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## CORRELATION OF TRIGLYCERIDE-GLUCOSE INDEX (TyG) WITH MAJOR CARDIOVASCULAR EVENTS (MACE) DURING TREATMENT IN NON ST ELEVATION (NSTEMI) ACUTE MYOCARDIAL INFARCTION PATIENTS IN ADAM MALIK GENERAL HOSPITAL MEDAN

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DOI: 10.29121/ijrsm.v9.i2.2022.1

**Keywords:** Acute Coronary Syndrome, NSTEMI, MACE, TyG Index.

### Abstract

**Background:** NSTEMI is caused by partial occlusion of coronary artery induced by ruptured atheromatous plaque. Major Adverse Cardiovascular Events is an advanced clinical event in the cardiovascular system, consisting of cardiovascular death, malignant arrhythmia, cardiogenic shock, and acute heart failure. TyG index is metabolite of fasting glucose and TG which are associated with the occurrence of cardiovascular disease.

**Objective:** to assessed correlation between TyG index and MACE in NSTEMI patients as a prognostic marker for MACE.

**Methods:** NSTEMI patients who were treated at HAM Hospital Medan in January 2020 were examined for fasting glucose and TG levels, then were observed for MACE during in-hospital treatment. There were two groups includes experiencing MACE and without MACE that classified into TyG index  $\leq 8.805$  and  $\geq 8.805$ .

**Results:** From 86 NSTEMI patients, 54 (62.8%) experienced MACE with mean age was 56.52 years old. There was significant relationship between MACE with higher TyG index, GRACE score, fasting glucose, post prandial glucose, history of DM and dyslipidemia. ROC curve analysis showed that TyG index was able to predict the incidence of MACE (cut-off point 9.0021, AUC = 0.646,  $p < 0.024$ , sensitivity 61.1%, specificity 65.6%).

**Conclusion:** TyG index can predicts the incidence of MACE in NSTEMI patients.

### Introduction

In 2016, the World Heart Organization (WHO) stated that 17.9 million deaths were caused by cardiovascular disease. The Sample Registration System (SRS) Survey in 2014 in Indonesia showed that Coronary Heart Disease (CHD) was the highest cause of death at all ages after stroke, amounting to 12.9%.<sup>1</sup> Acute coronary syndrome (ACS) consists of unstable angina pectoris (UAP), non-ST segment elevation acute myocardial infarction (NSTEMI), and ST segment elevation acute myocardial infarction (STEMI).<sup>2</sup> NSTEMI occurs as a result of partial occlusion by ruptured atheromatous plaques and ruptured coronary vessels associated with changes in plaque composition and thinning of the fibrous covering of the plaque.<sup>3,4</sup> The clinical features of NSTEMI are angina pectoris at rest (>20 minutes), new-onset angina (Canadian Cardiovascular Society Classification class II or III), and destabilization of previous stable angina (at least Canadian Cardiovascular Society Classification class II). For abnormal ECG features, ST depression, transient ST segment elevation, T wave changes can be found, so that a normal ECG also can be found in 1/3 of patients. The clinical features and ECG changes are also accompanied by a significant increase in cardiac enzyme levels.<sup>5,6</sup>

Major Adverse Cardiovascular Events (MACE) are defined as advanced clinical events or complications resulting from a major process in the cardiovascular system, includes cardiovascular death, malignant arrhythmias, cardiogenic shock, and acute heart failure.<sup>7</sup> Blood glucose is reported as an independent predictor of atherosclerosis which blood glucose >90mg/dl can cause atherosclerosis in the carotid arteries. A long follow-up data on patients with DM type 1 and 2 indicate hyperglycemia as a risk factor for diabetes and cardiovascular disease.<sup>8</sup> Patients with DM have endothelial dysfunction, impaired platelet activation and coagulation, and have a more fragile atherosclerotic plaque composition. Insulin resistance is a decrease in insulin sensitivity in peripheral tissues where there is impaired glucose uptake and oxidation which has an important role in the pathogenesis of diabetes and cardiovascular disease. The majority of individuals with insulin resistance do not always progress to DM2 but still have a high risk of atherothrombosis/cardiovascular disease even without dyslipidemia.<sup>9</sup> Hypertriglyceridemia is one of the most common causes of dyslipidemia, but the relationship between triglycerides and the risk of coronary heart disease is still unknown.<sup>10</sup>



