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Association of Mean Platelet Volume and Fibrinogen with Major Cardiovascular Events in Acute Coronary syndrome

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Abstract : Acute coronary syndrome (ACS) is a medical emergency that requires immediate hospitalization and is a major cardiovascular problem because it leads to hospital care and high mortality. Mean platelet volume (MPV) values reflecting platelet activation and fibrinogen as a prothrombotic factor are expected to provide early information about the overall risk of the patient given the limited time of diagnostic efficiency of cardiactroponin.
Keywords: Mean Platelet Volume, Fibrinogen, Cardiovascular Events, Acute Coronary syndrome.

Introduction

Acute coronary syndrome (ACS) is a medical emergency that requires immediate hospitalization and is a major cardiovascular problem because it leads to hospital care and high mortality. ACS is enforced based on anamnesis, physical examination, electrocardiogram (ECG) examination, and examination of cardiac marker. The pathophysiology of ACS is largely an acute manifestation of coronary artery atheroma plaque that is torn or broken. This is related to changes in the composition of the plaque and the depletion of the brushed hood that covered the plaque. This event will be followed by the process of platelet aggregation and the activation of the coagulation pathway. An oxygen supply that stops for approximately 20 minutes causes the myocardium to have necrosis (myocardial infarction).[1]

Platelets have an important role in the pathogenesis of ACS with clinical manifestations of unstable angina pectoris, myocardial infarction with ST segment elevation (STEMI), and myocardial infarction without ST segment elevation (NSTEMI). Platelets vary in size, density, and activity. Changes in these parameters may be associated with acute coronary syndrome triggers and their spread.[2]

The average platelet / MPV volume, is the average platelet size in blood obtained from routine blood tests. Larger enzymatic and metabolic platelets are more active and have a higher thrombotic potential than small platelets.[3]

MPV reflects activation of platelets. Large MPV have higher thrombotic potential, due to higher density, faster aggregation, higher A2 thrombosis rates, and more expression to the Ib and IIb / IIIa glycoprotein receptors.[2]

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Larger and hyperactive platelet size plays an important role in accelerating the formation and spread of intracoronary thrombus, leading to the occurrence of acute thrombotic events. This observation has resulted in the hypothesis that an increase in MPV may be a potential predictor of cardiovascular risk stratification. MPV is an index of platelet size that correlates with platelet activation. In patients with NSTEMI SKA, it has been shown that higher MPV show not only increased NSTEMI risk, but also ischemic complications. Other studies have been shown in a small observational study that MPV is higher in patients with myocardial infarction compared with stable angina pectoris and healthy control, suggesting that MPV is a risk factor for the severity of coronary artery disease.[3]

In addition to MPV, fibrinogen as a prothrombotic factor is associated with the degree of atherosclerosis. Fibrinogen is one of the markers acting as an acute phase protein and also plays a role in the process of blood coagulation, blood viscosity and platelet aggregation. In patients with Coronary Heart Disease (CHD) found increased levels of fibrinogen which also increases the risk of thrombosis.[4,5,6]

Fibrinogen Studies Collaboration (FSC) states that a long-term increase in plasma fibrinogen of 100 mg/dl may increase major cardiovascular risk. However, it remains unclear whether this increased fibrinogen is a cause or as a consequence of atherosclerosis.[7,8]

Diagnostic efficiency of cardiac troponin within 2 to 4 hours of onset of symptoms is limited. Therefore, a biochemical test laboratory capable of reducing emergency delays during hospital admissions for chest pain patients has the potential to significantly increase clinical and hospital income.[9]

Experimental

This study is a retrospective cross-sectional study was carried out on patients of Emergency Room at Haji Adam Malik Hospital, Medan, North Sumatera, Indonesia from January 2015 to September 2015. A total 56 adult subjects (both male and females) of aged ≥ 18years old were for in this study.

Result and Discussion

Characteristics of study subjects by age, sex and diagnosis can be seen in the table below

No.	Characteristic	Frequency	Percentage (%)
	Age		
1	30 - 40 years	5	8,9
2	41 - 50 years	11	19,6
3	51 - 60 years	20	35,7
4	61 - 70 years	16	28,6
5	71- 75 years	4	7,1
	Total	56	100
	Sex		
1	Male	44	78,6
2	Female	12	21,4
	Total	56	100
	Diagnose		
1	STEMI	37	66,1
2	NSTEMI	8	14,3
3	UAP	11	19,6
	Total	56	100

Based on the above table it can be seen that the subjects of ACS study more in the age group 51 - 60 years (35.7%) followed by the age group 61 - 70 years (28.6%) and the lowest with age group 71 - 75 years (7,1%).

