)	316 (25)	43 (33.6)	0.055	522 (24.6)	70 (20.6)	56 (39.2)	< 0.001*
LVEF [%]	48.2 ± 7.8	47.3 ± 7.8	41 ± 11.3†‡	< 0.001*	48.1 ± 7.6	46.5 ± 8.8	40.5 ± 11.3†‡	< 0.001*
Time of hospital stay [days]	6 (3)	6 (3)	7 (8)	0.374	6 (3)	6 (3)	7 (8)	0.326
Follow-up period [months]	9 (22)	18 (28)†	2 (9.8)†‡	< 0.001*	13 (25)	14 (28)	1 (9)†‡	< 0.001*

Continues variables are reported mean ± standard deviation or median (interquartile range). Categorical variables are reported n (%).*$p < 0.05$ was considered significant;†$p < 0.05$ vs. low risk (Bonferroni correction); ‡$p < 0.05$ vs. intermediate risk (Bonferroni correction); CABG — coronary artery bypass grafting; CS — cardiogenic shock; LVEF — left ventricular ejection fraction; MI — myocardial infarction; SBP — systolic blood pressure; PCI — percutaneous coronary intervention; WBC-MPV — white blood cell-mean platelet volume; WMR — white blood cell count to mean platelet volume ratio

Discussion

In this study, we have demonstrated for the first time that elevated admission WMR was associated with MACE and worse outcomes during in-hospital and long-term follow-up in patients with STEMI. Age, male gender, HT, anemia, RDW, PLR-NLR combination, WBC-MPV combination and WMR were the independent predictors of mortality in patients with STEMI. Moreover, higher WMR was associated with a significant increase in the risk of MACE incidence, and it was a stronger marker than MPV, RDW, PLR-NLR and WBC-MPV combinations in prediction of the in-hospital and long-term clinical outcomes.

Previous studies showed that some basic hematologic parameters such as MPV, RDW, NLR and PLR may have a role in predicting worse outcomes in patients with STEMI undergoing pPCI [7, 13–15]. As a constituent of the link between inflammation, thrombosis, and atherogenesis, platelets have a prominent role in progression of atherosclerosis and an increase in the platelet count can show advanced thrombocyte activation and megakaryocytic augmentation. Platelet surface molecules are essential in the interaction with endothelial cells, leukocytes and matrix molecules affecting atherogenesis. Platelets play an active role in platelet-fibrin formation and development of acute myocardial infarction. Several studies have showed that higher platelet count and lymphopenia were related with poor clinical outcomes in various cardiovascular diseases [10, 13]. Azab et al. [16] showed that increased PLR is an independent predictor of long-term mortality in patients with NSTEMI. MPV is a useful marker of platelet activity. Several studies showed close relationship between MPV levels and worse outcomes in patients with acute coronary syndromes (ACS) [8, 17]. Bigger platelets made from activated mega-