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Research by Zhang et al., stated that the cumulative risk of the incidence of DMT2 increases with the increase in the higher TyG index.<sup>11</sup> The TyG index is the product of fasting blood glucose levels and fasting triglyceride levels in the blood. Several recent studies have shown that the TyG index is associated with the occurrence of carotid atherosclerosis, coronary artery calcification, symptomatic CHD, and a high risk of cardiovascular disease.<sup>12,13</sup> The plasma TyG index has a parameter component that is always checked in patients with NSTEMI, is more affordable than other parameters, and can be calculated by a simple formula. Based on research from Salazar et al., insulin resistance can be assessed from the TyG index parameter with a cut off value of 4.49, sensitivity of 82.6%, and a specificity of 82.1%.<sup>11</sup> Jin et al in their study stated that the TyG index can predict major cardiovascular events in stable CHD patients during follow-up of 209 patients with 12.5% death, 24.14% having a stroke, 14.13% developing non-fatal infarction myocardial infarction, and 49.66% had to undergo PCI or emergency CABG.<sup>10</sup>

Several molecular mechanisms contribute to insulin resistance and cardiovascular disease, so we wanted to assess the relationship between the TyG index and MACE during in-hospital treatment in NSTEMI patients at Haji Adam Malik General Hospital Medan as a prognostic marker of MACE.

### Methods

#### Study Population

This research is an observational analytic study with an ambispective cohort design. This study compared the MACE between groups with TyG index values  $\leq 8.805$  and TyG values  $\geq 8.805$  in 86 samples. The sample must meet the inclusion criteria, including patients with a diagnosis of NSTEMI based on the PERKI diagnostic criteria (there is acute angina accompanied by a significant increase in cardiac enzymes without persistent ST-segment elevation in two adjacent leads and without left bundle branch block), the patient underwent therapy according to the medical service guidelines at the Integrated Heart Center of Haji Adam Malik Hospital Medan, and was willing to undergo fasting glucose and lipid profile examinations. As for ACS patients due to complications of elective percutaneous coronary intervention (IMA4), patients with AV block 2nd and 3rd degrees, anemia (Hb < 8) and history of hemoglobinopathy, AMI patients with KILLIP III and IV, patients with severe infectious disease, incomplete medical record data, and unwilling to participate in the study should be excluded.

#### Triglyceride-Glucose Index

Blood samples for diagnosis were taken when the patient was admitted to the ER for the first time, while the lipid profile and fasting blood sugar were taken after the patient fasted for 8 hours the next day. Blood tests were carried out at the Clinical Pathology Laboratory of Haji Adam Malik Hospital in Medan using Architech C4000 and C8000 tools. The ECG was assessed using the Bionet Cardiotech 3000 with a speed of 25 mm/s and an amplitude of 10 mV, while the echocardiography examination used a GE Vivid S6 heart probe 3.25 MHz or a Medison Accuvix 10 with a heart probe sector 3.50 MHz. Furthermore, the triglyceride levels and fasting glucose levels were into the TyG index formula, namely  $\ln [\text{fasting triglycerides (mg/dl)} \times 5 \text{ fasting glucose (mg/dl)} / 2]$ .

#### Statistical analysis

Statistical data processing and analysis used SPSS version 25 software. Categorical variables were presented with frequency (n) and percentage (%) which abnormal distributed data in the median form. The normality of numerical variables (sample >500) test is using the Kolmogorov-Smirnov test. Bivariate analysis for comparison between the two groups on categorical independent variables and categorical dependent variables used the Independent T-test (T-test). To determine the optimal value of the cut off point of TyG index to MACE was determined using the ROC curve. Then assessed Area Under Curve (AUC) to assess the prognostic power of the tested variables. P-value <0.05 is said to be statistically significant.

