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Association Between Mean Platelet Volume (MPV) with Major Adverse Cardiovascular Events in Acute Coronary Syndrome during Hospitalization

Hasanah Mumpuni, Hariadi Hariawan, Lucia Krisdinarti

Department of Cardiology and Vascular Medicine,
Faculty of Medicine Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia

Abstract

Background: Platelets play a central role in the pathogenesis of acute coronary syndrome with various clinical manifestations of unstable angina pectoris, myocardial infarction with ST segment elevation, and myocardial infarction without ST segment elevation. Mean platelet volume (MPV), the average size of platelets in blood obtained from routine blood tests, reflects the activation of platelets. Previous study revealed that higher MPV showed a higher thrombotic potential, by increasing the platelet activation, secretion of tromboxan A2 and the expression of glycoprotein Ib and IIb/IIIa receptors. This study aims to determine whether the MPV may predict the major cardiovascular events in patients with acute coronary syndrome.
Metode: We perform a retrospective cohort study involving 372 patients with acute coroanry syndrome who admitted to Intensive Cardiac Care Unit Dr. Sardjito Hospital Yogyakarta. The research is conducted between January 2009 to January 2011, comprising 180 (48.3%) STEMI patients, 87 (23.3%)NSTEMI patients and 105 (28.4%) unastable angina patients. Subjects are further grouped as those with high MPV and low MPV. MPV measurement is obtained on routine blood tests of those patients.The major adverse cardiovascular events are cardiovascular death, non fatal reinfarction, stroke, acute heart failure and cardiogenic shock.
Result: Cut-off value of MPV in this study is 8.85 fL determined with ROC curve analysis. The major adverse cardiovascular events is significantly higher in those with MPV >8.85 fL compared with those with the MPV ≤8.85 fL (incidence: 28.4% vs. 18.9%, p = 0.034), with the relative risk (RR) 1.65, 95% CI 1.037-2.783. The mean MPV in patients with major adverse cardiovascular events was significantly higher as compared to those without major adverse cardiovascular events (9.506 ± 1.76 fl vs.8.96 ± 1.45 fl, p = 0.001).
Conclusion: Mean platelet volume (MPV) are associated with major adverse cardiovascular events in acute coronary syndrome. The high MPV may be considered as a predictor of major cardiovascular events in patients with acute coronary syndrome.

Keywords: acute coronary syndrome, mean platelet volume, major adverse cardiovascular events.

Introduction

Coronary heart disease as an underlying cause of ischemic heart disease can be manifested as asymptomatic, stable angina pectoris, and acute coronary syndrome. The spectrum of acute coronary syndrome can be unstable angina, ST-elevation acute myocardial infarction (STEMI) and non STEMI. The pathogenesis of acute coronary syndrome is erosion, fissure or ruptur of unstable atherosclerotic plaque, which is followed by platelet activation and trombus formation in various degree of severity. Eventually, this event can be clinically manifested shortly.[1]

It has been known that platelet has a central role in initiation and propagation of acute coronary syndrome. It starts with platelet activation and followed by platelet-endothel adhesion, platelet aggregation, coagulation cascade activation and platelet-fibrin plug formation. The formation will reduce or block coronary artery lumen and potentially cause microinfarction and macroinfarction of distal myocardia.[2]

Platelet is a blood element which is heterogenous in its size, shape, density and reactivity. The changes in these parameters

associate with clinical manifestation of acute coronary syndrome as a precipitating and propagation factor. Mean platelet volume (MPV) is average platelet size in circulation and becomes one important biological variable. Large platelet has higher thrombotic potency as compared with the small ones. Large platelet has higher density, faster collagen aggregation, higher thromboxan A2 concentration and increased glicoprotein Ib and IIb/IIIa receptor expression.[3]

This research is performed to investigate whether high MPV as a biomarker of platelet activation in patients with acute coronary syndrome in early phase of admission is beneficial to predict the worsening clinical condition of patients under acute treatment of acute coronary syndrome. The worsening clinical condition includes major adverse cardiovascular events, i.e. cardiovascular death, reinfarction, stroke, acute pulmonary edema and cardiogenic shock.

Currently, several markers both clinical or laboratory markers have been developed as a risk predictor in acute coronary syndrome. However, not a single measurement consistently shows a powerful predictor of clinical worsening of acute coronary syndrome. An MPV value, routinely measured in blood count measurement in all patients hospitalised for acute coronary syndrome, can be used as a marker for clinical worsening during intensive hospitalisaton for acute coronary syndrome.

