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Mean Platelet Volume on Admission Improves Risk Prediction in Patients With Acute Coronary Syndromes

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Abstract

Our aim was to evaluate the incremental predictive value of adding mean platelet volume (MPV) to the Global Registry of Acute Coronary Events (GRACE) risk score. The MPV and GRACE score were determined on admission in 509 consecutive patients with acute coronary syndrome (ACS). Six-month mortality or nonfatal myocardial infarction (MI) was the study end point. Overall, 61 (12%) patients reached the combined end point. Cox multivariate analysis showed that an elevated MPV was an independent predictor of 6-month mortality or MI in patients with ACS. The addition of MPV to the GRACE model improved its global fit and discriminatory capacity. The new model including MPV allowed adequate reclassification of 16% of the patients. In conclusion, the inclusion of MPV into the GRACE risk score could allow improved risk classification, thereby refining risk stratification of patients with ACS.

Keywords

acute coronary syndrome, mean platelet volume, GRACE score, risk prediction

Introduction

Platelets play a key role in atherothrombosis leading to acute coronary syndrome (ACS), and patients with increased platelet activation are at higher risk of cardiovascular events in the setting of ACS.[1,2] Although many platelet function tests have been used, there is currently no consensus regarding the most appropriate method.[1-3] Furthermore, these methods are time consuming and require expensive equipment.[3] In contrast, mean platelet volume (MPV), a readily available laboratory test, is associated with platelet reactivity.[3] A recent cohort study suggested that the predictive power of admission MPV for cardiac death was more useful compared with platelet function tests in patients with ACS.[4] The short- and long-term prognostic significance of MPV has also been evaluated in patients with non-ST-segment elevation ACS or those undergoing percutaneous coronary intervention (PCI).[5,6] However, few studies have focused on the mid-term prognostic value of MPV in patients with ACS and used a widely accepted outcome measure.

Patients with ACS are heterogeneous in terms of their clinical presentation and prognosis. Recent clinical guidelines emphasize the value of early risk stratification to determine the appropriate therapeutic strategies according to an individual risk.[7-9] For this purpose, the use of established and validated risk scoring systems, such as the Global Registry of Acute Coronary Events (GRACE) risk score,[10] has been recommended by several guidelines.[7-9] However, because the laboratory-based variables included in the GRACE risk score are limited to serum creatinine and troponin, it is plausible that variables, such as MPV, which reflect other pathophysiological aspects of ACS could provide additional information. To date, little is known regarding the addition of MPV to the GRACE risk scoring system. Accordingly, the purposes of the present study were: (1) to assess the association between baseline MPV and 6-month mortality or myocardial infarction (MI) in patients with ACS and (2) to evaluate the predictive value of adding MPV to the GRACE score.

Methods

Study Population

Patients admitted to the Department of Cardiology of the First Hospital of Lanzhou University, from September 2012 to April 2013, with an initial diagnosis of ACS were screened. Acute

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coronary syndrome included ST-segment elevation MI (STEMI), non-STEMI (NSTEMI), and unstable angina (UA). Patients were excluded if their MPV levels were not determined, all data required for the GRACE risk score calculation were not available, they had significant noncardiovascular comorbidity such as trauma or surgery, or they did not undergo a complete follow-up at 6 months after admission. The STEMI was diagnosed based on the presence of at least 1 positive cardiac biochemical marker of necrosis (troponin I) with new-onset ST-segment elevation or left bundle-branch block in the index or subsequent electrocardiogram (ECG).[8] Cases of NSTEMI required at least 1 instance of elevated troponin I without new ST-segment elevation observed on the ECGs.[8] Unstable angina was defined as rest angina, new-onset angina, or increasing angina with or without ischemic ECG changes and negative troponin I levels.[9] The study was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki.