By sex, ACS patients were mostly male (78.6%) and women (21.4%).

Most patients with ACS were diagnosed with STEMI (66.1%) followed by UAP (19.6%) and other NSTEMI(14.3%).

Characteristics of study subjects based on history of disease.

No	History of disease	Frequency	Percentage (%)
	Hypertension		
1	No	32	57,1
2	Yes	24	42,9
Total		56	100
	Diabetes Melitus		
1	No	43	76,8
2	Yes	13	23,2
Total		56	100
	Family history		
1	No	49	87,5
2	Yes	7	12,5
Total		56	100
	Type of Arrhythmia		
1	None	36	64,3
2	First degree AV block	4	7,1
3	Second degree AV block	2	3,6
4	TAVB	2	3,6
5	AF	3	5,4
6	VT/VF	1	1,8
7	SVT	1	1,8
8	RBBB	7	12,5
Total		56	100
	Duration of hospitalization (days)		
1	<5	14	25,0
2	≥5	42	75,0
total		**56**	**100**

The above table explains that patients with ACS do not have a history of hypertension (57.1%), most have no history of Diabetes Mellitus (76.8%), generally have no family history with ACS (87.5%), and some there was no history of arrhythmias (64.3%) while those with a history of more arrhythmias with RBBB (12.5%). The duration of treatment of patients with ACS is most ≥5 days (75%).

Based on the literature states that risk factors of ACS include sex (men higher than women), family history with cardiovascular disease, and modifiable risk factors (hypertension, hyperlipidemia, diabetes mellitus, lifestyle with low physical activity, and smoking.[1]

Characteristics of research subjects based on major cardiovascular symptoms

No	Charateristic	Frequency	Percentage (%)
	Death		
1	No	52	92,9
2	Yes	4	7,1
Total		56	100
	Arrythmia		
1	No	36	64,3
2	Yes	20	35,7
Total		56	100

	Heart Failure		
1	No	36	64,3
2	Yes	20	35,7
Total		56	100
	Major cardiovascular		
1	No	21	37,5
2	Yes	35	62,5
Total		56	100

Based on the above table it can be seen that generally ACS patients have no death (inhospitality mortality) (92.9%), no Arrhythmia (64,3.2%), most have no Heart Failure (64.3%)but generally have a symptoms of cardiovascular major events (62,5%).

The association of MPV and Fibrinogen levels with Acute Heart Failure.

To analyze the relationship of MPV and Fibrinogen levels with Acute Heart Failure, statistical test was done with Chi-square. The results of statistical analysis are shown in the table below.

MPV (FL)	**Heart Failure**		**Total**	**P value***
	Yes	**No**		
<9,5	6 (37,5%)	10 (62,5%)	16 (100%)	0,86
≥9,5	14 (35%)	26 (65%)	40 (100%)	
Total	**20 (35,7%)**	**36 (64,3%)**	**56 (100%)**	

**Chi-square test*

Based on the above table it can be seen that ACS patients who have MPV level <9.5 FL as much as 28.6% and most have no heart failure (62.5%) while those with MPV ≥9.5 FL as much as 71.4 % is also mostly none of which are heart failure (65,%). From statistical tests showed no association of MPV levels with heart failure (p> 0.05).

The association of Fibrinogen levels with Heart Failure

Fibrinogen (mg)	**Heart Failure**		**Total**	**P Value***
	Yes	**No**		
<330	5 (23,8%)	16 (76,2%)	21 (100%)	0,15
≥330	15 (42,9%)	20 (57,1%)	35 (100%)	
Total	**20 (35,7%)**	**36 (64,3%)**	**56 (100%)**	

**Chi-square test*

Based on the above table it can be seen that patients with ACS who have levels of Fibrinogen <330 mg as much as 37.5% and most (76.2%) there is no heart failure while those with Fibrinogen ≥330 mg as much as 62.5%, more which had no heart failure (57.1%). From the statistical test showed no association of Fibronogen with heart failure (p> 0.05).

