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Correlation between Ratio Leukocyte / Mean Platelet Volume (MPV) in Acute Coronary Syndrome Patients

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ABSTRACT

Background: Acute Coronary Syndrome (ACS) is a major cardiovascular problem that has a high mortality rate and hospitalization rate. In America alone in 2020, there were more than 1,000,000 coronary heart disease sufferers. According to Riskesdas 2013, the prevalence of coronary heart disease in Indonesia (Central Java) was 0.5% or as many as 120,447 people (Kemenkes, 2013). Around 9-19% ACS causes death in the first 6 months after diagnosis and half of deaths occur within first 30 days.
Aim: To know the relationship between leukocyte ratio/mean platelet volume and GRACE score in acute coronary syndrome.
Method: This research is an analytical observational study using a cross sectional research design with consecutive sampling and using medical data from central installation patients at H.Adam Malik Hospital in the period January 2021 to Juny 2021 that meets the inclusion and exclusion criteria. The sample is calculated using the large proportion estimation formula. Then proceed with the post hoc Mann Whitney test to see which groups have differences. The magnitude of the desired deviation (α) is 0.05, statistically significant if p<0.05.
Results: 75 subjects participated in the study and there was a mean leukocyte/MPV ratio, in CAD 1021.05, STEMI 981.20, and NSTEMI 473.71. Based on the analysis carried out, a significant relationship was obtained with a p value <0.05 (p = 0.001). The mean GRACE score for CAD was 137, STEMI 125, NSTEMI 141.50. Based on the analysis carried out, a significant relationship was obtained with a p value <0.05 (p = 0.001).
Conclusion: The Leukocyte/MPV ratio has a strong positive correlation with the GRACE score with an r value of 0.723 and a p value of 0.001.

Keywords: leukocyte/MPV ratio, ACS, GRACE Score

INTRODUCTION

Acute Coronary Syndrome (ACS) is a major cardiovascular problem with high mortality and hospitalization rate. In America, there were more than 1,000,000 people with coronary heart disease (Singh et al., 2020). According to Riskesdas 2013, coronary heart disease prevalence in Indonesia (Central Java) was 0.5% or as many as 120,447 people (Ministry of Health, 2013). Chronic inflammation plays a role in atherosclerotic plaques formation, which can lead to unstable plaques and thrombus formation (Libby et al., 2011). Leukocytes play a role in inflammatory process and have role in ACS incidence (Göktaş et al., 2018; Grzybowski et al., 2004).

T-cells and macrophages present in atherosclerotic plaques are activated after endothelial injury, then trigger thrombus formation through cytokine and procoagulant stimulation. This process increases thrombogenicity and triggers ACS. Platelets have been reported to play a

role in ACS through inflammatory pathways. Both activated and inactivated platelets play a role in platelet-leukocyte adhesion in atherogenesis process. When the plaque ruptures, platelet activation and thrombus formation occur (Dehgani et al., 2015). The interaction of platelets and leukocytes causes increased leukocyte recruitment at site of plaque rupture and in incidence and prognosis of cardiovascular. (Dehgani et al., 2015; Niu et al., 2018)

Leukocyte/MPV ratio one of complete blood count parameters that can be assessed in ACS, but it has not been widely studied. Several existing studies have shown that increase in leukocyte/MPV ratio can independently predict long-term incidence of Major Adverse Cardiovascular Event (MACE) and risk of mortality in ACS patients (Çiçek et al., 2016; Dehgani et al., 2015; Dehgani et al., 2016). Research by Dehghani et al. (2015) showed that increase in leukocyte/MPV ratio (≥ 755) at attack episode onset was significantly associated with MACE incidence in NSTEMI patients. The Global Registry of Acute Coronary Events (GRACE) risk scoring system is used to stratify the risk of death in ACS patients to help determine the appropriate therapeutic strategy based on individual risk. Therefore, this research was conducted to evaluate leukocyte/MPV ratio, which is a composite picture of inflammatory conditions, can describe/related to GRACE score in ACS patients.

LITERATURE REVIEW

The leukocyte/MPV ratio is a new inflammatory biomarker that has been studied as an independent predictor of long-term cardiovascular events in ACS patients. Adam et al.'s research. (2017) showed that leukocyte/MPV ratio was best predictor of mortality at 30 days and MACE after ACS and better than other hematological parameters. The research of Çiçek et al. (2016) also showed that high leukocyte/MPV ratio at episode attack onset was a better predictor of long-term MACE compared to other complete blood count parameters such as MPV, RDW, platelet to lymphocyte ratio (PLR), and neutrophil to lymphocyte ratio (NLR). in STEMI patients. The leukocyte/MPV ratio value 1,653.47 is upper limit value for mortality in STEMI patients with sensitivity 75.4% and specificity 87.3% (Çiçek et al., 2016).