Table 2. Laboratory findings of patients

Variables	Combined WBC-MPV			P	WMR			P
	Low risk (n = 1,209)	Intermediate risk (n = 1,266)	High risk (n = 128)		Low risk (n = 2,120)	Intermediate risk (n = 340)	High risk (n = 143)	
Creatinine [mg/dL]	0.9 (0.3)	0.9 (0.3)	1 (0.4)†‡	< 0.001*	0.9 (0.2)	0.9 (0.3)	1.1 (0.4)†‡	< 0.001*
Peak CK-MB [U/l]	140 (165)	161 (183)	287 (285)†‡	< 0.001*	143 (170)	193.5 (211)†	278 (289)†‡	< 0.001*
Glucose [mg/dL]	132 (55)	132 (55)	175 (135)†‡	< 0.001*	132 (56)	132 (53.5)	178 (135)†‡	< 0.001*
Hemoglobin [g/dL]	13.6 ± 1.7	13.7 ± 1.9	13.2 ± 2†‡	0.009*	13.6 ± 1.8	13.9 ± 1.7	13.0 ± 2.1†‡	< 0.001*
Cholesterol [mg/dl]	190 ± 40.1	189.2 ± 38.7	181.7 ± 37.6	0.077	189.7 ± 39.8	191.1 ± 36.3	177.3 ± 37.2†‡	< 0.001*
LDL-C [mg/dL]	117.8 ± 30.4	118.4 ± 30.7	112.1 ± 27	0.084	118 ± 30.7	120.5 ± 29.4	109.4 ± 27†‡	< 0.001*
HDL-C [mg/dL]	40.3 ± 9	41 ± 8.5	40.6 ± 7.4	0.161	40.7 ± 8.8	40.7 ± 8.4	40.9 ± 7.4	0.996
Triglycerides [mg/dL]	132 (65)	129 (61)	123 (46.5)†‡	0.003*	132 (62)	131 (68)	121 (30)†‡	0.023*
GFR [mL/min/1.73 m^2]	88 (32)	89.3 (34)	70.1 (35.2)†‡	< 0.001*	88.9 (33)	88.2 (35.7)	69.4 (36.5)†‡	< 0.001*
RDW [%]	13.7 ± 1.3	13.9 ± 1.4	14.2 ± 1.4†‡	< 0.001*	13.8 ± 1.4	13.9 ± 1.3	14.3 ± 1.5†‡	< 0.001*
Lymphocytes [× 10^3/μL]	2 (1.9)	1.9 (1.6)	1.8 (1.3)	0.291	1.9 (1.7)	2.1 (1.8)	1.5 (1.2)†‡	< 0.001*