Determination of MPV and the GRACE Risk Score

Peripheral venous blood samples were drawn in the emergency department or on admission to the hospital. Blood samples were placed in tubes containing dipotassium EDTA (K_2-EDTA), and MPV was analyzed using a Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan) within 2 hours of collection.

As described previously,[10] the GRACE risk score model includes 8 weighted variables that are readily available at hospital admission (age, heart rate, systolic blood pressure, serum creatinine concentration, Killip class, ST-segment deviation, elevated cardiac enzymes, and cardiac arrest). Values for these variables were entered into a GRACE risk calculator (http://www.outcomes-umassmed.org/grace) to obtain scores for the cumulative risk of the combined end point of death or nonfatal MI within 6 months of admission.

Study End Point

The study end point was defined as the composite of all-cause mortality or nonfatal MI, including STEMI or NSTEMI, during the time interval from admission to 6 months.

Baseline Data and Follow-Up

After screening patients, 2 uniformly trained investigators collected data from the inpatient medical records on prespecified forms. The following information was included: demographic data, previous medication and diseases, clinical presentation, GRACE variables, laboratory and echocardiographic parameters, and clinical outcomes.

An individual blinded to the patient information performed the follow-up via telephone. When a patient reported another hospital admission for cardiovascular reasons at 6 months after discharge, the medical records were obtained and examined for a diagnosis of MI. A dual review of events was performed, and disagreements were resolved by consensus.

Sample Size

The sample size was adjusted for an event rate of 12.3% as reported in a previous study.[10] Cox regression of the log hazard ratio (HR) of a covariate with a standard deviation of 1.04 based on a sample of 500 observations achieved 80% power at a .05 significance level for detecting a regression coefficient equal to .34.[5,11]

Statistical Analysis

Receiver operating characteristic (ROC) curve analysis was performed to determine the use of MPV for distinguishing patients with and without events during follow-up. The optimal cutoff was calculated by determining the MPV that provided the greatest sum of sensitivity and specificity.

Continuous variables are summarized as medians (interquartile ranges) and were compared using the Mann-Whitney rank-sum test. Categorical data are expressed as numbers (percentages) and were compared using the chi-square test or Fisher exact test, as appropriate. Spearman rank correlation was used to assess the relationship between MPV and the GRACE risk score. Cumulative survival curves were generated by the Kaplan-Meier method, and the difference between the groups was assessed using the log-rank test. Univariate Cox proportional hazards regression analysis was conducted to identify predictors of mortality or nonfatal MI. Variables that showed an association ($P < .10$) with the study end point and those that were associated with a high MPV (> the cutoff point) were entered into the final multivariate model, and MPV was included as either a continuous variable or a categorical variable.

To assess the prognostic value of the change in MPV over the GRACE score for survival, we constructed 2 different Cox regression models: 1 with the GRACE score alone and 1 including MPV. Estimates of the C statistic for the 2 models were calculated to assess model discrimination. The increased discriminative value of the biomarkers was further examined using net reclassification improvement (NRI) and integrated discrimination improvement (IDI).[12,13] To determine clinical utility, 2 categorical NRIs were applied with prespecified risk thresholds of 12% and 21%. These risk thresholds were chosen in accordance with a previous study.[14] A categorical NRI defines upward and downward reclassification only if the estimated prediction probabilities move from one category to another. The IDI considers the change in the predicted risks as a continuous variable. We also calculated likelihood ratio statistics to evaluate whether the global model fit was improved after addition of the biomarkers. The likelihood ratio test rejects the null hypothesis if the value of the chi-square statistic is large and statistically significant. A 2-tailed $P < .05$ was considered significant. All analyses were performed with SPSS 11.0 software (SPSS Inc, Chicago, Illinois) and STATA 11.0 software (STATA Corp, College Station, Texas, USA).