The leukocyte/MPV ratio has several main characteristics that can become new cardiovascular prognostic parameters. The leukocyte/MPV ratio can be obtained easily from a complete blood count without any additional treatment or cost. The leukocyte/MPV ratio also provides information about risk of in-hospital and long-term mortality. In addition, leukocyte/MPV ratio is also useful for risk stratification of patients into risk groups based on value of this ratio, enabling doctors to determine patients at high risk and provide specific therapy. In patients with a high leukocyte/MPV ratio, more intensive management and more aggressive control of cardiovascular risk factors may be considered (Çiçek et al., 2016).

The incidence of MACE, cardiovascular-related death, decompensated heart failure, and ventricular tachycardia/fibrillation was higher with leukocyte /MPV ratio values 1,286 in STEMI patients undergoing PCI. The combination of leukocyte/MPV ratio with GRACE score has a better predictive value for MACE than the GRACE score alone (Emre et al., 2020).

MATERIALS & METHODS

This research is an analytic observational study using cross sectional design at RSUP. Haji Adam Malik from January - June 2021 after proposal process is approved until research results are presented in accordance with conditions determined by study program. Sampling of patients diagnosed with acute coronary syndrome by consecutive sampling that met inclusion criteria which is all patients diagnosed with acute coronary syndrome both with ST elevation and without ST elevation who were hospitalized and

recorded in medical record between October-December 2020, age ≥ 18 years; and exclusions criteria namely acute coronary syndrome patients with comorbidities such as infection, malignancy or undergoing chemotherapy or radiation, chronic liver disease, acute coronary syndrome patients with massive bleeding, patients with history of previous myocardial infarction, patients taking corticosteroid drugs, thrombolytic therapy, inhibitors gp IIb/IIIa.v.

Statistical Analysis

Patient data were collected based on demographic characteristics (gender and age), pulse, systolic blood pressure, classification of acute coronary syndrome diagnosis, Killip class, cardiac biomarkers, leukocyte count, mean platelet volume and GRACE score. The Kolmogorov-Smirnov test was used to assess whether the sample was normally distributed or not. The data is prepared in form of mean ± standard deviation if data is normally distributed, and in form of median and range (minimum-maximum) if data is not normally distributed. The analytical test used to assess correlation between leukocyte /MPV ratio and GRACE score is Pearson correlation test if data is normally distributed or Spearman correlation test if data is not normally distributed. P value < 0.05 indicates a significant relationship

RESULT

Based on medical records of patients with acute coronary syndrome who were hospitalized at Inpatient Installation of H. Adam Malik Hospital, Medan from January to June 2021, 75 research subjects were obtained.

Table 1. Research Sample Characteristics

Variable	N=75
Age	
Mean (SB)	56,71 (11,156)
Median	58
Gender	
Male	56 (74,7%)
Female	19 (25,3%)
HR (Median, Min- Max)	87(68-112)
Systolic Blood Pressure (Median, Min- Max)	147 (108-190)
Smoking	
Yes	50 (66,7)
No	25 (33,3)
DM	
Yes	33 (44)
No	42 (56)
Hypertension	
Yes	56 (74,7)
No	19 (25,3)
Creatinine (Median, Min-Max)	1,04 (0,64-9,33)
Cardiac Enzyme (Median, Min- Max)	
CKMB	44 (8-378)
Troponin I	1,53 (0,01-62)
Troponin T	98 (9-233)
Leucocyte (Median, Min- Max)	9180(4190-23000)
Platelet (Median, Min- Max)	234000(28300-456000)
MPV (Median, Min- Max)	10,2 (8,60-116)
Kilip	
I	25 (33,3)
II	46 (61,3)
III	4 (5,3)
Cardiac Arrest on Arrival	
Yes	13 (17,3)
No	62 (82,7)
ST Segment Deviation	
Yes	55 (69,5)
No	20 (26,7)
Leucocyte/MPV ratio(Median, Min- Max)	1054 (337,20-2017,86)
GRACE Score (Median, Min- Max)	137 (53-235)

