International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.11, No.04, pp 298-304, 2018

White Blood Cell Count Mean Platelet Volume Ratio as A Predictor of Major Adverse Cardiovascular Event in Acute Non St-Elevation Myocardial Infarction (NSTEMI)

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Abstract : Background : Recent studies have shown that complete blood count analysis can become a strong parameter to predict long term complication and reinfarction in acute coronary syndrome (ACS) but there are still no parameter known for predicting short term and in-hospital complication. White Blood Cell Count Mean Platelet Volume Ratio (WMR) is one of parameter from complete blood count analysis that can be used for predicting Major Adverse Cardiovascular Event (MACE) that has not been studied extensively. The main objective of this study is to determine whether WMR can be used as a MACE predictor for NSTEMI patient during hospitalization.

Method :A total of 104 patients with NSTEMI who undergo treatment at Haji Adam Malik Hospital since October 2017 until April 2018 were recruited in this prospective cohort study. The relationship of baseline White Blood Cell Count (WBC) to Mean Platelet Volume ratio (WMR) with MACE was assessed in hospital. The patients were divided into two groups: Group A [MACE-positive] and Group B [MACE-negative]. Multivariate COX regression was performed to calculate odds ratio (OR).

Result: In the ROC curve analysis, WMR had the highest area under receiver operating characteristics curve and highest discriminative ability amongst all CBC parameters in predicting MACE , the cut-off value of WMR in the prediction of MACE was 7.65 mm (AUC 0.74, 95% CI 0.645-0.835, p<0.001). The NSTEMI group with dengan WMR ≥ 1118 had a higher incidence of MACE than the group with WMR < 1118 of 24 people (70.6%) versus 10 people (29.4%). WMR ≥ 1118 is considered to predict the incidence of MACE with a sensitivity of 70.6%, a specificity of 70%, a negative predictive value (NPV) of 83% and a positive predictive value (PPV) of 53%. Multivariate analysis showed that WMR ≥ 1118 was an independent factor that could predict the occurrence of MACE during the hospitalization period (OR 10.49, 95% CI 3.01-36.65, p<0.001). **Conclusion**: WMR is an inexpensive indicator, can be done easily and can become an independent factor to predict MACE during hospitalization in NSTEMI patient with OR 10.49.

Keyword : WMR, MACE, NSTEMI, ACS.

DOI: http://dx.doi.org/10.20902/IJPTR.2018.11401

Introduction

It has been estimated that 17.5 million death because of cardiovascular disease in 2012[1]. Around 80% of all this dead caused by heart attack and stroke, and three quarter incidence happened in countries with low-moderate income[1,2].Prevalence of Non ST-Elevation Myocardial Infarction (NSTEMI) encompass around 70% of acute coronary syndrome (ACS) usually with older age and multiple comorbidities[3]. Even though heart failure and arrythmia seldom happens, patient wit NSTEMI had higher recurrence rate and worse prognosis in short and long term[4].

ACS caused by atherosclerosis, which is accumulation of lipid and other substance that became plaque in coronary artery. This atherosclerotic plaque causes narrowing of coronary arteries that will disturb myocardial blood flow and causing myocardial ischemia[5]. If the plaque ruptured, thrombosis will happen caused by inflammatory process, which is thrombus formation and activation by platelet, leukocyte, and other inflammatory mediator and could cause total or partial occlusion of the coronary arteries and necrosis of myocardium[5,6]. Because of that reason, inflammatory marker such as leukocyte and platelet can be used as prognosis parameter for predicting Major Adverse Cardiovascular Events (MACE) in ACS patient.

The effect of high leukocyte is closely related to complication such as ventricular arrythmia in early phase of ACS, reperfusion injury of the coronary arteries, and myocardial infarct size[7] This is caused by released intracellular granule that contain enzyme and free radical or oxidant as a response to acute inflammation[8]. Platelet activation has an important role in the pathophysiology of ACS and myocardial infarct progression. This process happened after plaque ruptured that stimulate platelet activation and eventually form thrombus. Activated platelet will progress to ACS and will cause changes in shape and size of the platelet that can be assessed by Mean Platelet Volume (MPV)[8,9]. Platelet secrete important mediator for coagulation, thrombosis, and atherosclerosis progression[10].