Platelet count [×10^9/L]	232.2 ± 58.5	265.4 ± 70†	283 ± 89.8†‡	< 0.001*	245.1 ± 65	275.9 ± 74.1†	276.8 ± 83.7†	< 0.001*
Neutrophils [× 10^3/μL]	7.3 (5.7)	7.8 (5.4)	10 (6.7)†‡	< 0.001*	7.3 (5.2)	10.1 (5.6)†	10 (6.4)†	< 0.001*
Hemoglobin A1c [%]	6.5 ± 1	6.5 ± 0.9	6.6 ± 0.7	0.644	6.5 ± 1	6.5 ± 0.8	6.6 ± 0.7	0.375
WBC count [× 10^3/μL]	10.8 ± 2.2	11.6 ± 2.7	17.4 ± 5.5†‡	< 0.001*	10.7 ± 2.3	14.2 ± 1.6†	16.4 ± 5.9†‡	< 0.001*
MPV [fL]	9.3 ± 2.1	8.1 ± 2.3†	7.6 ± 0.4†‡	< 0.001*	8.8 ± 2.4	8.2 ± 0.8†	7.6 ± 0.6†‡	< 0.001*
Combined WBC-MPV:				< 0.001*				< 0.001*
Low risk	–	–	–		1200 (56.6)	9 (2.6)	0 (0)	
Intermediate risk	–	–	–		920 (43.4)	316 (92.9)	30 (21)	
High risk	–	–	–		0 (0)	15 (4.4)	113 (79)	
WMR:	1178 ± 254.2	1446.7 ± 281.5†	2538 ± 582.9†‡	< 0.001*	1241.9 ± 256.9	1736.7 ± 49.6†	2498.3 ± 562.4†‡	< 0.001*
Low risk	1200 (99.3)	920 (72.7)	0 (0)		–	–	–	
Intermediate risk	9 (0.7)	316 (25)	15 (11.7)		–	–	–	
High risk	0 (0)	30 (2.4)	113 (88.3)		–	–	–	
PLR	114.6 (94.1)	133.7 (111.1)†	167.7 (113.8)†‡	< 0.001*	121.1 (103)	124.5 (116.4)	173 (121.6)†‡	< 0.001*
NLR	3.8 (4.5)	4.3 (4.8)	6.7 (4.6)†‡	< 0.001*	3.8 (4.4)	5.1 (5.4)†	6.7 (4.8)†‡	< 0.001*
PLR-NLR combination:				< 0.001*				< 0.001*
Low risk	839 (69.4)	733 (57.9)	44 (34.4)		1377 (65.0)	196 (57.6)	43 (30.1)	
Intermediate risk	166 (13.7)	236 (18.6)	29 (22.7)		349 (16.5)	47 (13.8)	35 (24.5)	
High risk	204 (16.9)	297 (23.5)	55 (43.0)		394 (18.6)	97 (28.5)	65 (45.5)	