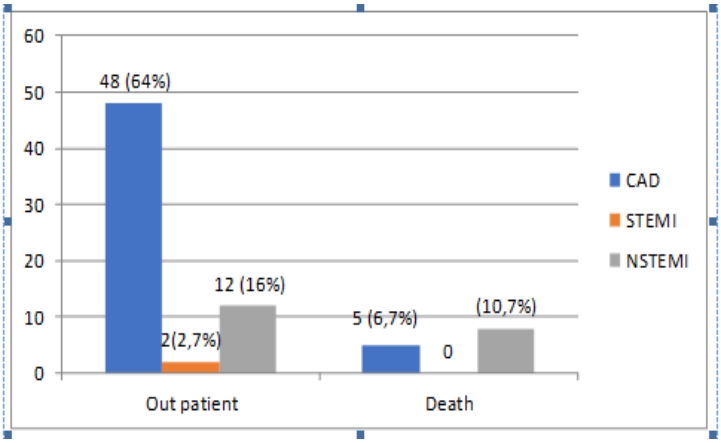

Figure 1 Patient Distribution. Patients who were discharged after the stable as many as 48 people (64%) who experienced ACS, 2 people who experienced STEMI (2.7%), 12 people who experienced NTEMI (16%). Distribution of patients who died was ACS 5 people (6.7%) and NSTEMI 8 people (10.76%).

Tabel 2. Comparison of Total Leukocyte /MPV Ratio Towards Mortality Risk Stratification

Leukocyte /MPV Ratio	Mortality Risk Stratification (GRACE Score)		
	Low Risk (<1%)	Moderate Risk (1-3%)	High Risk (>3%)
Low (%)	10 (13,3)	4 (5,3)	0
High (%)	0	31 (41,3)	30 (40)

Patients with low leukocyte/MPV ratio with low risk of death (<1%) as many as 10 people (13.3%), moderate risk (1-3%) as many as 4 people (5.3%), and patients with high leukocytes/ MPV ratio with medium risk as many as 31 people (41.3%) and high risk as many as 30 people (40%).

Tabel 3 Correlation between Leukocyte /MPV Ratio with GRACE Score on ACS

Parameter	Diagnosis			P value
	CAD (n=52)	STEMI (n=2)	NSTEMI (n=28)	
Leukocyte/MPV Ratio	1021,05	981,20	473,71	0,001
GRACE Score	137	125	141,50	0,001

Mean leukocyte/MPV ratio in CAD was 1021.05, STEMI was 981.20, NSTEMI was 473.71 and a significant relationship was obtained with p value <0.05 (p = 0.001). The mean GRACE score for CAD was 137, STEMI was 125, NSTEMI was 141.50. and significant relationship was obtained with a p value <0.05 (p = 0.001).

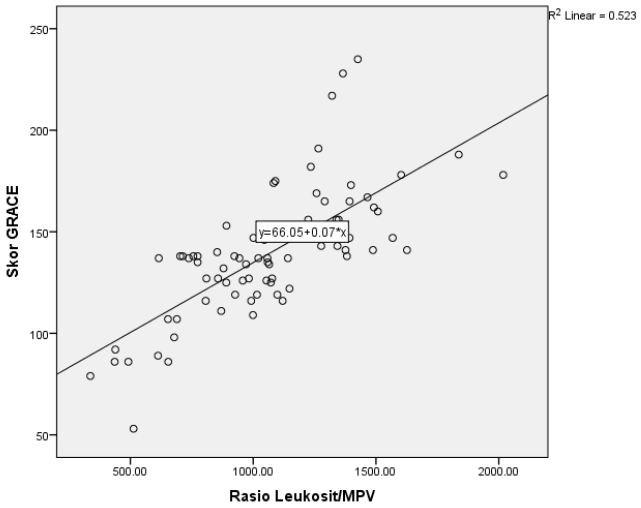

Figure 2. Correlation of Leukocyte /MPV Ratio and GRACE Score on ACS. The Leukocyte/MPV ratio has a strong positive correlation with GRACE score with r value 0.723 and p value 0.001.

DISCUSSION

A meta-analysis study by Sansanayudh et al (2014) found that Leukocyte/MPV Ratio was significantly greater in patients with CAD compared to controls with mean difference of 0.70 fL (95% CI: 0.55, 0.85). Based on research results conducted by Arsalan et al (2017) found that Leukocyte/MPV ratio is a stronger parameter than other laboratory parameters in predicting Acute Coronary Syndrome. This is in accordance with this study, it was found that the Leukocyte/MPV ratio was greater in patients with CAD, with mean value 1059.39 and p value <0.05 (p = 0.001).