Methods

Design and Subject

The design of this research is a retrospective cohort study. The research is performed in Dr. Sardjito Hospital, Yogyakarta, Indonesia. The subject of this study is patients with acute coronary syndrome undergoing intensive hospitalisation in ICCU of Dr. Sardjito Hospital, Yogyakarta, Indonesia between January 2009 and January 2011.

The inclusion criteria for subject enrollment are (1) patients with acute coronary syndrome which consist of those diagnose as STEMI, nonSTEMI and unstable angina, (2) male and female with age between 30 and 75 years old, (3) the data of MPV is accessible in medical record. The exclusion criteria are (1) the presence of clinical, laboratory and/or rontgenology evidence of chronic kidney disease need renal replacement therapy, severe congestive heart failure NYHA class III/IV, hepatic cirrhosis, severe infection or sepsis, chronic inflammation disease, thromboemboli disease and malignancy, (2) pregnancy and (3) incomplete variable data for analysis.

Measurement

The research is performed by examining medical records of the subjects. The medical records are containing patients with acute coronary syndrome hospitalised between January 2009 and December 2010. The data of the subjects were collected and recorded, i.e. years of age, gender, chest pain onset, history of disease of hypertension, diabetes mellitus, smoking, chronic inflammation disease, chronic kidney disease, 12-lead electrocardiogram, Killip class measurement, the interpretation of chest X ray and laboratory data. The laboratory data is hematology (leukocyte count, platelet count, MPV and platelet distribution width), biochemistry (liver function, renal function, glucose), electrolite, cardiac enzyme (CK-MB and troponin I) and lipid profile.

An MPV is measured from average size of platelets in circulation, readily available in routine hematology examination. The measurement of MPV is performed in the early hospital admission. Based on this MPV value, subjects are divided into two groups, i.e. group with high MPV and group with low MPV.

The clinical outcome is major adverse cardiovascular event during ICCU hospitalisation which consist of cardiovascular death, non

fatal reinfarction, stroke, acute heart failure and cardiogenic shock. Cardiovascular death is cardiac cause mortality such as profound cardiogenic shock, fatal arrhytmia or sudden death. Acute heart failure is indicated with the presence of acute pulmonary edema. Cardiogenic shock is determined by the presence of reduced systolic blood pressure (< 90 mmHg) and utilisation of inotropic/vasopressor drugs. Reinfarction is indicated by the presence of recurrent angina, ST segment elevation and increased cardiac enzyme during hospitalisation. The data of clinical outcome is recorded in the medical record.

Statistics Analysis

The baseline characteristics is presented in mean and standard deviation or median and interquartile range for continuous data. To compare the mean/median difference between two groups, Student T test or Mann Whitney U test is utilised. The cathegorical data is presented in proportion (percentage). To compare the proportion difference betwen two groups, the Chi square or Fisher exact test is utilised. Multivariable logistic regression analysis is performed to analyse several predictor variables. To determine the cut off value of MPV and allocate the groups, an ROC curve analysis is performed.

Result

From medical record, there are 372 subjects suitable the inclusion and exclusion criteria. They consist of 180 (48.3 %) subjects with STEMI, 87 (23.3 %) subjects with NSTEMI and 105 (28.4 %) subjects with unstable angina. The mean±standard deviation value of MPV in all subjects is 9.09±1.35 fL, with minimum value 5.5 fL and maximum value 13.4 fL.

To determine the impact of MPV on major adverse cardiovascular events, subjects are divided into two groups based on the cut off value. To determine the best cut off value, an ROC curve is constructed. The are under the curve of MPV is 0.598 , 95% CI 0.527 – 0.669. The cut off value is choosen for maximal sensitivity and specificity and the result is 8.85 fL with sensitivity 61.8 % and specificity 58.2 %. Figure 1 shows the result of ROC curve.

Based on the MPV value of 8.85 fL, subjects are divided into group with high MPV (MPV > 8.85 fL) and group with low MPV (MPV ≤ 8.85 fL).