Continues variables are reported mean ± standard deviation or median (interquartile range). Categorical variables are reported n (%); *p < 0.05 was considered significant; †p < 0.05 vs. low risk (Bonferroni correction); ‡p < 0.05 vs. intermediate risk (Bonferroni correction); CK-MB — creatine kinase myocardial band; GFR — glomerular filtration rate; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; NLR — neutrophil–lymphocyte ratio; MPV — mean platelet volume; PLR — platelet-lymphocyte ratio; RDW — red blood cell distribution with; WBC — white blood cell; WMR — white blood cell count to mean platelet volume ratio

Table 3. Angiographic and procedural characteristics of thepatients.

Variables	Combined WBC-MPV			P	WMR			P
	Low risk (n = 1,209)	Intermediate risk (n = 1,266)	High risk (n = 128)		Low risk (n = 2,120)	Intermediate risk (n = 340)	High risk (n = 143)	
Culprit lesion:				0.142				0.101
LMCA	3 (0.2)	3 (0.2)	0 (0)		5 (0.2)	1 (0.3)	0 (0)	
LAD	531 (43.9)	611 (48.3)	76 (59.4)		942 (44.4)	191 (56.2)	85 (59.4)	
CX	165 (13.6)	175 (13.8)	14 (10.9)		305 (14.4)	37 (10.9)	12 (8.4)	
RCA	501 (41.4)	468 (37)	37 (28.9)		850 (40.1)	111 (32.6)	45 (31.5)	
Saphenous vein graft	7 (0.6)	7 (0.6)	1 (0.8)		14 (0.7)	0 (0)	1 (0.7)	
Others	2 (0.2)	2 (0.2)	0 (0)		4 (0.2)	0 (0)	0 (0)	
No. of diseased vessels:				0.074				0.068
1	516 (42.7)	557 (44)	39 (30.5)		921 (43.4)	156 (45.9)	35 (24.5)	
2	391 (32.3)	398 (31.4)	51 (39.8)		674 (31.8)	110 (32.4)	56 (39.2)	
3	302 (25)	311 (24.6)	38 (29.7)		525 (24.8)	74 (21.8)	52 (36.4)	
Preprocedural TIMI grade:				0.192				0.364
1	1085 (89.7)	1127 (89)	121 (94.5)		1896 (89.4)	304 (89.4)	133 (93)	
2	78 (6.5)	96 (7.6)	3 (2.3)		143 (6.7)	28 (8.2)	6 (4.2)	
3	46 (3.8)	43 (3.4)	4 (3.1)		81 (3.8)	8 (2.4)	4 (2.8)	
Postprocedural TIMI grade:				< 0.001*				< 0.001*
1	82 (6.8)	95 (7.5)	31 (24.2)		137 (6.5)	31 (9.1)	40 (28)	
2	53 (4.4)	57 (4.5)	22 (17.2)		89 (4.2)	22 (6.5)	21 (14.7)	
3	1074 (88.8)	1114 (88)	75 (58.6)		1894 (89.3)	287 (84.4)	82 (57.3)	
Proximal locationof the lesion	651 (53.8)	700 (55.3)	88 (68.8)	0.006*	1155 (54.5)	194 (57.1)	90 (62.9)	0.112
Volume of contrast medium [mL]	250 ± 100	250 ± 100	250 ± 125	0.994	250 ± 100	250 ± 100	250 ± 100	0.902
Tirofiban use	597 (49.4)	579 (45.7)	53 (41.4)	0.082	1027 (48.4)	145 (42.6)	57 (39.9)	0.067
Success of the procedure:				< 0.001*				< 0.001*
Yes	1123 (92.9)	1159 (91.6)	95 (74.2)		1970 (92.9)	305 (89.7)	102 (71.3)	
No	86 (7.1)	107 (8.4)	33 (25.8)		150 (7)	35 (10.3)	41 (28.7)	
Postprocedural TIMI grade:				0.027*				0.003*
1	218 (18)	252 (19.9)	38 (29.7)		392 (18.5)	69 (20.3)	47 (32.9)	
2	294 (24.3)	314 (24.8)	24 (18.8)		528 (24.9)	76 (22.4)	28 (19.6)	
3	696 (57.6)	700 (55.3)	66 (51.6)		1199 (56.6)	195 (57.4)	68 (47.6)	
Stent use	993 (82.1)	1017 (80.3)	91 (71.1)	0.013*	1732 (81.7)	272 (80)	97 (67.8)	0.001*
Stent length [mm]	18 ± 7	18 ± 5	18 ± 8	0.709	18 ± 8	18 ± 7	18 ± 8	0.129
Stent diameter [mm]	3 ± 0.5	3 ± 0.5	3 ± 0.2	0.743	3 ± 0.5	3 ± 0.5	3 ± 0.5	0.213
Stent type:				0.674				0.466
Bare metal stent	970 (97.6)	988 (97.1)	89 (97.8)		1683 (97.1)	269 (98.9)	95 (97.9)	
Paclitaxel-eluting stent	12 (1.2)	11 (1.1)	0 (0)		22 (1.3)	1 (0.4)	0 (0)	
Sirolimus-eluting stent	12 (1.2)	18 (1.8)	2 (2.2)		28 (1.6)	2 (0.7)	2 (2.1)	