Estevez-Loureiro et al (2009) found that MPV increase is a predictor of mortality within 30 days in patients with Acute Coronary Syndrome where MPV is a marker of platelet activation whose examination is very easy to do in a complete blood count. Larger platelets contain more dense alpha granules, express more adhesive receptors, and have higher thrombotic activity. Large platelets with high hemostatic activity can lead to increased platelet aggregation and higher enzyme activity, which increases adverse events through inflammatory mediators release, increased thrombosis, exacerbated microvascular dysfunction, inflammation and myocardial injury, microcirculatory insufficiency, large infarction areas and impaired cardiac function. Many recent studies have investigated correlation between MPV and CAD. Based on these studies, MPV is implicated in acute coronary syndromes and a high MPV is associated with a poor prognosis for acute thrombotic events. In addition, atherosclerosis and cardiovascular risk factors are often associated with CAE (Ozbek et al., 2016).

However, there is some disagreement with regard to disease ecstasy, where a higher Leukocyte /MPV ratio was shown for patients with heart disease in some studies when compared with healthy individuals, whereas the opposite was shown in other studies. Among these studies, Keser et al (2016) observed no significant difference between a group of ectatic patients and a group of healthy people in relation to the Leukocyte/MPV Ratio. However, the research conducted by Sarli et al (2013) showed that there was a significant difference between the two groups. A large number of studies have examined the role of MPV as a possible risk factor for ecstatic heart disease, with inconsistent results. Strong, weak, and no associations between MPV and ectasia have been reported. These conflicting results led to all studies being systematically reviewed to investigate the association between MPV and ectatic heart disease by conducting meta-analyses to provide overall uniform results. The mean platelet volume (MPV) is used as an indicator of platelet reactivity that can be used as a prognostic marker in patients with coronary artery disease (Sansanayudh et al., 2021).

American and European clinicians recommend using Global Registry of Acute Coronary Events (GRACE) risk score as main predictor in ACS patients. The GRACE score is a useful tool for risk stratification in patients with coronary syndromes (ACS). This risk stratification model, consisting of various clinical, laboratory, and electrocardiographic parameters as examined on admission, is commonly used in clinical practice to estimate the risk of death or myocardial infarction within six months, including hospitalization (Collet et al., 2021).

Based on a study conducted by Sofidis et al (2021) argued that GRACE score could not significantly predict severe CAD in patients with STEMI (AUC = 0.510, 95% CI = 0.361-0.659) and in UA (AUC = 0.585, 95% CI = 0.435-0.735). The GRACE Score is largest and best-known database of prospective studies used for ACS. Registered patients from 30 countries in North and South America, Australia, New Zealand, Asia and Europe have been widely used to identify high-risk patients with AMI and assess prognosis (Tang et al., 2007).

However, the GRACE scoring system has some limitations, such as not taking into account thrombotic activity and inflammatory. Therefore, there is a lack of biomarkers associated with adverse outcomes. Thus, there is a need for objective biomarkers for evaluation of AMI patients prognosis (Moady et al., 2019).

Based on this research, a significant relationship was found between Lymphocyte/MPV Ratio and GRACE Score on Acute Coronary Syndrome, with p value=0.001 on Lymphocyte/MPV Ratio and p=0.001 also on GRACE Score. This is in line with research conducted by Chen et al., 2019 in China which proved that with an increase in GRACE risk stratification and the Leukocyte/MPV ratio of each group increased significantly ($P<0.05$). Spearman rank correlation results show that there is a significant linear correlation between Leukocyte/MPV ratio and GRACE score ($\rho=0.304$; $P<0.001$). The current results show that, Leukocyte/MPV ratio is a simple, non-invasive, economical and feasible biomarker, which can explain the shortcomings of GRACE scoring system. It also shows that Leukocyte/MPV ratio has easy clinical value in predicting ACS patients prognosis. This finding indicates that, Leukocyte/MPV ratio combined with GRACE score has a stronger prediction.

CONCLUSION

The Leukocyte/MPV ratio has a strong positive correlation with GRACE score in acute coronary syndrome patients and Leukocyte/MPV ratio combined with GRACE score can be used as a predictor for acute coronary syndrome patients' prognosis.

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