### Results

#### Subjects Characteristics

The subjects who participated in this study were 86 NSTEMI patients who met the inclusion and exclusion criteria. The results showed that the incidence of MACE was 54 patients (62.8%) with several parameters found to have a significant relationship to MACE, namely the average TyG index in the group with MACE was  $9.26 \pm 0.79$  while without MACE  $8.98 \pm 0.69$  ( $p = 0.024$ ), the mean GRACE score was higher in the MACE group  $117.43 \pm 27.71$



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than without MACE  $104.16 \pm 22.03$  ( $p=0.023$ ), the mean fasting glucose was higher in the MACE group  $160.57 \pm 72, 27$  than without MACE  $138.34 \pm 76.57$  ( $p=0.037$ ), and there was a relationship between MACE and history of DM ( $p=0.035$ ). Characteristics and baseline parameter data from NSTEMI patients who experience MACE are presented in table 1.

**Table 1. Characteristics of NSTEMI patients with MACE**

Parameter	MACE		P value
	Yes (n=54)	No (n=32)	
Age (years old)	56,52±8,683	56,25±10,144	0,897*
IMT (kg/m <sup>2</sup> )	25,252±2,847	24,438±3,368	0,235*
Sex			
Man	41(60,3%)	27(39,7%)	0,352**
Woman	13(72,2%)	5(27,8%)	
Revascularization			
Yes	19(61,3%)	12(38,7%)	0,829**
No	35(62,6%)	20(36,4%)	
Family History with MACE			
Yes	10(52,6%)	9(47,4%)	0,299**
No	44(65,7%)	23(34,3%)	
Hypertension			
Yes	32 (58,3%)	23 (41,8%)	0,239**
No	22(71,0%)	9(29,0%)	
Diabetes Mellitus			
Yes	46(68,7%)	21(31,3%)	0,035**
No	8(43,1%)	11(57,9%)	
Dyslipidemia			
Yes	16 (48,5%)	17(51,5%)	0,03**
No	38(71,7%)	15(28,3%)	
Smoking			
Yes	36(60,0%)	24(40,0%)	0,416**
No	18(69,2%)	8(30,8%)	
GRACE	117,43±27,71	104,16±22,03	0,023*
TyG	9,26±0,79	8,98±0,69	<b>0,024**</b> *
Troponin I	5,1007±7,81	3,5209±4,12	0,727** *
CKMB	63,17±42,20	63,63±62,03	0,607** *
Fasting glucose	160,57±72,27	138,34±76,57	0,037** *
Post prandial glucose	200,02±63,17	156,47±70,55	0,001** *
HbA1C	8,26±2,12	7,72±2,28	0,189** *
Total Cholesterol	179,17±53,108	185,94±52,647	0,568*
TG	159,98±104,08	141,63±90,12	0,535** *
HDL	34,09±9,91	37,84±7,70	0,071** *
LDL	124,74±64,48	133,47±54,17	0,167** *
Ureum	55,65±30,71	44,28±31,23	0,029** *



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Creatinine	1,47±0,88	1,17±0,47	0,091** *
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\*Independent t-test; \*\*Chi-Square test; \*\*\*Mann-Whitney test; \*\*\*\* Fisher Exact Test

In addition to assessing the relationship of various parameters to the incidence of MACE, this study also examined the relationship of blood laboratory results to the TyG index. Table 2 shows a significant relationship between high TyG index with higher fasting glucose levels ( $p=0.0001$ ), higher post prandial glucose levels ( $p=0.0001$ ), higher HbA1C ( $p=0.001$ ), higher TG levels ( $p=0.0001$ ), higher creatinine serum ( $p=0.009$ ), and low HDL levels ( $p=0.0001$ ).