Continues variables are reported mean ± standard deviation or median (interquartile range). Categorical variables are reported n (%);*p < 0.05 was considered significant; CX — circumflex coronary artery; LAD — left anterior descending coronary artery; LMCA — left main coronary artery; MPV — mean platelet volume; RCA — right coronary artery; TIMI — thrombolysis in myocardial infarction; WBC — white blood cell; WMR — white blood cell count to mean platelet volume ratio

Table 4. In-hospital and long-term cardiac events.

Event	Combined WBC-MPV			P	WMR			P
	Low risk (n = 1,209)	Intermediate risk (n = 1,266)	High risk (n = 128)		Low risk (n = 2,120)	Intermediate risk (n = 340)	High risk (n = 143)	
In-hospital event and complications:								
In-hospital mortality	10 (0.8)	37 (2.9)	55 (43)	< 0.001*	24 (1.1)	14 (4.1)	64 (44.8)	< 0.001*
Reinfarction	25 (2.1)	26 (2.1)	6 (4.7)	0.153	39 (1.8)	12 (3.5)	6 (4.2)	0.031*
TVR	52 (4.3)	49 (3.9)	9 (7)	0.214	84 (4)	15 (4.4)	11 (7.7)	0.112
MACE	59 (4.9)	83 (6.6)	60 (46.9)	< 0.001*	104 (4.9)	29 (8.5)	69 (48.3)	< 0.001*
Stroke	1 (0.1)	10 (0.8)	5 (3.9)	< 0.001*	6 (0.3)	4 (1.2)	6 (4.2)	< 0.001*
CPR	22 (1.8)	45 (3.6)	56 (43.8)	< 0.001*	40 (1.9)	18 (5.3)	65 (45.5)	<0.001*
Hemodialysis	6 (0.5)	8 (0.6)	7 (5.5)	< 0.001*	10 (0.5)	3 (0.9)	8 (5.6)	< 0.001*
VT/VF	42 (3.5)	56 (4.4)	39 (30.5)	< 0.001*	72 (3.4)	22 (6.5)	43 (30.1)	< 0.001*
Heart failure	85 (7)	139 (11)	64 (50.0)	< 0.001*	172 (8.1)	47 (13.8)	69 (48.3)	< 0.001*
Requaring inotrope	47 (3.9)	89 (7)	67 (52.3)	< 0.001*	99 (4.7)	29 (8.5)	75 (52.4)	< 0.001*
Cardiogenic shock and IABP	18 (1.5)	37 (2.9)	48 (37.5)	< 0.001*	34 (1.6)	17 (5)	52 (36.4)	< 0.001*
Atrial fibrillation	20 (1.7)	20 (1.6)	7 (5.5)	0.019*	32 (1.5)	7 (2.1)	8 (5.6)	0.007*
Complete AVB	39 (3.2)	37 (2.9)	20 (15.6)	< 0.001*	67 (3.2)	10 (2.9)	19 (13.3)	< 0.001*
Transient pacemaker	41 (3.4)	26 (2.1)	23 (18.0)	< 0.001*	59 (2.8)	8 (2.4)	23 (16.1)	< 0.001*
GI bleeding	7 (0.6)	14 (1.1)	5 (3.9)	0.008*	15 (0.7)	6 (1.8)	5 (3.5)	0.004*
Access site complication	56 (4.6)	47 (3.7)	7 (5.5)	0.367	87 (4.1)	17 (5)	6 (4.2)	0.775
Acute stent thrombosis	16 (1.3)	12 (0.9)	3 (2.3)	0.229	26 (1.2)	2 (0.6)	3 (2.1)	0.329
Blood transfusion	39 (3.2)	39 (3.1)	13 (10.2)	0.001*	61 (2.9)	17 (5)	13 (9.1)	< 0.001*
Long-term cardiac events:								
Cardiovascular mortality	14 (1.2)	81 (6.4)	68 (53.1)	< 0.001*	42 (2)	29 (8.5)	92 (64.3)	< 0.001*
Heart failure	58 (4.8)	79 (6.2)	27 (21.1)	< 0.001*	106 (5)	24 (7.1)	34 (23.8)	< 0.001*
Stroke	12 (1)	15 (1.2)	2 (1.6)	0.693	24 (1.1)	1 (0.3)	4 (2.8)	0.068
Reinfarction	50 (4.1)	90 (7.1)	14 (10.9)	0.001*	108 (5.1)	26 (7.6)	20 (14)	< 0.001*
TVR	171 (14.1)	207 (16.4)	14 (10.9)	0.126	311 (14.7)	64 (18.8)	17 (11.9)	0.076
MACE	204 (16.9)	293 (23.1)	68 (53.1)	< 0.001*	383 (18.1)	92 (27.1)	90 (62.9)	< 0.001*

*p < 0.05 was considered significant; Mean values (standard deviation [SD]) and n (%) are reported for continuous and categorical variables, respectively; AVB — atrioventricular block; CPR — cardiopulmonary resuscitation; GI — gastrointestinal; IABP — intra-aortic balloon pump; MACE — major adverse cardiovascular event (cardiovascular death, reinfarction, TVR); TVR — target vessel revascularization; VT/VF — ventricular tachycardia/fibrillation; WBC-MPV — white blood cell-mean platelet volume; WMR — white blood cell count to mean platelet volume ratio