Table 1 shows several variables that may influence the MPV value such as age, gender, haemoglobin level, leukocyte count, platelet count, systolic and diastolic blood pressure, diabetes mellitus, hypertension, smoking, dyslipidemia and blood glucose level. The variable that is significantly different is systolic blood pressure with mean value 125.6±26.0 mmHg versus 133.4±30.1 mmHg in subjects with high MPV as compared to subjects with low MPV. The risk factor for coronary heart disease, i.e. diabetes mellitus and smoking is greater in subjects with high MPV as compared to those with low MPV. In contrast, the proportion of hypertension and dyslipidemia is higher in subjects with low MPV. Glucose level is higher in subjects with high MPV if compared with subjects with low MPV, the value is 175.8±102.4 g/dL compared with

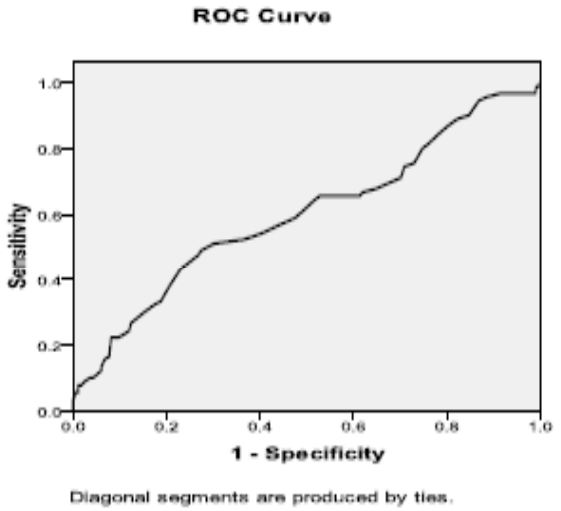

Figure 1. The ROC curve of MPV value in association with major adverse cardiovascular events. Area under the ROC curve is 0.598, 95% CI 0.527-0.669.

Table 1. The baseline characteristics data of the research subjects

Baseline Characteristics	High MPV (MPV > 8.85 fL) n = 208	Low MPV (MPV ≤ 8.85 fL) n = 164	p value
Male gender	157 (75.5 %)	118 (72 %)	0.441
Diabetes mellitus	65 (31.3 %)	37 (22.6 %)	0.062
Hypertension	115 (55.3 %)	98 (59.8 %)	0.387
Smoking	118 (56.7 %)	78 (47.6 %)	0.079
Dyslipidemia	121 (58.2 %)	99 (60.4 %)	0.430
Age	58.7±11.24	59.2±11.9	0.716
Systolic blood pressure	125.6±26.0	133.4±30.1	0.009
Diastolic blood pressure	75.5±17.3	78.2±15.9	0.132
Hemoglobin	13.84±1.83	13.69±1.87	0.464
Leukocyte count	11.67±4.59	11.71±4.96	0.941
Platelet	249.2±82.8	241.6±65.0	0.345
Glucose	175.8±102.4	163.0±82.8	0.238

163.0±82.8 g/dL, the p > 0.05.

The incidence of major adverse cardiovascular events during intensive hospitalisation in acute coronary syndrome is influenced by several factors. Platelet activation is one of factors that influence the adverse events. In this research, we analyse the value of MPV, which is a parameter of platelet activation, as a factor that may affect the incidence of major adverse cardiovascular events. The major adverse cardiovascular events in this research is cardiovascular death, reinfarction, stroke, cardiogenic shock and acute heart failure.

The role of the MPV value on major adverse cardiovascular events in 372 subjects with acute coronary syndrome which is allocated into two groups is presented in table 2. It shows that the major adverse cardiovascular event occurs in 90 (24.2 %) of 372 subjects. The proportion of MACE in the subjects with high MPV is significantly higher as compared to subjects with low MPV (26.4 % versus 16.9 % respectively, the p value of difference is 0.024).

Table 3 indicates that the proportion of major adverse cardiovascular events in subjects hospitalised with acute coronary syndrome in those with high MPV is 1.65 higher as compared with subjects with low MPV. The 95% confidence interval is 1.027 – 2.762 and the significance with p value = 0.024.

In table 1, it is shown that systolic blood pressure is the only variable that is significantly higher in subjects with high MPV as compared to subjects with low MPV. It indicates that systolic blood pressure may be a confounding factor taht influence the incidence of major adverse cardiovascular events. The regression analysis of this variable is shown in table 4.

The incidence of cardiovascular death in this research is 8.3 %, i.e. 31 out of 372 subjects. The incidence of death in subjects with high MPV is 10.6 % and in subjects with low MPV is 5.5 %.

