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Mean Platelet Volume Addition in Grace Score as Predictor of Major Cardiovascular Events during Treatment among Acute Coronary Syndrome Patients

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Abstract : Background: Acute Coronary Syndrome (ACS) is a term used to describe symptoms caused by Acute Myocardial Infarction (AMI). At present, risk stratification is carried out with the use of a Global Registry of Acute Coronary Events (GRACE) score as a validated predictor for cardiovascular events among ACS patients. Mean platelet volume (MPV) is an accurate marker of platelet size and can be considered that to be added to the GRACE score to increase the predictive value of the occurrence of major cardiovascular events (MACE). This study aims to seek the comparison between GRACE score independently and GRACE score with the addition of MPV values in predicting major cardiovascular events during in-hospital care in ACS patients.
Methods: This study was ambispective cohort study of 219 ACS patients from November 2017 to November 2018. GRACE scores and MPV values were calculated and mace was observed during hospital treatment. An analysis was performed to see the role of MPV addition to GRACE scores in predicting MACE.
Results: MPV values and GRACE scores were found to be increased in patients with MACE compared with those who did not. Area under curve (AUC) on the ROC curve obtained 0.786 (95% CI: 0.717-0.855, p<0.001) when the GRACE score was calculated independently, and increased to 0.810 (95% CI: 0.620-0.775, p<0.001) with addition MPV which indicates a combination of MPV and GRACE score increases predictive value.
Conclusion: The addition of the MPV value to the GRACE score provides a higher predictive value in predicting MACE in ACS patients in hospital care.
Keyword : GRACE, MPV, ACS.

Background

Cardiovascular disease is the number one cause of mortality globally. It is estimated that around 17.7 million people died of cardiovascular disease in 2015 which showed 31% of global mortality. Almost half of cardiovascular death are the result of acute myocardial infarction (AMI).[1,2,6,19]

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Acute coronary syndrome (ACS) is a term used to describe symptoms caused by AMI. This syndrome is a series of conditions ranging from unstable angina pectoris to the incidence of extensive acute myocardial infarction, which is an irreversible condition of heart muscle necrosis. [3,4,17]

ACS consists of acute myocardial infarction with ST segment elevation (STEMI), acute myocardial infarction with non ST segment elevations (NSTEMI), and unstable angina pectoris (UAP). In addition to mortality, patients with SKA also have a high risk of experiencing major cardiovascular events (MACE) during treatment. These events include rehospitalization, recurrent ACS, heart failure and arrhythmias.[2,5,7,9]

Platelets are closely related to the activation and coordination of the endothelium, regardless of their role in the systemic inflammatory response.[4] Mean Platelet Volume (MPV) is the average size of platelets in peripheral blood circulation and is one of the important biological variables of platelets. MPV is a marker of platelet function and is associated with platelet activity which includes the aggregation and release of thromboxane A2, platelet factor 4, and thromboglobulin. MPV represent reactivity of platelets. In addition, MPV was found increasing significantly in groups with a high risk of cardiovascular disease, such as smoking, hypertension, diabetes, dyslipidemia, and obesity.[10,12,13,20]

At present, risk stratification is carried out with the use of Global scores Registry of Acute Coronary Events (GRACE) as a validated predictor for cardiovascular events in ACS patients. However, laboratory variables in these scores are limited to examination of serum creatinine and troponin. Therefore, it is considered that other variables such as MPV, which describe other pathophysiological aspects of ACS, can provide additional information.[13,15,17,20]

This study aims to seek the comparison between GRACE scores independently and GRACE scores with the addition of MPV values in predicting major cardiovascular events during in-hospital care among ACS patients. This study aims to seek the comparison between GRACE scores independently and GRACE scores with the addition of MPV values in predicting major cardiovascular events during in-hospital care among ACS patients.