**Table 2. Analysis of TyG index with laboratorium results**

Parameter	TyG Index (mean)		P value
	≤8,805	≥8,805	
Troponin I	3,01±3,59	5,32 ±7,9	0,647**
CKMB	64,43±55,15	62,75±47,75	0,856**
Fasting glucose	103,60±35,804	178,39±76,52	0,0001**
Post prandial glucose	145,07±43,01	204,57±71,49	0,0001**
HbA1C	6,94±1,52	8,652±2,26	0,001**
Total Cholesterol	179,90±56,28	182,64±51,23	0,820*
TG	101,30±35,85	180,93±110,50	0,0001**
HDL	39,57±8,64	33,30±8,94	0,0001**
LDL	130,87±52,70	126,45±64,93	0,559**
Ureum	44,33±24,64	55,21±33,81	0,146**
Creatinine	1,07±0,36	1,511±0,88	0,009**

\*Independent t-test; \*\*Chi-Square test

## Factors induced MACE

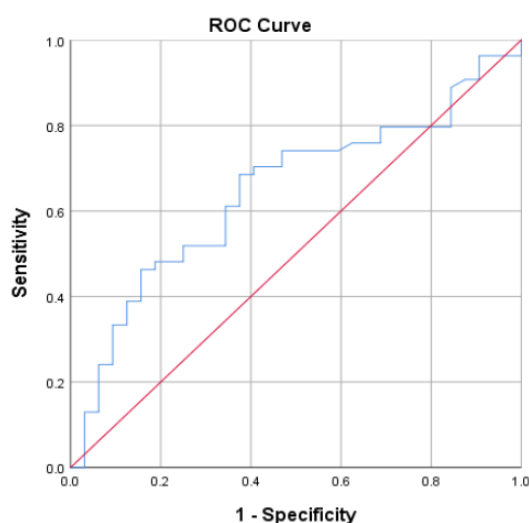
An analysis of the factors that induce MACE was performed by logistic regression, which variables that statistically significant in the bivariate test (GRACE score, fasting glucose, post-prandial glucose, ureum, and TyG index) were included in the analysis. The strongest OR value is the TyG index, which is 1.825.

**Table 3. Multivariate Analysis of Factors that induce MACE**

	Coefisien	S.E.	Wald	df	Sig	OR	IK95%	
							Min	Max
GRACE	0,028	0,012	5,592	1	0,018	1,029	1,005	1,053
Fasting glucose	-0,006	0,006	1,180	1	0,277	0,994	0,982	1,005
Post-prandial glucose	0,012	0,006	4,366	1	0,037	1,012	1,001	1,024
Ureum	-0,006	0,010	0,400	1	0,527	0,994	0,974	1,013
TyG Index	0,601	0,496	1,471	1	0,225	<b>1,825</b>	0,690	4,822

## Cut-off point, sensitivity, and specificity of TyG to MACE

Based on ROC curve analysis, it was found that the curve is located on the left side of the diagonal line, the small part that passes through the diagonal line with AUC = 0.646 ( $P = 0.024$ ; 95% CI 0.528-0.765). The cut-off value of TyG index from the ROC curve is 9.0021, but has a sensitivity of 61.1% and specificity of 65.6%, which means that TyG can be used to predict the incidence of MACE in NSTEMI patients with a possible false positive rate (1-specificity) of 34.4% (fig.1).



*Fig.1 Kurva ROC (Receiver Operating Characteristic) indeks TyG dengan MACE*

## Discussion

Major Adverse Cardiovascular Events (MACE) is defined as a follow-up clinical event or complication caused by a major process which in the early phase can occur due to myocardial necrosis itself, while further complications that occur within a few days to weeks usually occur due to the inflammatory process and healing of necrotic tissue. This event is the most severe complication of acute cardiovascular emergencies because it increases morbidity and mortality.<sup>7</sup>

There were no significant differences between age, BMI, sex, and family history of MACE. Existing studies do not compare the prevalence of MACE based on the subject's age because the prevalence of cardiovascular disease is majority found at the age of >40 years and will increase with age.<sup>14,15</sup> Regarding BMI, the study by Hartopo et al stated that there was no relationship between BMI and MACE, but it was detected that 47.7% of that research subjects were obese.<sup>16</sup> The relationship between sex and the incidence of MACE studied by Mozaffarian et al also did not show a significant difference even though males were found to be higher than females.<sup>15</sup> History of revascularization also found no significant difference in the two test groups. This is different with the study of Chako et al which stated that early revascularization with PCI in unstable ACS can reduce MACE cardiac death (RR 0.69).<sup>17</sup>