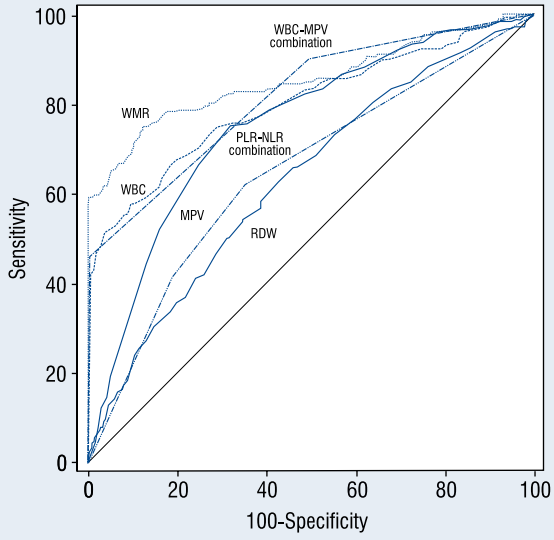
karyocytes are more sensitive than normal size platelets. Larger platelets are likely to be available well before the acute coronary artery occlusion responsible for ACS. For this reason, it is reasonable that hyperactive and larger platelets constitute a significant determinant of the thrombogenic process underlying the total occlusion of the coronary artery leading to STEMI. Several studies have suggested that MPV could be a marker of coronary perfusion in STEMI patients. Huczek et al. [18] showed MPV to be an independent predictor for the no-reflow phenomenon after pPCI. Estévez-Loureiro et al. [15] found that increased MPV is an independent predictor of both a patent IRA and 30-day mortality in patients with STEMI undergoing pPCI. RDW is a marker of variation in the size of circulating red cells (anisocytosis), and increased RDW levels can be considered the production of humoral mediators by the bone marrow. Inflammatory cytokines and neurohumoral mediators are activated in the process of STEMI. Elevated RDW was an independent predictor of mortality and morbidity in patients with heart disease. Tonelli et al. [19] found an independent relation between higher RDW levels and the risk of death and CV events in patients with CAD. Activated neutrophils release several proteolytic enzymes which increase the tissue destruction, such as acid phosphatase, myeloperoxidase, and elastase [20–22]. Activation of the neurohormonal

Table 5. Cox-regression models revealing independent predictors of long-term cardiovascular mortality in all study patients.

Variables	Model I		Model II	
	HR (95% CI)	P	HR (95% CI)	P
Age ≥ 70 [years]	1.726 (1.298–2.294)	< 0.001*	1.800 (1.354–2.393)	< 0.001*
Male gender	0.725 (0.534–0.984)	0.039*	0.597 (0.454–0.784)	0.001*
Hypertension	1.336 (1.005–1.775)	0.046*	1.427 (1.086–1.876)	0.011*
Diabetes mellitus	1.440 (1.061–1.955)	0.019*	1.432 (1.052–1.949)	0.022*
Killip class > 1	2.166 (1.478–3.174)	< 0.001*	2.043 (1.395–2.991)	< 0.001*
Heart rate > 100 bpm	2.646 (1.714–4.085)	< 0.001*	2.349 (1.539–3.584)	< 0.001*
Admission anemia	1.407 (1.064–1.862)	0.017*	1.452 (1.101–1.915)	0.008*
RDW	1.097 (1.016–1.183)	0.018*	1.213 (1.138–1.291)	0.001*
PLR-NLR combination:				
Low risk (PLR ≤ 162.0 and NLR ≤ 6.32)	Reference		Reference	
Intermediate risk (PLR > 162.1 or NLR > 6.32)	1.423 (0.977–2.072)	0.066	1.269 (0.866–1.860)	0.222
High risk (PLR > 162.0 and NLR > 6.32)	1.821 (1.328–2.496)	< 0.001*	1.672 (1.212–2.305)	0.002*
WBC-MPV combination:				
Low risk (WBC ≤ 14,400 and MPV > 8.1)	Reference		–	–
Intermediate risk (WBC > 14,400 or MPV ≤ 8.1)	2.441 (1.529–3.895)	< 0.001*	–	–
High risk (WBC > 14,400 and MPV ≤ 8.1)	5.375 (3.230–8.947)	< 0.001*	–	–
WMR:				
Low risk (WMR ≤ 1,653.47)	–	–	Reference	
Intermediate risk (1,653.47 < WMR ≤ 1,824.18)	–	–	2.639 (1.752–3.975)	< 0.001*
High risk (WMR > 1,824.18)	–	–	7.075 (4.869–10.280)	< 0.001*
Omnibus tests of model coefficients	–2 LL = 2,675.6, χ^2 = 635.7, p < 0.001		–2 LL = 2,564.8, χ^2 = 811.5, p < 0.001	