The association of levels of MPV and Fibrinogen with Heart Failure

Fibrinogen &MPV	**Heart Failure**		**Total**	**P Value***
	Yes	**No**		
Both are increasing (≥330&≥9,5)	10 (41,7%)	14 (58,3%)	24 (100%)	0,60
Not simultaneously increasing	10 (31,3%)	22 (68,8%)	32 (100%)	
Total	**20 (35,7%)**	**36 (64,3%)**	**56 (100%)**	

**Continuity correction test*

Based on the above table it can be seen that ACS patients who have levels of Fibrinogen and MPV both increased (≥330 & ≥9.5) as much as 42.8% and most (58.3%) none of which are heart failure whereas MPV and Fibrinogen levels are not simultaneously increased (only 1 of which increased) by 57%, more that no heart failure (68.8%). From statistical tests showed no association of levels of Fibrinogen and / or MPV that increased with heart failure (p> 0.05).

The association of MPV and Fibrinogen levels with the arrhythmia of ACS patients.

The association of MPV with arrhythmias

MPV (FL)	Arrythmia		Total	P Value*
	Yes	No		
<9,5	8 (50%)	8 (50%)	16 (100%)	0,15
≥9,5	12 (30%)	28 (70%)	40 (100%)	
Total	**20 (35,7%)**	**36 (64,3%)**	**56 (100%)**	

**Chi-square test*

Based on the above table it can be seen that ACS patients who have MPV levels <9.5 FL as much as 28,6 % and 50 % have no arrhythmia while those with MPV ≥9.5 FL as much as 71.4% are also mostly there is no arrhythmia (70%). The statistical test showed no association of MPV levels with arrhythmias (p> 0.05).

The association of Fibrinogen with Arrhythmias

Fibrinogen (mg)	Arrythmia		Total	P Value*
	Yes	No		
<330	7 (33,3%)	14 (66,7%)	21 (100%)	0,77
≥330	13 (37,1%)	22 (62,9%)	35 (100%)	
Total	**20 (35,7%)**	**36 (64,3%)**	**56 (100%)**	

**Chi-square test*

Based on the above table it can be seen that patients with ACS who have levels of Fibrinogen <330 mg as much as 37,5% and most (66.7%) have no arrhythmia while those with Fibrinogen ≥330 mg as much as 62,5 %, more which had no arrhythmia (62.9%). From the statistical test showed no association of Fibronogenwith arrhythmia (p> 0,05).

The association of MPV and Fibrinogen levels with Arrhythmias

Fibrinogen &MPV	Aritmia		Total	P Value*
	Yes	No		
Both are increasing (≥330&≥9,5)	6 (25%)	18 (75%)	24 (100%)	0,24
Not simultaneously increasing	14 (43,8%)	18 (56,2%)	32 (100%)	
Total	**20 (35,7%)**	**36 (64,3%)**	**56 (100%)**	

**Continuity correction test*

Based on the above table it can be seen that patients with ACS who have levels of Fibrinogen and MPV increased (≥330 & ≥9,5) mostly (75%) no arrhythmia while the MPV and Fibrinogen levels are not simultaneously increased (only one that increased) have no arrhythmia (56.2%). From the statistical test showed no associationof Fibronogen and / or MPV levels increased with arrhythmias (p> 0.05).

The Association of levels of MPV and Fibrinogen with Death of ACS patients.

Association of MPV with Death

MPV (FL)	Death		Total	P Value
	Yes	No		
<9,5	2 (12,5%)	14 (87,5%)	16 (100%)	0,68
≥9,5	2 (5%)	38 (95%)	40 (100%)	
Total	**4 (7,1%)**	**52 (92,9%)**	**56 (100%)**	

**Continuity correction test*

Based on the above table it can be seen that ACS patients who have MPV levels <9.5 FL as much as 28,5% and generally no death(87,5%) whereas having MPV ≥9.5 FL as much as 71.4% also generally no death (95%). From statistical tests showed no association of MPV levels with mortality in patients with ACS (p> 0.05).