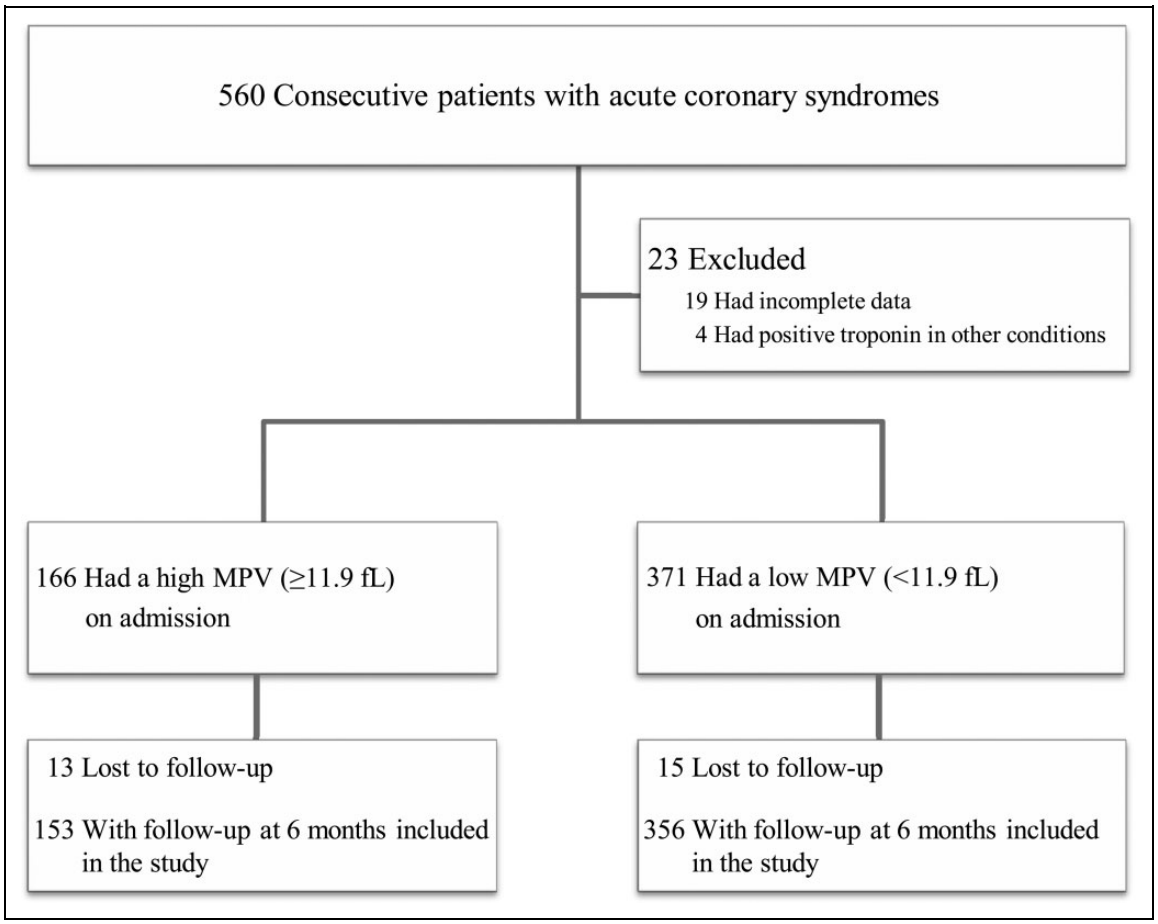

Figure 1. Flowchart of the study population. MPV indicates mean platelet volume.

Results

Population Characteristics

Of 560 consecutively screened patients, 509 (91%) met the inclusion criteria and were included in the analyses. The study flowchart is shown in Figure 1. The median age of the study population was 61 (54-69) years, with a predominance of males (79%). Six months after admission, 61 (12%) patients had reached the combined end point of death (35 patients) or nonfatal MI (26 patients). The median MPV for the overall population was 10.9 (9.8-12.0) fL. When the MPV cutoff level was set to 11.9 fL using the ROC curve, the sensitivity was 62% and the specificity was 74% for discriminating patients with the combined end point (area under the curve = 0.731; 95% confidence interval [CI], 0.661-0.802; $P < .001$). Therefore, the population was divided into 2 groups based on this optimized MPV value (11.9 fL).