Methods

This study is an ambispective cohort study conducted on ACS patients treated at the Cardiovascular Care Unit and integrated heart care ward at H. Adam Malik Hospital Medan from November 2017 to November 2018. The subjects of the study were 219 people who met the inclusion and exclusion criteria. The inclusion criteria were ACS patients, who underwent MPV examination and supporting examinations for GRACE score assessment. While the exclusion criteria ACS patients with advanced stage disease, kidney failure, cancer, valvular heart disease, stroke, atrial fibrillation, post cardiac resuscitation, peripheral arterial disease, and other vascular diseases. This study requested approval from the Health Research Ethics Committee of the Medical Faculty of the University of North Sumatra and the Ethics Committee of the General Hospital. H. Adam Malik Medan.

In ACS patients whom meet the inclusion and exclusion criteria, an ECG, chest radiograph, and blood laboratory was performed. Blood samples for diagnosis were taken when the patient enters the hospital, except for lipid profiles and fasting blood sugar, which were taken after the patient has been fasted for around 8 hours. Then the calculation of the GRACE score and the MPV value were carried out and observed during treatment at the hospital. Optimal and standard medical therapy is given to all patients during treatment. The selection of reperfusion measures was carried out according to the clinical assessment of the respective responsible physician. Then the MACE was observed during treatment.

All data in this study were processed using SPSS. Categorical variables were presented by number or frequency (n) and percentage (%). Numerical variables were presented with mean with standard deviations for normally distributed data. Test of normality were conducted using the Kolmogorov-Smirnov test. Comparison between the two groups were performed using the chi square test. To see the correlation of the two categorical variables, the Spearman test was used. Multivariate analysis of numerical independent variables with categorical dependent variables was tested by logistic regression. Score discrimination power using ROC curve value analysis. Variables were considered statistically significant if the p value <0.05.

Result

There were 219 patients who had met the inclusion and exclusion criteria. The characteristics of the research subjects are shown in Table 1. Around 175 patients (79.9%) were male and 44 were female (20.1%) with a median age of 56 years. Based on the risk factors possessed by the study subjects, smoking history was the highest approximately around 147 patients (67.1%), followed by hypertension in the second place around 63.0%, dyslipidemia around 53.9%, and 41.6% had a history of diabetes mellitus . Based on the patient's body mass index, the median BMI of the patient is 24.0 which can be categorize as overweight.

Based on the Mean Platelet Volume (MPV) results, the median was 10.1 fL. Based on the cut-off research obtained in this study, 88 patients (40.2%) had MPV <9.85 fL and 131 patients (59.8%) had MPV ≥9.85 fL. Based on the GRACE score, around 78.1% patients had a score of <140 and 21.9% had a GRACE score ≥140 with a median score of 110.5, and median Killip class 1.

Based on the patient's hemodynamic status, the median heart rate was 84.5 times per minute, the median systolic blood pressure was 120 mmHg, and the median diastolic blood pressure was 80 mmHg. Based on the complete blood count, the median hemoglobin level of the patient was 14.15 g / dl, the median number of leukocyte counts was 13,030 cells / mm3, the mean and standard deviation of platelet counts was 242,307 ± 67,213 cells / mm3. The kidney function resulted as median creatinine 1.09 mg / dl. Blood glucose examination showed, median fasting blood glucose was 123 g / dl, median 2 hours post prandial was 156 g / dl, and median HbA1c level was 6.5 g / dl. From lipid profile, median LDL level was 120 g / dl and median level HDL was 39 g / dl.

Cardiac enzyme biomarkers showed median troponin of 0.44 ng / ml, while the median CKMB enzyme was 53.0 ng / ml. From echocardiographic examination, ejection fraction ≤40% was found in 110 patients (50.2%) while patients with EF ≥40% was 109 patients (49.8%).

There was 103 STEMI patients (47.0%), 92 NSTEMI patients (42.0%), and 24 UAP patients(11.0%). Among 219 ACS patients, around 53 of them had MACE. The most frequent MACE found was acute heart failure around 49 patients, 35 patients with cardiogenic shock, 25 patients with arrhythmias.