The association of MPV and Fibrinogen with Death

Fibrinogen &MPV	Death		Total	P Value*
	Yes	No		
Both are increasing (≥330&≥9,5)	0 (0%)	24 (100%)	24 (100%)	0,2
Not simultaneously increasing	4 (12,5%)	28 (87,5%)	32 (100%)	
Total	**4 (7,1%)**	**52 (92,9%)**	**56 (100%)**	

**Continuity correction test*

Based on the above table it can be seen that ACS patients who have levels of Fibrinogen and MPV both increased (≥330 & ≥9.5) as much as 100% and no one experienced death while the MPV and Fibrinogen levels are not simultaneously increased (only one that increased) as much as 57%, generally no death (87,5%). From statistical tests showed no association of levels of Fibrinogen and / or MPV that increased with death or mortality (p> 0.05).

The association of MPV and Fibrinogen levels with Major Cardiovascular Events overall in ACS patients.

MPV relationship with Major cardiovascular events

MPV (FL)	major cardiovascular events		Total	P Value*
	Yes	No		
<9,5	11 (68,8%)	5 (31,3%)	16 (100%)	0,54
≥9,5	24 (60%)	16 (40%)	40 (100%)	
Total	**35 (62,5%)**	**21 (37,5%)**	**56 (100%)**	

**Chi-square test*

Based on the above table it can be seen that ACS patients who have MPV levels <9.5 FL are also mostly (68.8%) have major cardiovascular events, while those with MPV ≥9.5 FL are also mostly major cardiovascular events (60%). The statistical test showed no association of MPV levels with major cardiovascular events in patients with ACS (p> 0.05).

The association of MPV and Fibrinogen levels with major cardiovascular events

Fibrinogen &MPV	major cardiovascular events		Total	Nilai p*
	Yes	No		
Both are increased (≥330&≥9,5)	14 (58,3%)	10 (41,7%)	24 (100%)	0,2
Not simultaneously increased	21 (65,6%)	11 (34,4%)	32 (100%)	
Total	**35 (62,5%)**	**21 (37,5%)**	**56 (100%)**	

**Chi-square test*

Based on the above table it can be seen that ACS patients who have levels of Fibrinogen and MPV increased (≥330 & ≥9,5) more (58.3%) have major cardiovascular events, whereas the MPV or Fibrinogen only increases mostly have major cardiovascular events (62 , 5%). From the statistical test showed no association of Fibrinogen and / or MPV levels increased with major cardiovascular events (p> 0.05).

No significant differences were found in this study because MPV was assessed only when the patient entered the hospital and the SKA prognosis itself was also influenced by other factors, such as comorbidities, and the type of therapy given. Similarly, a study conducted in Makassar by Sukmawaty et.al found no significant differences between surviving and non-viable STEMI patients, so MPV can not be used as a prognostic marker of ACS.[10]

Where relatively small risk factors such as hypertension (42.9%), Diabetes mellitus (23.2%), and 12.5% with family history and most of the absence of arrhythmia (64%) and adequate treatment and treatment can also affect outcomes of ACS patients.

Platelet size and activity were correlated, and MPV was found to increase before the onset of acute myocardial infarction.[11] Similarly, from Martin et al's research, there was an increase in MPV before AMI incidence, most of the platelets taken samples at admission, were already circulating before AMI events, because the mean age of platelets in blood was 7-10 days; most of the platelet samples at the time of admission, will be circulated prior to the occurrence of AMI. Show that elevation in MPV remains high 6 weeks after hospital discharge; this explains that it is a chronic disease rather than an acute process.[12]This also can be used as the basis why in this study, MPV in ACS patients did not show significant improvement compared to non ACS.

Becker et al showed decreased initial fibrinogen levels in the first 12 to 24 hours, exceeding baseline levels in 96 hours. This result is consistent with the level of fibrinogen measured as admitted in the Mouco et al. Study, when lower values were found, compared with the control group, which increased until the outcome of the hospital. In short, the level of fibrinogen during the acute phase seems to peak between three to five days, returning gradually to its initial value after the resolution of inflammation.[13]While in this study, Fibrinogen examined at the time of acute attacks only.

Limitations of this study was using medical records, making it difficult to assess previous history or history of drug use that affects unrecorded platelet functionalities that may cause bias, other than that the course of the patient's illness is not followed until the patient is discharged from the hospital.

Conclusions

By sex, ACS patients were predominantly male compared with women and most with STEMI diagnosis (66.1%) followed by UAP and later NSTEMI.From the statistical test showed no relation between MPV and Fibrinogen levels with heart failure, arrhythmia or death (p> 0.05) in ACS patients.

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