The baseline characteristics of the study population are presented in Table 1. Compared to patients in the lower MPV (<11.9 fL) group, those with a high MPV (≥11.9 fL) had a higher prevalence of an advanced Killip class, higher GRACE risk scores, and higher white blood cell counts; they also showed a lower platelet count and a lower hemoglobin level. Moreover, prior use of clopidogrel and β-blockers was less frequent in the higher MPV group (Table 1). There was a weakly positive, but significant, correlation between MPV and the GRACE score ($r = .115$, $P = .009$).

Event-Free Survival

The Kaplan-Meier event-free survival curves during follow-up, according to the MPV cutoff points, are shown in Figure 2. Mortality and MI rates were significantly increased in the higher MPV group compared with the lower MPV group (27% vs 6%, log-rank $P < .001$).

Cox Regression

In the multivariate analyses, MPV as a continuous (per fL) or categorical (≥11.9 fL) variable was independently associated with the combined end point of death or nonfatal MI. Cox regression analysis showed that this relationship persisted after adjusting for age, comorbidities, condition at admission, and laboratory findings (Table 2).

When combined in a prediction model based on the variables used for the GRACE risk score (Table 3), high MPV (≥11.9 fL) remained an independent predictor of the combined

Table 1. Comparison of Clinical Characteristics, Treatments, and Outcomes According to MPV Levels (< or ≥11.9 fL).[a]

Variables	Total (n = 509)	MPV < 11.9 fL (n = 356)	MPV ≥ 11.9 fL (n = 153)	P[c]
Male sex	404 (79)	285 (80)	119 (78)	.560
GRACE variables				
Age, years	61 (54-69)	61 (55-69)	60 (53-69)	.696
Heart rate, per min	72 (66-82)	72 (65-80)	74 (68-84)	.133
Systolic blood pressure, mm Hg	122 (110-140)	122 (110-140)	122 (110-140)	.781
Creatinine, μmol/L	79 (68-89)	79 (68-88)	81 (69-91)	.345
Killip class I	410 (81)	306 (86)	104 (68)	**<.001**
Killip class II	62 (12)	33 (9)	29 (19)	
Killip class III	23 (5)	9 (3)	14 (9)	
Killip class IV	14 (3)	8 (2)	6 (4)	
Cardiac arrest	3 (1)	1 (0)	2 (1)	.216[b]
ST-segment deviation	271 (53)	185 (52)	86 (56)	.379
Elevated cardiac marker	248 (49)	171 (48)	77 (50)	.635
GRACE score, points	144 (99-176)	137 (97-174)	153 (101-190)	**.034**
Medical history				
Current smoker	271 (53)	185 (52)	86 (56)	.379
Hypertension	240 (47)	159 (45)	81 (53)	.086
Type 2 diabetes	103 (20)	71 (20)	32 (21)	.803
Dyslipidemia	205 (40)	136 (38)	69 (45)	.146
Previous myocardial infarction	146 (29)	107 (30)	39 (26)	.296
Chronic medical therapy				
Aspirin	209 (41)	150 (42)	59 (39)	.452
Clopidogrel	95 (19)	75 (21)	20 (13)	**.034**
Statins	156 (31)	112 (32)	44 (29)	.544
β-Blockers	132 (26)	103 (29)	29 (19)	**.019**
ACEI or ARB	162 (32)	115 (32)	47 (31)	.725
Laboratory tests				
MPV, fL	10.9 (9.8-12.0)	10.2 (9.4-11.0)	12.2 (12.1-12.8)	**<.001**
Platelet count, $\times 10^9$/L	158 (125-200)	170 (141-213)	132 (107-163)	**<.001**
Hemoglobin, g/L	145 (133-157)	146 (133-158)	143 (132-153)	**.033**
White blood cell count, $\times 10^9$/L	6.6 (5.6-7.9)	6.5 (5.5-7.9)	6.8 (5.9-8.2)	**.018**
Echocardiographic features				
Left ventricular ejection fraction, %	57 (50-66)	58 (50-65)	57 (49-66)	.522
Clinical presentation				
STEMI	240 (47)	167 (47)	73 (48)	.868
NSTEMI/unstable angina	269 (53)	189 (53)	80 (52)	
Clinical outcomes				
Death	35 (7)	10 (3)	25 (16)	**<.001**
Nonfatal myocardial infarction	26 (5)	13 (4)	13 (9)	**.023**
Combined end point	61 (12)	20 (6)	41 (27)	**<.001**