Table 1. Baseline Characteristic

Characteristics	**n=219**
Gender, n (%)	
Male	175 (79.9%)
Female	44 (20.1%)
Age (years, Median (Min-Maks)	56 (29 – 88)
Risk Factors, Yes, n (%)	
Hypertension	138 (63.0%)
Diabetes Melitus	91 (41.6%)
Dislipidemic	118 (53.9%)
Smoker	147 (67.1%)
BMI, Median (Min – Maks)	24.0 (17.48 – 35.56)
MPV (fL), Median (Min – Maks)	10.1 (8.0 – 12.9)
MPV Category, n (%)	
<9.85	88 (40.2%)
≥9.85	131 (59.8%)
GRACE Score, Median (Min-Maks)	110.5 (62 – 215)
GRACE Score Category, n (%)	
<140	171 (78.1%)
≥140	48 (21.9%)
Killip Class, Median (Min – Maks)	1 (1 – 4)
Haemodynamic	
Heart Rate (x/minutes), Median (Min-Maks)	84.5 (34 – 120)
SBP (mmHg), Median (Min-Maks)	120 (70 – 210)

DBP (mmHg), Median (Min-Maks)	80 (40 – 190)
Laboratory Results	
Hb (g/dl), Median (Min-Maks)	14.15 (7.50 – 16.4)
Leukocyte (/mm^3), Median (Min-Maks)	13,030 (4,060 – 44,240)
Platelet (/mm^3), Mean±S.D	242,307±67,213
Ceatinine (mg/ml), Median (Min-Maks)	1.09 (0.40 – 6.35)
Fasting BG (g/dl), Median (Min-Maks)	123 (44.0 – 482.0)
2hPP BG (g/dl), Median (Min-Maks)	156 (90.0 – 527.0)
HbA1c, Median (Min-Maks)	6.5 (2.90 – 15.1)
LDL, Median (Min-Maks)	120 (12 – 332)
HDL, Median (Min-Maks)	39 (5 – 150)
Troponin (ng/ml), Median (Min-Maks)	0.44 (0.00 – 2.80)
CKMB (ng/ml), Median (Min-Maks)	53.0 (0.0 – 715)
Ejection Fraction, n (%)	
<40%	110 (50.2%)
≥40%	109 (49.8)
ACS, n (%)	
NSTEMI	92 (42.0%)
STEMI	103 (47.0%)
UAP	24 (11.0%)
MACE, Yes n (%)	53 (24.2%)
Acute Heart Failure	49 (22.4%)
Cardiogenic Shock	35 (16.0%)
Arhytmias	25 (11.4%)
In hospital death	21 (9.6%)

Characteristics Relationship of Research Subjects and MACE

Bivariate analysis was performed to determine the relationship or difference in mean between the characteristics of the research subjects towards MACE occurrence. A statistically significant relationship ($p < 0.05$) was found among reseach subject in terms of Killip class, heart rate, blood pressure, haemoglobin, leukocytes, troponin, CKMB, ejection fraction, and ACS diagnosis.

Table 2 Correlation between Subject Studies Characteristic and MACE

Characteristics	**MACE**	***P***	
	Yes (n=53)	**No (n=166)**	
Gender			
Male	41 (23.4%)	134 (76.6%)	0.400
Female	13 (29.5%)	31 (70.5%)	
Age (years)	58.72±11.26	56.62±9.61	0.371
Risk Factors, Yes			
Hypertension	31 (57.40%)	23 (42.59%)	0.267
Diabetes Melitus	24 (44.4%)	30 (55.5%)	0.527
Dislipidemic	24 (44.4%)	30 (55.5%)	0.109
Smoker	39 (72.22%)	15 (27.78%)	0.663
BMI	23.82±2.761	24.30±3.212	0.515
Killip Class	2.77±1.16	1.28±0.52	**<0.001**
Haemodynamic			
HR, x/minutes	96.53±35.73	90.90±82.89	**0.004**
SBP, mmHg	103.15±25.68	131.95±22.69	**<0.001**
DBP, mmHg	67.96±15.09	82.92±15.46	**<0.001**