After analyzing those two parameter, author want to evaluate White Blood Cell Count e MPV Ratio (WMR) as a prognostic parameter for MACE during hospitalization in ACS especially NSTEMI patient.

Method

Study Design and Population

This prospective cohort study was carried out atHaji Adam Malik Hospital Medan (RSHAM) with approval from Komite Etik Penelitian Fakultas Kedokteran Universitas Sumatera Utara-RSHAM for ethical clearance.From October 2017 until April 2018,all patient who diagnosed as NSTEMI according to ESC diagnostic criteria such as acute angina accompanied by significant increase of cardiac enzyme without persistent ST segment elevation in two adjacent lead and without left bundle branch block[11,12]. Exclusion criteria including 2nd and 3rd degree AV block, cardiogenic shock (Killip IV), patient with other condition that become the primary cause of increased cardiac enzyme such as tachyarrythmia, decompensated heart failure not caused by ACS, Hypertensive crisis, several critical condition including sepsis, non cardiogenci shock, burn wound, myocarditis, Tako-Tsubo cardiomyopathy, aortic stenosis, pulmonary embolism, acute renal failure, coronary spasm, acute neurological condition (stroke, subarachnoid haemorrhage), patient that having cardiac surgery, hypo and hyperthyroidism, connective tissue disease (scleroderma, haemochromatosis), Rhabdomyolisis, also excluding patient with condition that could disturb Leukocyte and MPV value such as infection, septic, blood malignancy, antibiotics, severe bleeding, liver disease, and drugs usage (immunosuppressor agent and previous anticoagulation).

The outcomes of this study was major cardiovascular adverse events such as mortality, acute heart failure, malignant arrythmia, and cardiogenic shock. All patients were given standard treatment of NSTEMI in cardiology department at Haji Adam Malik Hospital.

After the inclusion criteria is fulfilled then the data such as patient characteristic was recorded by using study form, laboratory examination and transthoracal echocardiography was also done. Standard echocardiography measurement was done by the cardiology resident in charge in cardiac emergency and/or intensive cardiac care unit (CVCU/ICCU) within first 24 hour after admittance by using GE Vivid S6 Heart Probe Sector 3.50 MHz in lateral decubitus position. Related coronary arteries was evaluated by using coronary

angiography. Laboratory sample was obtained by using venous blood sample taken within 30 minutes after admission in cardiac emergency by clinical pathology staff and then complete blood analysis was done by using *Hematology Analyzer Sysmex XP-300*added with renal function test (urea and creatinin) lipid profile, blood glucose profile, Troponin I, and CKMB. Then all data were collected and analyzed.

Statistical Analysis

Statistical analysis was done by using statistic software. Categorical variable represented by total or frequency (N) and percentage (%). Numerical variable represented by mean with standard deviation for data that distributed normally. Normality test for all numerical variable was done by using Kolmogorov-Smirnov test with n > 50. Cut off point for numerical data was obtained by using ROC curve. Comparison between independent and dependent variable was done by using Pearson Chi Square.

Multivariate analysis from independent and dependent variable was tested by logistic regression. Variablethat had p value< 0,05in multivariate analysis would be shown as odds ratio (OR) with confidence interval 95%. All statistical analyses were performed using SPSS, version 18.0 and p value < 0,05 was considered as statistically significant

Result

Total study subject was 104 patient that fulfilled inclution and exclution criteria, 70 people(67.3%) with MACE and 34 people(32.7%) without MACE. From 34 with MACE, 26 people(76.5%) were male and 8 people(23.5%) werefemale. Mean age of study subject was 57 years old in MACE group and 54 years old in non MACE group, but this is not statistically significant (p>0.05).