Table 2. The 2x2 table showing the relation between MPV and major adverse cardiovascular event in patients with acute coronary syndrome

	With major adverse cardiovascular events n = 90	Without major adverse cardiovascular events n = 282	Total n = 372	p value
High MPV (> 8.85 fL)	59 (28.4 %)	149 (71.6 %)	208	0.034
Low MPV (≤ 8.85 fL)	31 (18.9 %)	133 (81.1 %)	164	
Total	90	282	372	

Table 3. The relative risk for developing major adverse cardiovascular events in subjects with MPV > 8.85 fL

	High MPV (> 8.85 fL)	Low MPV (≤ 8.85 fL)	RR (95% CI)	p value
Major Adverse Cardiovascular Events (%)	59 (28.4 %)	31 (18.9 %)	1.65 (1.037-2.783)	0.034

RR is relative risk

The significance p value is 0.076. The odd ratio for death is 2.027, 95% confidence interval is 0.911 – 4.55. Although the result shows no statistical significance, clinical significance shows that high MPV value has valuable role on predicting cardiovascular death twice as compared with subjects with low MPV (shown in table 5). Acute heart failure (acute pulmonary edema) occurs in 50 subjects (13.4 %). In subjects with high MPV the proportion of acute heart failure is 15.9 % and subjects with low MPV the proportion is 10.4 %. The p value for difference is 0.123. Although the statistical significance is not reached, the clinical significance is important because the odd ration is 1.631 (95 % confidence interval 0.631-3.046) (shown in table 5).

In the subset of subjects with acute myocardial infarction, both with STEMI and NSTEMI, the major adverse cardiovascular events occurs in 79 (29.6 %) out of 267 subjects with acute myocardial infarction. In subjects with high MPV, the proportion of major adverse cardiovascular events is higher as compared with subjects with low MPV, i.e. 33.85 % versus 23.9 % with p value for significance 0.061. The proportion of death during hospitalisation is 10.5 % in subjects with acute myocardial infarction. In subjects with high MPV the proportion of death is 13 % whereas in subjects with low MPV the proportion of death is 7.1 %, the p value for significance is 0.120. The incidence of acute pulmonary edema (acute heart failure) is also higher is subjects with high MPV as compared with subjects with low MPV, i.e. 16.2 % versus 12.4 % with p value for significance 0.199 (shown in table 6).

The incidence of major adverse cardiovascular events, cardiovascular death and acute pulmonary edema indicates higher in subjects with high MPV as compared to those with low MPV in the subset of patients with acute myocardial infarction. Although statistically not significance, clinical significance may be important especially in the incidence of death since it has twice risk in subjects with high MPVas compared to subjects with low MPV.

According to the pathophysiology of thrombosis, in subjects with STEMI the thrombosis is more severe as compared to nonSTEMI and unstable angina. The subanalysis in subjects with STEMI (n = 180 subjects) indicated that the incidence of major adverse cardiovascular events is 30.6 % (55 out of 180 subjects), death is 9.4 % (17 out of 180 subjects) and acute pulmonary edema is 17.2 % (31 out of 180 subjects). In subjects with high MPV, the incidence of major adverse cardiovascular events , cardiovascular death and acute pulmonary edema is higher

Table 4. Multivariable regression analysis of factors that influence the relation between MPV and major adverse cardiovascular events

	Univariate RR (95 % CI)	p value	Multivariable RR (95% CI)	p value
High MPV (> 8.85 fL) versus Low MPV (≤ 8.85 fL)	1.65 (1.037-2.782)	0.034	1.523 (0.921-2.518)	0.100
Mean systolic blood pressure			0.990 (0.981 – 0.999)	0.034

RR is relative risk

Table 5. The impact of high MPV on major adverse cardiovascular event, death and acute heart failure (pulmonary edema) in acute coronary syndrome

	High MPV (> 8.85 fL)	Low MPV (≤ 8.85 fL)	RR (95% CI)	P value
Major adverse cardiovascular events (%)	59 (28.4 %)	21 (18.9 %)	1.65 (1.027-2.783)	0.034
Death (%)	22 (10.65 %)	9 (5.5 %)	2.04 (0.911-4.553)	0.078
Acute pumonary edema (%)	33 (15.9 %)	17 (10.4 %)	1.63 (0.831-3.046)	0.123

RR is relative risk

as compared with subjects with low MPV, i.e. 32.7 % versus 27.54 %, p value 0.447 for major adverse cardiovascular events, 11.2 % versus 6.8 %, p value 0.325 for cardiovascular death and 17.8 % versus 16.4 %, p value 0.818 foe acute pulmonary edema. Although statistically not significance, clinically the difference is important especially in the incidence of major adverse cardiovascular events (shown in table 7).