Abbreviations: MPV, mean platelet volume; GRACE, Global Registry of Acute Coronary Events; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[a] Data are shown as n (%) or median (interquartiles).

[b] By Fisher exact test.

[c] Boldface values represent statistically significant values ($P < .05$).

end point (HR, 4.76; 95% CI, 2.77-8.18; $P < .05$). Similarly, as a continuous variable (per fL), MPV was also independently associated with 6-month mortality or MI (HR, 1.78; 95% CI, 1.43-2.22; $P < .05$).

Discrimination

The addition of MPV to a model containing the GRACE score improved the C statistic (0.747 vs 0.806) for predicting the combined end point of death or nonfatal MI in patients with ACS (Table 3).

The reclassification of patients with events and those without events is summarized in Table 4. For 11 (18%) patients with events, reclassification was more accurate when the model with MPV was used, whereas for 5 (8%) patients, it became less accurate. Among the participants without events, 70 (16%) were reclassified in a lower risk category and 49 (11%) were reclassified in a higher risk category. Overall, the reclassification was considered appropriate (the "new" risk prediction corresponded to the actual event category) in 16% (81 patients) of the whole population and inappropriate in 11% (54 patients). The net improvement in reclassification was

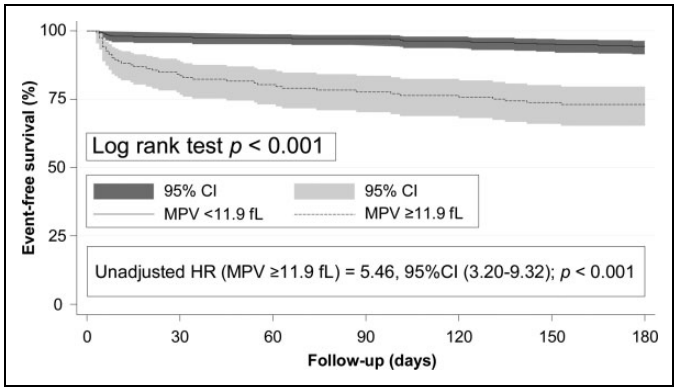

Figure 2. Event-free survival according to the MPV cutoff value (11.9 fL). MPV indicates mean platelet volume.

estimated at 0.15 ($P = .038$) after the addition of MPV, and the IDI was estimated as 0.06 ($P < .001$).

Global Model Fit

The addition of MPV to GRACE led to significant improvements in model performance, as evaluated by likelihood ratio tests ($P < .001$; Table 3).

Discussion

The present study showed that an elevated MPV at admission in patients with ACS was an independent predictor of the 6-month combined end point of death or nonfatal MI. Moreover, combining this information with the GRACE risk score improved the discriminatory capacity of the model and allowed reclassification of a substantial proportion of the study population into different risk categories.