From clinical parameter, there are significant difference in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (p=0.001, p=0.033, p=0.001). higher heart rate and lower SBP and DBP was found in MACE group.

From risk factor variable, patients with MACE had higher smoking rate [28 (82.4%) *vs* 31 (44.3%) (p<0.001)]and higher rate of Diabetes Melitus [19 (55.9%) *vs* 23 (32.9%)(p=0.025)] compared to without MACE group.

Other significant difference were found in Leukocye count(p<0.001), glomerular filtration rate (GFR) (0.036), random blood glucose (p=0.001),fasting blood glucose (p=0.002), post prandial blood glucose(p=0.001), HbA1c (p=0.024), MPV (p=0.001), and White Blood Cell Count MPV Ratio (1283.2 ± 304.5 *vs* 1020.6 ± 313.9, p<0.001).

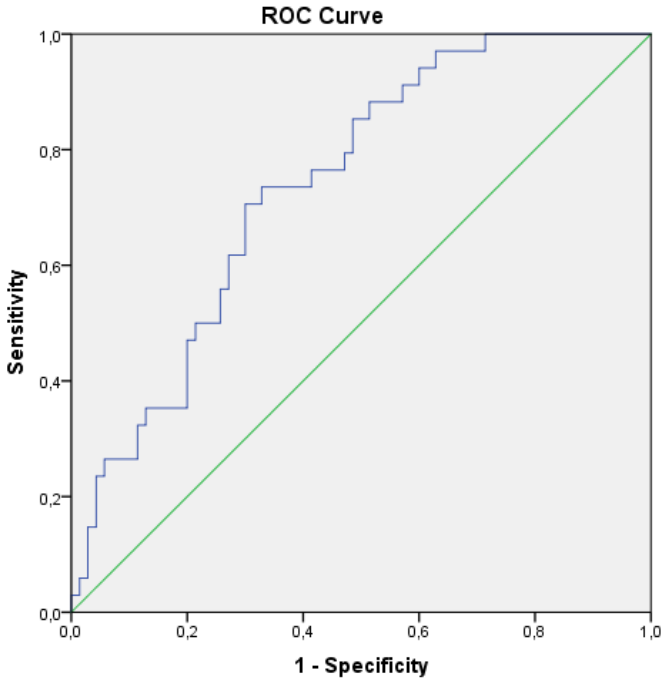
Significant difference was also found in TIMI score (p=0.041), GRACE score (p=0.007), and number coronary lession (p=0.001), MVCAD was found with higher rate in MACE group which is 30 subject (88.3%) compared to 40 subject (55.7%) in non MACE group. (Table. 1)

Table1.Baseline Characteristic of Study Subject According to MACE

Parameter	**MACE (-) n=70**	**MACE (+) n=34**	**P value**
Sex (n, %)			0.809
Male	52 (74.3)	26 (76.5)	
Female	18 (25.7)	8 (23.5)	
Age (years old)	54 ± 10	57 ± 8	0.195
BMI (kg/m^2)	25.6 ± 3	26.4 ± 3	0.218
SBP (mmHg)	136 ± 21	119 ± 31	0.001*
DBP (mmHg)	81 ± 11	75 ± 17	0.033*
Heart rate(x/minutes)	83 ± 16	98 ± 32	0.001*
Risk Factor (n, %)			
Hypertension	48 (68.6)	24 (70.6)	0.834
DM	23 (32.9)	19 (55.9)	0.025*