Laboratory Results			
Haemoglobin, g/dl	13.35±2.10	16.71±17.80	**0.001**
Leukocytes (/mm^3),	15,390±5,299	14,081±5,726	**0.042**
Platelet (/mm^3x10^3),	245.3±78.89	241.2±63.13	0.696
Creatinin, mg/dl	1.41±0.922	1.25±0.75	0.118
Fasting BG, g/dl	154.40±76.810	143.23±68.136	0.292
2hPP BG, g/dl	196.72±93.15	183.03±82.14	0.398
HbA1c, g/dl	7.02±1.94	7.11±1.97	0.901
LDL, g/dl	139.38±39.52	129.20±38.90	0.074
HDL, g/dl	43.01±19.24	40.19±13.07	0.585
Troponin, ng/ml	0.88±0.71	0.65±0.65	**0.029**
CKMB, ng/ml	128.74±121.92	103.17±127.12	**0.041**
Ejection Fraction			
<40%	43 (79.62%)	67 (61.8%)	**<0.001**
≥40%	11 (10.1%)	98 (89.9%)	
ACS Diagnosis			
NSTEMI	16 (29.62%)	76 (46.06%)	**0.009**
STEMI	35 (64.81%)	68 (41.21%)	
UAP	3 (5.55%)	21 (12.72%)	

Table 3 presented the relationship between MPV and GRACE scores and correlation of MPV and GRACE scores towards MACE were showed in table 4. Statistically significant mean differences were found between the two groups with p value<0.05.

Table 3 Correlation between MPV and Grace Score

Characteristics	**MPV Value**			***p****
	<9.85	**≥9.85**		
GRACE Score				
<140	73 (48.14%)	98 (87.8%)	171	0.153
≥140	15 (51.85%)	33 (12.12%)	48	
Total	88	131	219	

Table 4 Correlation of MPV and GRACE Scores towards MACE

Characteristics	**MACE**	***p****	
	Yes (n=53)	**No (n=166)**	
MPV (fL)	10.64±0.931	9.96±1.070	**<0.001**
<9.85	11 (20.37%)	77 (46.67%)	**0.001**
≥9.85	43 (79.62%)	88 (53.33%)	
GRACE Score	139.31±31.76	105.91±26.17	**<0.001**
GRACE Score			
<140	26 (48.14%)	145 (87.8%)	**<0.001**
≥140	28 (51.85%)	20 (12.12%)	

Logistic Regression Analysis Predicts MPV and GRACE Score towards MACE

Risk factors with p value <0.25 were included in multivariate analysis. The analysis was carried out using the Backward Stepwise method, five stages had been carried out, backward stepwise which had no meaningful value could be removed until the last stage of the most significant predictive value were the first stage analysis (Table 5) and second stage (Table 6).

From The MPV , GRACE score, MPV value ≥11.2, GRACE score ≥140, and the combination of interaction between GRACE score and MPV analyzed in the first stage, MPV addition to GRACE score was statistically significant to predict MACE but not to the GRACE score that were combined with the MPV. The second stage analysis was continued by removing the non-significant variable, that was the combined GRACE score with the MPV. Table 6 showed that MPV and GRACE Score was independently significant towards MACE occurence.

Table 5 First Stage Logistic Regression Analysis

Variable	B	Wald	*p*	OR	CI 95%
MPV ≥9.85 (vs <9.85)	1.311	6.241	**0.012**	3.709	1.326-10.373
GRACE Score ≥140 (vs <140)	2.205	9.869	**0.002**	9.067	2.291-35.875
GRACE Score*MPV	-0.212	0.065	0.789	0.809	0.159-4.118
Constanta	0.074				