The prognostic significance of admission MPV in patients with coronary artery disease has been previously explored. In a study of 1082 patients with acute MI, a higher MPV was associated with an increased risk of the composite end point of heart failure, ACS recurrence, and death before discharge.[15] Huczek et al showed that an elevated MPV was a strong independent predictor of 6-month mortality in 398 patients with STEMI.[16] More recently, Taglieri et al reported that MPV was independently associated with the composite end point of death and recurrent MI in 1041 patients with non-ST-segment elevation ACS for up to 1 year.[5] Goncalves et al demonstrated that MPV was an independent predictor of 1-year mortality or MI in 1432 patients undergoing PCI.[6] These findings are corroborated by the majority of studies assessing the association between MPV and clinical outcomes in patients with STEMI[17,18] or non-ST-segment elevation ACS[19,20] as well as those undergoing PCI.[4] Importantly, in a cohort of 39 531 individuals from the Copenhagen General Population Study,[21] MPV was found to be the strongest independent predictor of acute MI over a 4-year study period when compared with known cardiovascular risk factors. The accumulated data suggest that MPV is a useful prognostic biomarker in patients with coronary artery disease. However, in the entire clinical spectrum of ACS, few studies have assessed the prognostic significance of MPV during a 6-month follow-up. Additionally, statistical significance in a multivariate analysis is not a sufficient indicator of a clinically relevant improvement in prognostic assessment.[12] Therefore, our study investigated the mid-term prognostic significance of MPV in patients with ACS and determined its additional prognostic value in relation to a comprehensive predictor model.

Our results confirmed that MPV could independently predict 6-month mortality or nonfatal MI in patients with ACS, regardless of the method of correction. Although the relationship between increased MPV and prognosis in patients with ACS is not clearly understood, some explanations have been proposed. First, activated platelets play a key role in the pathogenesis of ACS, including STEMI, NSTEMI, and UA. The MPV, as an accurate indicator of platelet size, can indicate whether platelets are activated.[3] Hyperactive platelets can produce many prothrombotic factors, such as thromboxane A_2, P selectin, β-thromboglobulin, and adhesion molecules.[3] Recently, investigators have shown that MPV is the greatest contributor to increased levels of integrin $\alpha_{IIb}\beta_3$ (a platelet receptor) in normal individuals and patients with ACS.[22] Thus, a high MPV can indicate a major risk of atherothrombotic vascular events. Indeed, a case–control study found that patients with larger platelets on admission had a higher incidence of early stent thrombosis and that a larger platelet size was correlated with future residual platelet reactivity despite dual antiplatelet therapy (aspirin and clopidogrel).[23] Second, an increased number of reticulated platelets is correlated with an elevated MPV in patients with ACS.[24] Previous studies have shown that reticulated platelet counts are highest in patients in whom platelet aggregation is not well inhibited by dual antiplatelet therapy.[24] A further prospective study found that MPV was an independent predictor of platelet response to clopidogrel in 276 consecutive patients with acute MI undergoing PCI.[25] In our study, patients pretreated with clopidogrel had a lower MPV. Similar results were reported in a study of 1432 patients undergoing PCI.[6] These findings suggested that there was a correlation between MPV and responsiveness to antiplatelet therapy, which has been correlated with short- and long-term ischemic outcomes after PCI.[1,2] Third, platelet reduction occurs in ACS secondary to platelet consumption, and in an attempt to maintain hemostasis, newer platelets are produced from megakaryocytes with increased expression of prothrombotic RNA in the bone marrow.[3] The resulting production of large, dense, hyperactive platelets might cause thrombosis of a coronary artery.[3] Experiments in animal models have also shown that endothelial dysfunction can cause short- or long-term, low-grade increases in platelet destruction.[26] This pathological process would mimic hemorrhage, and the slow response to this hemorrhage would result in a greater number of megakaryocytes with higher ploidy and cytoplasmic volume.[3] In accordance with previous studies,[5,20] we also observed an inverse correlation between MPV and platelet count, and there was no significant association between platelet count and adverse events. This result supports the

Table 2. Univariate and Multivariate Cox proportional Hazards Analyses for the Study End Points.