*p < 0.05 was considered significant; CI — confidence interval; HR — hazard ratio; LL — Log Likelihood; NLR — neutrophil–lymphocyte ratio; MPV — mean platelet volume; PLR — platelet-lymphocyte ratio; RDW — red blood cell distribution with; WBC — white blood cell; WMR — white blood cell count to mean platelet volume ratio

system, oxidative stress and inflammation in ACS increase the catecholamine levels and the plasma cortisol levels cause bone marrow suppression and down-regulation of the lymphocyte proliferation and differentiation with aggravated lymphocyte apoptosis. In a recent study, He et al. [23] showed that average NLR was a useful and powerful predictor of mortality and adverse-outcomes in Chinese patients presenting with STEMI. Elevated leukocytes are associated with increased mortality in patients with myocardial infarction [24]. Several mechanisms can explain this relationship; 1) leukocytes can cause injury of endothelial cells by oxidative and proteolytic damage, 2) leukocytes can plug the microvascularization, 3) leukocytes can stimulate hypercoagulability and activated monocytes [25]. In a recent study, Dharma et al. [25] reported that high blood leukocyte count on admission was an independent predictor of CV events in patients with NSTEMI. Furthermore, Sabatine et al. [26] found that an elevated baseline WBC count correlated with impaired myocardial perfusion and increased 6-month mortality in patients with STEMI. Maden et al. [27] showed that higher WBC and MPV is associated with occluded IRA in patients with STEMI. Karahan et al. [28] observed that increased WBC and MPV are independent predictors of impaired microvascular perfusion in patients with STEMI. Increased WBCs may appear as a significant factor showing impaired microvascular reperfusion. Recently, Dehghani et al. [11] investigated a novel parameter called WMR as a marker predicting long-term outcomes in patients with NSTEMI. They suggested that WMR is a better predictor of worse outcomes in patients with NSTEMI than WBC and MPV [11]. In light of these evidences, we decided to evaluate the prognostic value of WMR with a large number of patients with STEMI undergoing pPCI and demonstrated that WMR is a better indicator of predicting the poor



	AUC	SE[a]	95% CI[b]
MPV	0.756	0.0161	0.739 to 0.773
WBC	0.803	0.0178	0.788 to 0.819
WMR	0.856	0.0166	0.842 to 0.869
WBC-MPV combination	0.817	0.0142	0.801 to 0.831
PLR-NLR combination	0.649	0.0175	0.630 to 0.667
RDW	0.634	0.0188	0.615 to 0.652

[a]DeLong et al. 1988
[b]Binomia l exact

Pairwise comparison of ROC curves

WMR ~ MPV	
Difference between areas	0.0998
Standard error[c]	0.0183
95% confidence interval	0.0639 to 0.136
z statistic	5.451
Significance level	p < 0.0001
WMR ~ WBC	
Difference between areas	0.0526
Standard error[c]	0.00665
95% confidence interval	0.0369 to 0.0657
z statistic	7.913
Significance level	p < 0.0001
WMR ~ WBC-MPV combination	
Difference between areas	0.0396
Standard error[c]	0.0114
95% confidence interval	0.0172 to 0.0619
z statistic	3.471
Significance level	p = 0.0005
WMR ~ PLR-NLR combination	
Difference between areas	0.208
Standard error[c]	0.0223
95% confidence interval	0.164 to 0.251
z statistic	9.308
Significance level	p < 0.0001
WMR ~ RDW	
Difference between areas	0.222
Standard error[c]	0.0249
95% confidence interval	0.174 to 0.271
z statistic	8.936
Significance level	p < 0.0001

[c]DeLong et al. 1988

Figure 1. Receiver operating characteristic curves identifying the discrimination thresholds of white blood cell (WBC)--mean platelet volume (MPV) combination, white blood cell count to mean platelet volume ratio (WMR), platelet to lymphocyte ratio and neutrophil to lymphocyte ratio (PLR-NLR) combination and their components for long-term mortality; RDW — red blood cell distribution with.

