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[*Pane* et al., 6(12): December, 2019*] ISSN: 2349-5197
Impact Factor: 3.765

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

IMPACT OF ACUTE / CHRONIC GLYCEMIC RATIO ON IN-HOSPITAL MAJOR ADVERSE CARDIOVASCULAR OUTCOMES IN PATIENT WITH ACUTE CORONARY SYNDROMES AND DIABETES MELLITUS

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DOI: 10.5281/zenodo.3582286

Keywords: Acute/Chronic Glycemic Ratio, Major Cardiovascular Events, Acute Coronary Syndrome, Diabetes Mellitus.

Abstract

Background : Hyperglicemia is common and known as a determinant of adverse outcomes in Acute Coronary Syndrome (ACS), but acute fluctuation of blood glucose rather than chronic and stable hyperglicemia produces more oxidative stress. Therefore, combined acute and chronic blood glucose will reveal true acute glycemic rise. Particularly in patients with diabetes, in whom elevated blood glucose do not necessarily indicate the occurrence of acute hyperglicemia.

Methods : Data were collected from 126 consecutive patients with ACS and diabetes in Cardiac Centre Haji Adam Malik General Hospital Medan. We measured acute/chronic glycemic ratio by comparing blood glucose at admission and chronic estimation ([28.7 x HbA1c] – 46.7). Then we observed in hospital Major Adverse Cardiovascular Outcomes (MACEs) which consist of cardiovascular mortality, acute heart failure, malignant arrhythmia and cardiogenic shock. Statistical analysis was performed using mean difference, logistic regression, and receiver operating curve (ROC).

Results : Among 126 patients, MACEs were observed in 61 (48.4%) patients with the most common MACE was acute heart failure (25.2%). Bivariate analysis showed a significant relationship between the acute/chronic glycemic ratio and in hospital MACEs ($p < 0.001$). Acute/chronic glycemic ratio had AUC value 88.8%. The optimal cut-off value was 1.05 (sensitivity 83.6% ; specificity 75.4%). In multivariate logistic regression analysis, the acute/chronic glycemic ratio was the strongest predictor with an OR value of 15.781 (95% CI 6.15-40.46; p value <0.001).

Conclusions : Acute/chronic glycemic ratio can predict in-hospital MACE in ACS and DM patients with the cut-off value obtained was 1.05.

Introduction

Cardiovascular disease remains a major burden globally with high morbidity and mortality where 7.4 million deaths are caused by coronary artery disease (CAD). [1] In 2014, CAD was the most common cause of death in Indonesia at 12.9%. [2] In North Sumatra, the estimated incidence of CAD ranges from 44698 to 98336 people (0.5-1.1%). [3] Acute manifestations of CAD disease is acute coronary syndrome (ACS), consisting of three clinical spectrums, namely unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). [4]

Diabetes Mellitus (DM) is an independent risk factor and even considered equivalent to CAD. Riskesdas 2007 mentioned the prevalence of DM in urban areas by 5.7% and WHO predicted an increase in DM to reach 21.3 million in 2030. [4] Hyperglycemia is often found in ACS and is a strong predictor of death and complications in hospitals, in response to stress through the activation of a series of simpatoadrenal system which will affect carbohydrate metabolism. [5, 6]

An acute increase of blood glucose (BG) levels plays a greater role in terms of prognosis values, because acute fluctuations in BG produce greater oxidative stress compared with chronic and persistent hyperglycemia. For

this reason, comparing the BG value at admission and calculating the estimated chronic BG will reveal actual increase of BG and producing a better prognostic value compared to the absolute value of BG at admission only. This is especially useful in the DM patient where hyperglycemia at admission cannot be ascertained whether an acute increase in BG or chronic hyperglycemia conditions. [7, 8, 9]

Marenzi et al mentioned that the acute/chronic glycemic ratio was a better predictor of morbidity and mortality in IMA patients with DM compared to the BG at admission alone. Liao et al also found a similarity where the difference in acute and chronic BG or glycemic gap significantly in univariate and multivariate regression analyzes caused major adverse cardiovascular event (MACE). In addition, the glycemic gap also has a higher value of area under the curve (AUC) than the admission BG and HbA1c. [7, 8]

Based on the data above, it is necessary to have an objective assessment of the acute increase of BG by using a comparison parameter of acute and chronic BG. Therefore, the authors are interested in making research that aims to determine the ability of acute/chronic glycemic ratio in predicting in-hospital MACE in patients with ACS and DM, so it is expected to be a consideration in the management of ACS in daily practices.