Dyslipidemia	39 (55.7)	21 (61.8)	0.558
Smoking history	31 (44.3)	28 (82.4)	<0.001*
Family history	21 (30)	13 (38.2)	0.401
Hb (mg/dL ± SD)	15.7 ± 16	13.3 ± 2	0.399
Leukocyte (10^3/uL ± SD)	9909 ± 2836	10284 ± 3226	<0.001*
Ureum (mg/dL ± SD)	34 ± 16	28.5 ± 12	0.103
Creatinin (mg/dL ± SD)	1.3 ± 1.6	1.1 ± 0.4	0.207
GFR (mL/min/1.73m2 ± SD)	71.1 ± 30	84.4 ± 30	0.036*
Random BG (mg/dL ± SD)	147 ± 64	206 ± 109	0.001*
fasting BG (mg/dL ± SD)	120 ± 51	166 ± 91	0.002*
Prandial BG (mg/dL ± SD)	152 ± 60	208 ± 100	0.001*
HbA1C (%±SD)	6.8 ± 1.9	7.7 ± 2.1	0.024*
Total Cholesterol (mg/dL ± SD)	180 ± 46	188 ± 53	0.404
Troponin (µg/L)	1.58 ± 3.6	1.95 ± 4.8	0.69
CKMB (U/L)	49 ± 35	55 ± 64	0.56
TG (mg/dL ± SD)	145 ± 57	150 ± 78	0.701
LDL (mg/dL ± SD)	120 ± 43	133 ± 50	0.166
HDL (mg/dL ± SD)	36.28 ± 10.42	36.3 ± 11.84	0.997
MPV (fL)	9.8 ± 0.73	10.3 ± 0.7	0.001*
WMR	1020.6 ± 313.9	1283.2 ± 304.5	<0.001*
Neutrofil (10^3/uL ± SD)	30.5 ± 30.3	30.4 ± 32.2	0.996
Limfosit (10^3/uL ± SD)	9.8 ± 10.6	9.7 ± 12.3	0.956
NLR	3.6 ± 2.2	4.6 ± 5.2	0.168
EF (%)	51.4 ± 12.9	42.1 ± 12.1	0.562
TIMI			0.041*
<3	28 (40.6)	8 (23.5)	
>3	42 (59.4)	26 (76.5)	
GRACE			0.007*
<109	51 (72.9)	20 (58.8)	
>109	19 (27.1)	14 (41.2)	
Coronary Lesion			
SVCAD	30 (42.9)	4 (11.7)	0.001*
MVCAD	40 (57.1)	30 (88.3)	0.004*

By using ROC curve, the Area Under the Curve (AUC) value of parameter White Blood Cell Count*MPV*Ratio (WMR) can be found, which will show the ability of WMR to predict MACE during hospitalization for NSTEMI patient. In this study, we found AUC 0.74with p value < 0.001 that shows that WMR value is clinically significant as MACE predictor during hospitalization in NSTEMI patient. With cut-off point ≤ 1118 can predict MACE with sensitivity 71% and specificity 70%. (Table 2)



Picture 1. ROC Curve for WMR to predict MACE during hospitalization

Table 2.Results from ROC analysis

Titik Potong	Sens	Spes	AUC	P value	95% CI
1118	71%	70%	0.74	<0.001	0.645-0.835

From 104 study subjects, 45 subjects have WMR ≥ 1118 and 59 subjects have WMR< 1118. Subjects with WMR≥ 1118 group had higher MACE compared to WMR< 1118 group [24 (70.6%) *vs*10(29.4%)]. 49subject (70%) in WMR < 1118 group and 21subject (30%) in WMR ≥ 1118 mm group did not have MACE. (Table3)

WMR value ≥ 1118can predict MACE with sensitivity70.6%, spesificity70%, *negative predictive value* (NPV) 83% and*positive predictive value* (PPV) 53%.

Table3.Diagnostic test for WMR cut off point

LMR	MACE		Total	P value	Sens	Spes	NPV	PPV
	Yes	No						
≥ 1118	24 (70.6)	21 (30)	45 (43.3)	<0.001	70.6%	70%	83%	53%
<1118	10 (29.4)	49 (70)	59 (56.7)					
Total	34 (100)	70 (100)	104 (100)					

Multivariate analysis in this study showed that there were three independent factor that could predict MACE during hospitalization which is **smoking history**[OR 5.57 (1.67-18.67), p=0.005], **SBP<100** [OR 11.63 (1.86-72.71), p=0.009] and **WMR**≥ 1118 [OR 10.49 (3.01-36.65), p<0.001] (Table4).