Table 6 Second Stage Logistic Regression Analysis

Variabel	B	Wald	p	OR	CI 95%
GRACE score ≥140 (vs <140)	2.054	29.800	**<0.001**	7.796	3.730-16.297
MPV value ≥9.85 (vs <9.85)	1.228	9.274	**0.002**	3.413	1.549-7.520
Konstanta	0.074				

GRACE Score and MPV ROC Analysis Towards MACE Occurrence

ROC analysis was used to assess the relationship between GRACE score and MPV towards the MACE occurrence. It was found that the MPV has a cut off point of 9.85 fL with a sensitivity of 79.2%; specificity of 46.4% (Table 7 and Figure 1) with a weak correlation towards MACE ($p < 0.05$). An independent increase in the GRACE score AUC was 0.786 and increased to 0.810 with the addition of the MPV to the GRACE score (Figure 2).

Table 7 AUC and MPV Cut Off

Parameter	AUC	Cut Off	*p*	95%CI
MPV	0.698	9.85 Sensitivity 79.2% Spesificity 46.4%	0.001	0.620 – 0.775

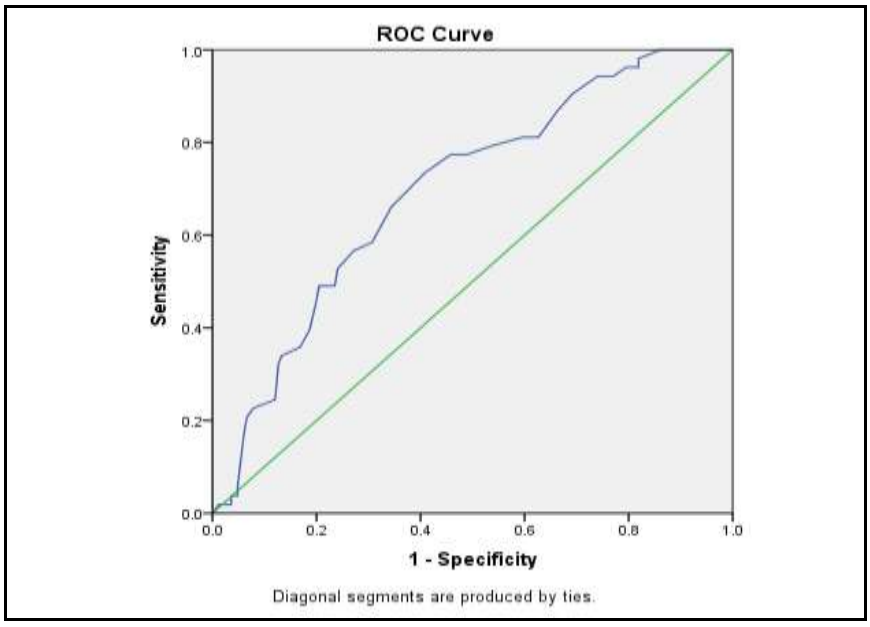

Figure 1 AUC and MPV Cut Off

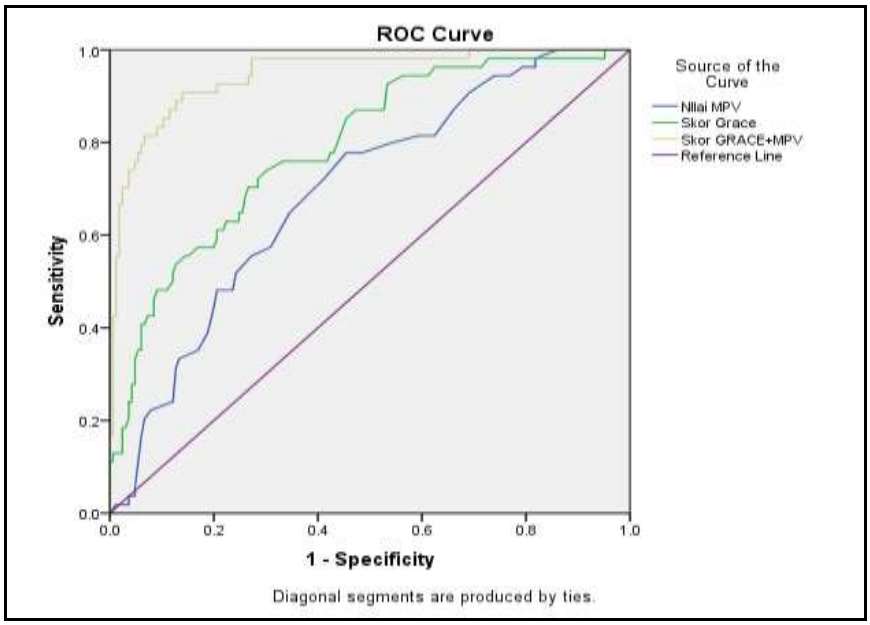

Figure 2 AUC and GRACE and MPV independent cut-off point and GRACE plus MPV

Discussion

Of the 219 research subjects various parameters were found to have a statistically significant relationship with MACE ($p < 0.05$). They were TIMI scores, Killip classes, heart rate, systolic and diastolic blood pressure, haemoglobin levels, leukocytes, troponin, CKMB, ejection fraction, and ACS diagnosis.

No significant relationship between MPV and GRACE score found. This findings was different from the studiy by Wan et al., which showed that GRACE scores correlates significantly and positively to MPV . In addition, MPV were found to have statistically significant differences in the subject group with and without MACE. This is in line with the research conducted by Mumpuni et al., showed that high MPV (> 8.85 fL) had a higher incidence of MACE compared with low MPV (≤8.85 fL) in ACS patients. Relative risk for MACE was 1.65 times more risky in patients with higher MPV.

The relationship between GRACE scores and MACE was also analyzed and a significant difference was found between the mean and GRACE score categories for MACE. Similar results were noted from Wan et al., in his study, with mean ± SD 187.1 ± 53.4 in the MACE group and 152.3 ± 48.6 in the group without MACE with p <0.001. The study states that both MPV and GRACE scores can independently predict cardiovascular events.