Methods

Population and Research Design

This is a case control study conducted at Cardiac Centre Haji Adam Malik General Hospital, Medan. Involving 126 consecutive patients based on inclusion and exclusion criteria from November 2018 to August 2019. Patients with a diagnosis of ACS and DM were the population in this study. Patients with complications of percutaneous coronary intervention (IMA type 4), anemia (Hb <8 g / dl), history of hemoglobinopathy, long-term steroid treatment, and admission hypoglycemia (BG <70 mg / dl) will be excluded from this study.

After looking at medical record data, the study sample was divided into two groups based on MACE, namely patients with MACE and patients without MACE. MACE is assessed during hospital stay which includes cardiovascular death, malignant arrhythmias, cardiogenic shock, and acute heart failure. The parameters were obtained through BG at admission and HbA1c taken after the patient was fasted for about 8 hours the next day. Next, we estimate the estimated chronic BG using the formula ([28.7 x HbA1c] - 46.7) to get the value of the acute/chronic glycemic ratio.

Statistical analysis

Data will be presented descriptively by displaying frequency distribution and percentage for categorical variables. Numerical variables that are normally distributed are represented by mean values and standard deviations, while data that are not normally distributed are presented in the form of medians and minimum-maximum values. Analysis for comparison between the two groups on numerical and categorical independent variables using the T-Independent test (T-test). If the T-Independent test requirements are not met, the Mann Whitney test is used. A receiver Operator Characteristic (ROC) curve was plotted to analyze the discriminative power of the prediction tools, and the Area Under the Curve (AUC) and the corresponding 95% confidence intervals (CI) were calculated. Variables that are considered significant in the bivariate analysis will be included in the multivariate analysis which is displayed in the form of Odds Ratio (OR) with a 95% confidence interval. Processing and analysis of statistical data using SPSS version 25, the variable is considered significant if the p value <0.05.

Results

This study included ACS and diabetic patients who were treated both in intensive care units and regular ward in Cardiac Centre Haji Adam Malik General Hospital, Medan

ISSN: 2349-5197
Impact Factor: 3.765

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Table 1. Baseline Characteristics

Variables	n=126
Age (years)	56.6 ± 9.7
Male	96 (76.2%)
Family History	29 (23%)
Dyslipidemia	55 (43.7%)
Smoker	88 (69.8%)
Hypertension	84 (66.7%)
Diagnosis	
STEMI	54 (42.9%)
NSTEMI	55 (43.7%)
UAP	17 (13.5%)
MACE	
Acute Heart Failure	32 (25.2%)
Malignant Arrhytmia	15 (11.8%)
Cardiogenic Shock	21 (16.5%)
Cardiovascular Mortality	5 (4.5%)

From the entire sample, it was found that the majority were male, 96 people (76.2%) with an average age of 56.6 ± 9.7 years. Risk factors consisted of 55 people with dyslipidemia (43.7%), 88 people smoker (69.8%), 84 people with hypertension (66.7%), and 29 people (23%) with a family history. The most common diagnosis in this study were NSTEMI as many as 55 people (43.7%). MACE was found in 61 people (48.4%) with acute heart failure was the most common finding, 32 patients (25.2%). Cardiogenic shock occurs in 21 people (16.5%), malignant arrhythmias 15 people (11.8%), and cardiovascular mortality occurs in 13 people (10.2%).

Table 2. Clincal Characteristics

Variables	MACE		P value
	Yes (n=61)	No (n=65)	
Systolic Blood Pressure (mmHg)	120.0 (70-180)	130.0 (90-220)	**0.027**
Diastolic Blood Pressure (mmHg)	80.0 (6-110)	80.0 (50-110)	0.248
Heart Rate (x/i)	92 ± 19.0	79 ± 19.6	**0.010**
Diagnosis			
STEMI	21 (34.4%)	33 (50.8%)	
NSTEMI	33 (54.1%)	22 (33.8%)	0.072
UAP	7 (11.5%)	10 (15.4%)	
GRACE *Score*	106.5 ± 31.1	105.3 ± 27.5	0.816
LVEF (%)	40 (24-59)	45 (20-67)	0.050
Coronary Lesion***			
CAD 1VD	8 (22.8%)	12 (29.2%)	
CAD 2VD	10 (28.5%)	14 (34.1%)	
CAD 3VD	15 (42.8%)	12 (29.2%)	0.744
LM Disease	2 (5.7%)	3 (7.3%)	

***76 Patients

From table 2 above we can see statistically significant differences between two groups in terms of some parameters, namely systolic blood pressure (SBP) and heart rate (HR). SBP in the group with MACE (120 mmHg) was lower than the group without MACE (130 mmHg). The average HR of the MACE group was higher than the group without MACE. The diagnosis of STEMI was more common in the group without MACE (33 people, 50.8%), while NSTEMI was more common in the group with MACE (33 people, 54.1%). Risk stratification with the GRACE score was found to be higher in the MACE group with a mean value of 106.5. Although statistically the diagnosis and GRACE score were not found to be significant differences between the two groups.