Table 4.Multivarite Logistic Regression Analysis of WMR to Predict MACE in NSTEMI Patients during Hospitalized

Parameter	P value	OR	Lower	Upper
Smoking History	0.005	5.57	1.67	18.67
SBP< 100	0.009	11.63	1.86	72.71
LMR ≥ 1118	<0.001	10.49	3.01	36.65

Discussion

This prospective cohort study showed that increasing of WMR was related to MACE during hospitalization in NSTEMI patient. Smoking history and SBP < 100 mmHg was also found to be independent predictor for MACE. WMR was also found to be a strong predictor for increased MACE and had higher value compared to other complete blood analysis component to predict outcome during hospitalization.

Older studies from MukhtarZ (1994) showed that leukocyte value was a strong predictor for MACE and AMI patient with initial leukocyte value > 15.000/µl had higher risk for left ventricle dysfunction as much as 4x higher, 4x higher mortality risk and 2x higher ventricular arrythmia (VT/VF) risk compared to initial leukocyte value < 15.000/µlwith 95,9%sensitivity[13]. Leukocyte could cause delayed microvascular reperfusion, increased free radical and proteolytic enzyme which will induce hypercoagulability state and activate tissue factor that will increase thrombus formation and infarct size. If those marker added with *MPV*that showed higher platelet size that had higher thrombogenicity, this could cause larger occlusion in coronary arteries. Because of that reasoning, a new parameter called WMR was found.

This study match the previous study by Dehgani MR et al (2015) which found that WMR value is a stronger predictor compared only leukocyte or only MPV. Dehghani et al also found that average WMR value was haigher in MACE group compared to non MACE group(863.2 vs731.5 with p=0.001), but average WMR value in Dehghani studies were lower compared to this study[14]. Variation in the WMR value possibly caused by several metabolic factor that exist in the study subject, because Leukocyte and MPV level can be affected by several factor such as Metabolic Syndrome, medication usage or several other factor.

WMR value ≥ 1118considered optimal to predict MACE according to ROC curve with sensitivity71% and specificity 70%. Study subject with WMR value ≥ 1118had higher MACE compared to WMR value < 1118which is 24subjects(70,6%) vs10subjects (29.4%). Cut off point by Arsalan MA et al (2017) that comes from ROC curve were > 1068.75 as an optimal cut off point to predict MACE with lower sensitivity and specificity comapared to this study which is 68.3% and 63,7% (AUC 0.734, p<0.001, 95% CI 0.656-0.812). Other studies also found lower optimal cutoff point compared to this study which is > 750[15]. Possible cause of variability in WMR cut-off point is because of difference in population where Arsalan et al (2017) include all patient with ACS and Dehghani et al (2015) include patient with metabolic syndrome also possibly caused by difference in *Hematology Analyzer* device and calibration[14,15].

After multivariate analysis has done, we found three independent factor that could predict MACE during hospitalization for NSTEMI patient, which is **Smoking History**[OR 5.57 (1.67-18.67), p=0.005], **SBP<100**[OR 11.63 (1.86-72.71), p=0.009] and **WMR ≥ 1118** [OR 10.49 (3.01-36.65), p<0.001].

Study Limitation

There are several limitation in this study such as lower number of study sample in this study as opposed to previous study and this study is only done in one centre therefore, further study needed with larger sample size.In this study MACE observation was only done during hospitalization meanwhile WMR value as a predictor usually done in for longer period of time such as 30 days or longer there longer follow up needed.This study also did not compare WMR value in all ACS patient, therefore further studies needed to find correlation between WMR value in this type of population and also revascluarization during hospitalization was not considered as outcome modificator so further studies needed to find correlation between intervention with MACE.

Conclusion

WMR is a cheap indicator, easy to be done, and can become a strong independent factor to predict MACE during hospitalization for NSTEMI patient compared to other complete blood parameter.

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