Variables	Univariate HR (95% CI)	P^a	Multivariate HR (95% CI)	P^a
Age, per 10 years	1.03 (1.01-1.06)	**.018**	1.05 (1.02-1.09)	**<.001**
Male sex	1.17 (0.61-2.24)	.642		
Smokers	1.38 (0.83-2.31)	.215		
Type 2 diabetes	0.78 (0.40-1.53)	.461		
Hypertension	2.10 (1.25-3.55)	**.005**	1.95 (1.07-3.56)	**.031**
Dyslipidemia	0.65 (0.38-1.11)	.113		
Previous myocardial infarction	1.25 (0.74-2.14)	.407		
SBP, per mm Hg	0.98 (0.97-0.99)	**.017**		
Heart rate, per bpm	1.01 (0.99-1.03)	.480		
Creatinine, per 88 μmol/L	1.02 (1.01-1.03)	**.005**		
Killip class $\geq$ 2	5.71 (3.45-9.45)	**<.001**	3.63 (2.06-6.38)	**<.001**
Cardiac arrest at admission	8.63 (2.10-35.52)	**.003**		
ST-segment deviation	2.63 (1.48-4.65)	**.001**		
Elevated cardiac marker	2.09 (1.23-3.54)	**.006**		
LVEF, per %	0.96 (0.94-0.98)	**<.001**		
Prior use of clopidogrel	0.76 (0.37-1.54)	.442		
Prior use of β-blocker	0.70 (0.37-1.31)	.258		
STEMI	2.09 (1.24-3.53)	**.006**		
WBC, per 1000 cells/mm^3	1.11 (1.01-1.22)	**.035**		
Hemoglobin, per g/L	0.99 (0.98-1.00)	**.065**		
Platelet count, per 1000 cells/mm^3	1.00 (0.99-1.01)	.791		
MPV $\geq$ 11.9 fL	5.46 (3.20-9.32)	**<.001**	4.14 (2.36-7.27)	**<.001**
MPV (per fL)	1.82 (1.48-2.23)	**<.001**	1.66 (1.32-2.09)	**<.001**

Abbreviations: SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; WBC, white blood cell count; MPV, mean platelet volume; CI, confidence interval; HR, hazard ratio.
[a] Boldface values represent statistically significant values.

Table 3. Additional Contribution of MPV to the GRACE Score for the Prediction of 6-Month Mortality or Myocardial Infarction.

	Model			
	GRACE		GRACE + MPV	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
GRACE score	1.02 (1.01-1.02)	<.001	1.02 (1.01-1.02)	<.001
MPV $\geq$11.9 fL	–		4.76 (2.77-8.18)	<.001
MPV, per fL	–		1.78 (1.43-2.22)	<.001
Discrimination				
C statistic	0.747 (0.658-0.835)	<.001	0.806 (0.732-0.880)	<.001
Global model fit				
Likelihood ratio chi-square	90.79	<.001	84.93	<.001
Likelihood ratio chi-square test				<.001

Abbreviations: MPV, mean platelet volume; GRACE, Global Registry of Acute Coronary Events; CI, confidence interval; HR, hazard ratio.

hypothesis that platelet activity is a more sensitive indicator of "vulnerable patients" than platelet number.[3] Additionally, a study by Ozdemir et al demonstrated that MPV was closely associated with increased sympathetic activity in patients with acute MI.[27] Indeed, in the present study, a lower MPV was found in patients pretreated with β-blockers.

The second finding of our study was the ability of the MPV to improve the prognostic value of the GRACE risk score. To our knowledge, the study of Wan et al[28] is the only study to date which evaluated the additive value of MPV in relation to the GRACE score in patients with ACS. In that study, there was a modest increase (0.11) in the C statistic for predicting 52-month adverse cardiovascular disease events; however, no reclassification analysis was reported. In contrast, we created optimal conditions in which the GRACE score could predict outcome by utilizing the follow-up interval (admission to 6 months) and the combined end point (death or nonfatal MI) for which the score was developed. Moreover, the risk reclassification after the introduction of MPV to the GRACE score demonstrated that a substantial proportion of patients were better categorized, and the reclassification was considered adequate in 16% of the population. A weak correlation between the MPV and GRACE risk score was also found in our study, which suggests that they both predict risk.