The mean value of MPV in subjects with major adverse cardiovascular events is significantly higher as compared to subjects without major adverse cardiovascular events, i.e. 9.506±1.76 fL versus 8.96±1.45 fL with the significance p value 0.001. It indicates that mean value of MPV is significantly higher in subjects with high MPV. The mean value of MPV in subjects suffering from cardiovascular death is significantly higher as compared with subjects who survive, i.e. 9.945±1.77 fL versus 9.010±1.500 with the significance p value 0.003. The mean value of MPV in subjects with acute pulmonary edema is higher as compared to subjects without acute pulmonary edema, i.e. 9.48±1.61 fL versus 9.03±1.49 fL with the significance p value 0.055.

Discussion

Mean platelet volume (MPV) is a marker of platelet size, function and activation including aggregation, release of thromboxan A2 , platelet factor 4 and beta-thrombomodulin, expression of glicoprotein Ib and glicoprotein IIb/IIIa receptors.[5] Larger platelet has more active metabolism and eznyme system and more production of thromboxan A2 as compared to smaller platelet. The MPV value has negative correlation with platelet count in patients with peripheral artery disease and healthy individual.[6]

Platelet activation occurs just before the episode of acute coronary syndrome. The need of platelet is increasing in the site of coronary atherosclerosis plaque which cause larger platelet being release from bone marrow. In the observation, increased platelet volume can persist during hospital treatment in patients with acute coronary syndrome. It indicates that MPV is an early indicator of prolonged disturbance and a marker to longterm outcome.[7]

The normal value of MPV is 7.5 – 11.5 fL. The cut off value of MPV to discriminate between large and small in several studies is varied. In the subjects with acute myocardial infarction, 2

Table 6. The impact of high MPV on major adverse cardiovascular event, death and acute heart failure (pulmonary edema) in patients with acute myocardial infarction

	High MPV (> 8.85 fL)	Low MPV (≤ 8.85 fL)	RR (95% CI)	P value
Major adverse cardiovascular events (%)	52 (33.8 %)	27 (23.9 %)	1.62 (0.940-2.804)	0.081
Death (%)	20 (13.0 %)	8 (7.1 %)	1.96 (0.830-4.624)	0.830
Acute pumonary edema (%)	28 (18.0 %)	14 (12.4 %)	1.57 (0.785-3.144)	0.199

RR is relative risk

Table 7. The impact of high MPV on major adverse cardiovascular event, death and acute heart failure (pulmonary edema) in patients with STEMI

	High MPV (> 8.85 fL)	Low MPV (≤ 8.85 fL)	RR (95% CI)	P value
Major adverse cardiovascular events (%)	35 (32.7 %)	20 (27.4 %)	1.29 (0.670-2.477)	0.447
Death (%)	12 (11.2 %)	5 (6.8 %)	1.72 (0.578-5.103)	0.325
Acute pumonary edema (%)	19 (17.8 %)	12 (16.4 %)	1.09 (0.497-2.426)	0.818

RR is relative risk

studies use the cut off value of ≥ 10.3 fL [5,8] and 1 study use the cut off value 9 fL.[9] The ROC curve analysis in this research yields the cut off value of MPV 8.85 fL which has sensitivity of 61.8 % and specificity of 58.2 %. In several studies, mean MPV in the same population show different value. In this research mean value of MPV in acute coronary syndrome is 9.09±1.35 fL with minimal value of 5.5 fL and maximal value of 13.4 fL. The multicenter study involving 3134 patients with cerebrovascular disease and risk of stroke, the mean value of MPV is different in every regions, with the all mean value of 10.0 fL.[10]

The MPV in subjects with risk factor of cardiovascular disease shows that in prehypertensive patients, the MPV value is significantly higher as compared to normal subjects. The MPV has positive correlation with systolic blood pressure, body mass index and insulin resistance in subjects with prehypertension.[11] In this research, there is a significant different in systolic blood pressure in which the higher systolic blood pressure in subjects with lower MPV. The blood glucose level is significantly higher in subjects with higher MPV as compared to those with low MPV. This contradictory result needs to be corroborated. The MPV is increased in condition with cardiovascular risk factore such as hyperkholesterolemia, diabetes mellitus but not in essential hypertension. In acute myocardial infarction, acute ischemic stroke, preeklampsia and renalis artery stenosis, the MPV value is increasing.[12]