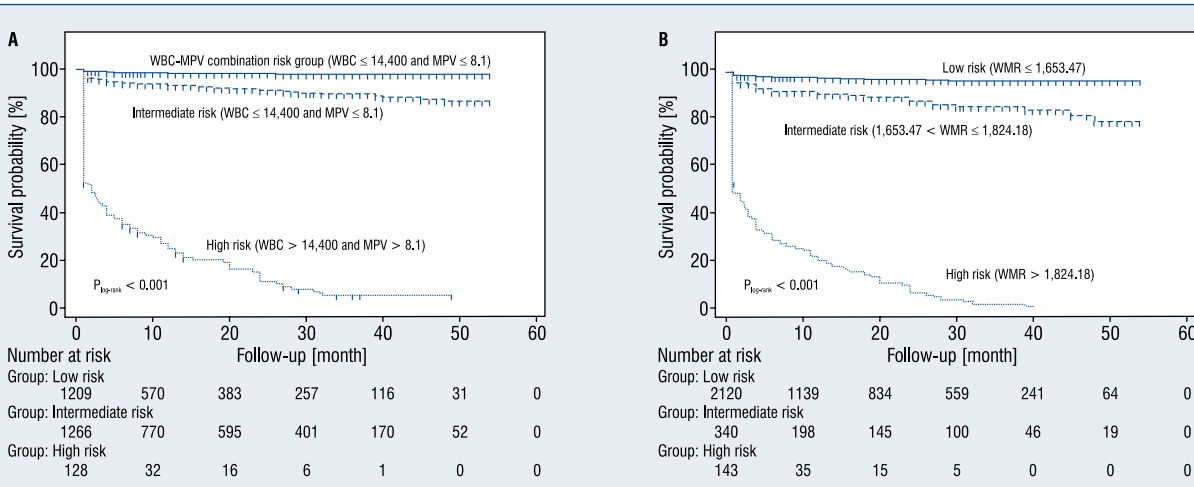


Figure 2. Kaplan-Meier cumulative survival curves for patients with mortality according to combined white blood cell (WBC) (**A**)-mean platelet volume (MPV) and white blood cell count to mean platelet volume ratio (WMR) (**B**) risk stratification.

outcomes in STEMI than MPV, RDW, PLR-NLR and WBC-MPV combinations.

White blood cell count to mean platelet volume ratio has some key properties that a novel CV prognostic marker should have [29, 30]. First, WMR is obtained easily from routine complete blood counts without additional work or cost. Second, it provides information about hard endpoints such as in-hospital an long-term mortality. Moreover, it is also useful for risk stratification in patients classified into risk groups according to WMR levels. Such risk stratification may allow clinicians to determine patients who are at higher risk and individualizing the therapy. In patients with elevated WMR, more intensive medical therapy and more aggressive control of CV risk factors may be considered. In this high-risk population, more close follow-up visits can also be arranged. However, further studies with long-term follow-up and large-scale prospective data are needed to elucidate the exact role of WMR in patients with CAD.

Limitations of the study

Our study findings should be interpreted with some limitations. First, it was a single-center, retrospective study without randomization. Inflammatory markers, such as high-sensitivity C-reactive protein, B-type natriuretic peptide, other pro-inflammatory cytokines, and markers of oxidative stress were not analyzed. Using a spot laboratory value of complete blood counts rather than values at a time-interval is another limitation of this study.

Conclusions

In conclusion, higher WMR value on admission was associated with worse outcomes in patients with STEMI and independently predicted the long-term mortality better than other complete blood count components, such as MPV, RDW, PLR-NLR and WBC-MPV combinations.

Conflict of interest: None declared

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