Logistic regression was performed and it was found that the MPV and GRACE score were independently a strong predictors of the MACE occurrence. However, it was found that the combination of GRACE scores and MPV did not correlate significantly with MACE. A 9.85 fL MPV cut off was obtained with a sensitivity of 79.2% and specificity of 46.4%. Different numbers of MPV were obtained by Niu et al., in which the cut-off of MPV was 11.9 fL with a sensitivity of 62% and specificity of 74%.

To assess whether a combination of MPV for GRACE scores can improve predictions of cardiovascular events, an ROC analysis was performed on the combination. An independent AUC GRACE score was found of 0.786 (95% CI 0.717−0.855, p <0.001) and increased to 0.810 (95% CI 0.744−0.876, p <0.001) with the MPV score on the GRACE score. The results of this study was in line with Wan et al. study, who also obtained an AUC increase of 0.70 in the GRACE score to 0.85 in combination (95% CI 0.81−0.90, p <0.001). However, there were differences in which this study discusses cardiovascular events during treatment and Wan et al. discuss long-term cardiovascular events.

In this study the MPV was significantly higher in the MACE group. In a study involving 1716 patients, in which MPV was assessed six months after AMI, it was found that MPV was an independent predictor of both recurrent and mortality caused by AMI at a two-year follow-up. MPV was independent and more predictive than other variables, such as blood pressure, cholesterol, or smoking.[14]

Limitation

Larger number of patient are needed to get a more representative picture of adding MPV values to GRACE scores. Research subjects observation in this study was carried out only as long as the subject was hospitalized. It is expected that short-term and long-term monitoring of the addition of MPV to GRACE scores can be done in further research.

Conclusion

MPV and GRACE scores were respectively independent predictors of MACE among ACS patients during hospitalization. There was no strong relationship between the combination of GRACE scores and MPV with the occurrence of MACE. The addition of the MPV value to the GRACE score provides a higher predictive value in predicting MACE among ACS patients in hospital care.

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