The study by Yilmaz et al. (2008) that differentiate the MPV value in subjects with nonSTEMI,unstable angina and stabil coronary artery disease, yield the result as follows : 10.4±0.6 fL, 10.0±0.7 fL and 8.9±0.7 fL respectively and significantly different.[3] Other study shows similar result, i.e. the highest MPV value is found in acute myocardia infarction, and then in unstable angina pectoris and the least is found in stabil coronary heart disease.[7] In this study, the mean value of MVP is 9.18±1.55 fL in STEMI, 9.14±1.6 fL in NSTEMI and 8.89±1.47 fL in unstable angina. Furthermore the higher mean value of MVP is found in subset of acute myocardial infarction than in unstable angina pectoris.

The current meta analyses for MPV as a predictor of cardiovascular risk involve 16 cross sectional studies in acute myocardial infarction, 3 cohort studies in acute myocardial infarction and 5 cohort studies in post angioplasty patients. The cross sectional studies show that acute myocardial infarction has higher MPV value as compared with non acute myocardial infarction. Non acute myocardial infarction consists of unstable angina pectoris, stable coronary heart disease and non coronary heart disease patients.[13]

The incidence of major adverse cardiovascular event in this study is 24.2 %. The incidence of major adverse cardiovascular event is significantly higher in patients with higher MPV as compared with patients with lower MPV. The relative risk to develop major adverse cardiovascular event is 1.65 time in partients with higher MPV. It indicates that high MPV is a predictor for the development of major adverse cardiovascular events in acute coronary

syndrome patients. Previous study supported the result of our study by showing the positive association between admission MPV value with major adverse cardiovascular events during hospitalisation. [5]

In other study, it was shown that MPV is an independent risk factor for recurrent ischemia and death.[13] The association between MPV 6 month post myocardial infarction in male patients is associated with mortality within 2 years follow up. The high MPV value associates with independent risk factor for recurrent infarct and cardiovascular mortality.[14] In patients with a history of stroke, high MPV value is a independent predictor for recurrent stroke.[12] The increasing MPV in acute myocardial infarction associates with the extent of infarction and increase risk to develop left ventricular dysfunction and mural thrombus.[2] Elevated MPV is an independent risk factor for acute heart failure in patients with acute myocardial infarction. [9] The impact of MPV value on the incidence of acute pulmonary edema in this research is higher in subjects with high MPV as compared to those with low MPV. The odd ratio of high MPV value to develop heart failure is 1.631, however there is no statistically significant. Previous study indicates that platelet indices, i.e. MPV, PDW and platelet large cell ratio independently associated with infarct/ ischemia type (transmural or subendocardial), infarct location (anterior, lateral, posterior or other wall location), infarct consequence as measured with Killip class, time before treatment, ischemic episode and the extent of occluded coronary vessels.[7]

Increased MPV value associated with worse clinical outcome and disturbance in reperfusion in patients with acute myocardial infarction. Relative and absolute neutrophil count and elevated MPV value on admission associated independently with microvascular perfusion disturbance in patients undergoing primary percutaneous coronary intervention. The combined markers are indication of worsened microvascular injury in patients with acute myocardial infarction.[15] In patients with STEMI, MPV value may have implication in treatment strategy.[5] Only patients with increased MPV response well with abciximab. Therefore, by measuring MPV value, the efficacy of glycoprotein IIb/IIIa inhibitor and other antiplatelets can be determined. [13] The incidence of major adverse cardiovascular events is higher in subjects with high MPV value as compared to subjects with low MPV value. The incidence of death and acute pulmonary edema is also higher in subjects with high MPV value. Although statistically not significant, the clinical value may be of significant.

Conclusion

The high MPV (> 8.85 fL) has higher incidence of major adverse cardiovascular event in patients with acute coronary syndrome as compared with patients with lower MPV (≤ 8.85 fL), this difference is statistically significant ($p < 0.05$). The high MPV is a significant predictor for major adverse cardiovascular event in acute coronary syndrome with relative risk 1.65.

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