Table 4. Reclassification Across Risk Thresholds by MPV.[a]

	GRACE adjusted by MPV			
	<12%	12%-21%	>21%	All
Patients without events				
GRACE score				
<12%	275 (61)	18 (4)	7 (2)	300 (67)
12-21%	56 (13)	31 (7)	24 (5)	111 (25)
>21%	2 (0)	12 (3)	23 (5)	37 (8)
All	333 (74)	61 (14)	54 (12)	448 (100)
Patients with events				
GRACE score				
<12%	13 (21)	2 (3)	2 (3)	17 (28)
12-21%	1 (2)	1 (2)	7 (11)	9 (15)
>21%	1 (2)	3 (5)	31 (51)	35 (57)
All	15 (25)	6 (10)	40 (65)	61 (100)

Abbreviations: MPV, mean platelet volume; GRACE, Global Registry of Acute Coronary Events.

[a]The number (percentage) of patients in each risk category is shown. MPV was modeled as a continuous variable. Patients were divided into subgroups that did or did not reach the end point of 6-month mortality or nonfatal myocardial infarction. Reclassifications in the appropriate or inappropriate directions are highlighted in black and gray, respectively. The net reclassification improvement was estimated at 0.15 ($P = .038$).

Another platelet volume index, platelet distribution width (PDW), measures the variability in platelet size and is a marker of platelet activation.[17,29] Several retrospective analyses have suggested that an elevated PDW on admission was associated with increased rates of thrombolysis failure[29] and in-hospital major adverse cardiac events[17] in patients with STEMI. In patients with coronary artery disease, PDW was also found to predict the presence of chronic coronary total occlusions.[30] However, few data exist regarding whether PDW may improve the prognostic value provided by MPV in patients with ACS. We do not have detailed data on PDW; therefore, we were unable to explore the difference between MPV and PDW. Prospective studies with larger numbers of patients are needed to address this question.

Recently, Akin et al reported that atorvastatin significantly decreased MPV levels and platelet count in patients with hypercholesterolemia.[31] Choi et al showed that a high MPV level without statin treatment worsened cardiac death or event-free survival in patients with ACS.[4] These findings suggested a possible role for statins in the inhibition of increased platelet size and its resulting sequelae. We did not find any association between MPV and previous statins treatment; the reason for this could be that the sample size of patients treated with statins was small. Further studies will be required to clarify the biological mechanism underlying the effect of statins on MPV.

Limitations

First, the study was retrospective in nature, and it had potential sources of bias. Although we attempted to correct our results for known prognostic factors using multivariate analysis, the influence of other confounding factors cannot be excluded. Second, we used a cutoff point of 11.9 fL, which was established by ROC curve analysis, whereas others have used different cutoff points ranging from 8.2 to 11.9 fL.[4,5,19,28] The MPV values are likely to be affected by environmental conditions such as altitude[32] in addition to the patients' own conditions; thus, some variation in these cutoff points might be expected. Third, given that the GRACE score was derived from a sample population with both ST-segment elevation and non-ST-segment elevation ACS and that the subdivision of our data into several smaller subgroups would cause a lower event rate, we did not perform a subgroup analysis using different population groups or separate end points. Fourth, the patient population was relatively small.

Conclusion

An elevated MPV on admission was an independent predictor of 6-month mortality or nonfatal MI in patients with ACS. The inclusion of MPV into the GRACE risk score could allow improved risk classification of patients with ACS at admission. Large, prospective, multicenter registries are necessary to confirm our results.

Declaration of Conflicting Interests

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