The insulin resistance that occurs in diabetes mellitus and impaired endothelial signaling contribute to inflammation, disrupt the balance between endothelial vasodilator and vasoconstrictor mechanisms, and increase cardiovascular risk.<sup>8</sup> The study by Yap et al, showed that DM was a predictor of mortality and MACE.<sup>18</sup> Another study also found that increasing 1 mmol/L in fasting glucose levels can increased the risk of cardiac death by 17%.<sup>19</sup> In contrast to our study which found there was no significant difference in the mean HbA1C of the two test groups. This study also found non-significant differences in TG, HDL, and LDL levels which may be explained by the administration of statins in all patients with or without MACE. Statins can provide anti-inflammatory, pleotropic, and protective effects that can prevent the occurrence of MACE.<sup>20</sup>

Triglyceride-Glucose index (TyG) is a new marker that has been shown to have high sensitivity and specificity in identifying the metabolic syndrome and insulin resistance. Several recent studies have stated that the TyG index is also associated with the occurrence of carotid atherosclerosis, coronary artery calcification, and a high risk of cardiovascular disease.<sup>21</sup> Our results showed that the mean TyG index was higher in the MACE group as much as  $9.26 \pm 0.79$  than without MACE  $8.98 \pm 0.69$  ( $p=0.024$ ). Correspondingly, Jin et al stated that an increase in 1-SD of TyG index was associated with a 23.2% higher risk for cardiovascular events, which was superior to triglycerides or other glycemic markers.<sup>10</sup> The study of Mao et al also confirmed our results that the incidence of MACE in NSTEMI patients was found to be more in patients with higher TyG index (>8,805), and Luo et al also stated that higher TyG index was a strong predictor of cerebral and cardiovascular events at 1 year in post-PCI-STEMI



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patients.<sup>22,23</sup> A meta-analysis involving 13.684 subjects showed that higher TyG index was also associated with two times risks of MACE (RR 2.09 [1.59, 2.76],  $p < 0.001$ ).<sup>24</sup> A study involving 4.319 Korean adults also indicated the TyG index was significantly associated with the presence of coronary calcifications. Furthermore, in 888 asymptomatic DMT2 patients, it was shown that a higher TyG index was also associated with an increased risk of coronary stenosis. The addition of TyG index on the Framingham variable resulted in an effective high prediction of cardiovascular disease.<sup>25,26</sup> The exact mechanism underlying the association between the TyG index and cardiovascular events remains unclear. It should be noted that the inflammatory markers responsible for the instability of atherosclerotic plaques, including TNF-, interleukins, leukocytes, and fibrinogen, also play important roles in the metabolic syndrome and other disorders. So the TyG index becomes a better marker in estimating cardiometabolic risk.<sup>10</sup>

Salazar et al. stated that insulin resistance can be assessed from the TyG index parameter with a cut off value of 4.49 with a sensitivity of 82.6% and a specificity of 82.1%.<sup>11</sup> Another study showed similar results, namely the TyG index threshold of 9.323 was considered good enough to predict MACE (Sensitivity 46.0%; specificity 63.6%; area under the curve 0.560;  $P = 0.001$ ).<sup>27</sup> Accordingly, our study obtained a cut-off point of TyG index of 9.0021 with a sensitivity of 61.1%, a false positive rate (1-specificity) of 34.4%, and a specificity of 65.6% in predicting MACE in NSTEMI patients.

### Conclusion

Of the total 86 NSTEMI patients treated at Haji Adam Malik Hospital Medan, the group with MACE had a higher TyG index with a cut-off point of 9.0021 (sensitivity 61.1%, specificity 65.6%). TyG index can be used as a new parameter in predicting the incidence of MACE in NSTEMI patients.

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