Table 3. Laboratory Findings

Variables	MACE		P Value
	Yes (n=61)	No (n=65)	
Hemoglobin (g/dl)	13.4 ± 1.9	13.3 ± 2.1	0.683
Hematokrit (%)	39 (26-54)	42 (28-52)	0.456
White Blood Cells (/mcgl)	11630 (5710-33490)	10480 (329-25590)	0.113
Mean Platelet Volume ($mcgm^3$)	10.3 (8.5-14.8)	9.9 (8.5-14.8)	0.090
Creatinin (mg/dl)	1.19 (0.63-7.18)	1.14 (0.59-4.60)	0.439
Troponin I (ng/ml)	1.4 (0-32)	1.2 (0-32)	0.339
CK-MB (ng/ml)	41 (16-673)	50 (13-541)	0.691
Osmolality (mOsm/L)	**291 (262-333)**	**284 (248-318)**	**0.002**
HbA1C (%)	8.6 (4.8-14.1)	8.6 (5.2-15.4)	0.909
Admission BG (mg/dl)	**290 (117-665)**	**164 (69-426)**	**<0.001**
Acute/Chronic Glycemic Ratio	**1.30 (0.80-2.50)**	**0.9 (0.40-1.60)**	**<0.001**
LDL (mg/dl)	108 (53-473)	117 (47-283)	0.246
HDL (mg/dl)	35 (13-60)	32 (9-61)	0.651

The table above shows the laboratory characteristics of the subjects, found statistically significant differences in the parameters of osmolality, admission BG, and the acute/chronic glycemic ratio. These three parameters were found to be higher in the MACE group compared to the group without MACE. The MACE group had a median osmolality value of 291 mOsml/L, an admission BG value of 290 mg / dl, and acute/chronic glycemic ratio value of 1.3. While other laboratory parameters such as hemoglobin, hematocrit, leukocytes, MPV, creatinine, troponin-I, CK-MB, HbA1c, LDL, and HDL did not find statistically significant differences in the two groups.

Tabel 4. Characteristics Based on Management

Variables	MACE		P Value
	Yes (n=61)	No (n=65)	
Dual Antiplatelet			
Aspirin + Clopidogrel	52 (85.2%)	49 (75.4%)	0.245
Aspirin + Ticagrelor	9 (14.8%)	16 (24.6%)	
ACEi/ARB	49 (80.3%)	53 (81.5%)	>0.999
Beta Blocker	47 (77.0%)	51 (78.5%)	>0.999
Statin	61 (100%)	65 (100%)	
Insulin	61 (100%)	65 (100%)	
Anticoagulant			
Enoxaparin	37 (60.7%)	41 (63.1%)	
Fondaparinux	21 (34.4%)	19 (29.2%)	0.712
Unfractioned Heparin	3 (4.9%)	5 (7.7%)	
Coronary Angiography	35 (57.4%)	41 (63.1%)	0.797
Revascularization Strategy			
Conservative	39 (63.9%)	35 (53.8%)	0.333
PCI	22 (36.1%)	30 (46.2%)	

The table above shows the management obtained by research subjects where no statistically significant differences were found between two groups. All study subjects received insulin therapy and statin regimens. The MACE group received more dual antiplatelet therapy with aspirin and clopidogrel (52 patients, 85.2%), fondaparinux (21 people, 34.4%), and received a conservative strategy (39 people, 63.9%). In the group without MACE, received more dual antiplatelet therapy with aspirin and ticagrelor (16 people, 24.6%), ACEi/ARB (53 people, 81.5%) and beta blockers (51 people, 78.5%), enoxaparin (41 people, 63.1%). Patients in this group also performed more coronary angiography (41 people, 63.1%) and PCI (30 people, 46.2%) even though it was not statistically significant.

The acute/chronic glycemic ratio cut-off value was obtained using the ROC curve as shown in Figure 1, then AUC value to predict MACE is 88.8% with a p value <0.001. The cut off value was 1.05 with a sensitivity of 83.6% and a specificity of 75.4%.

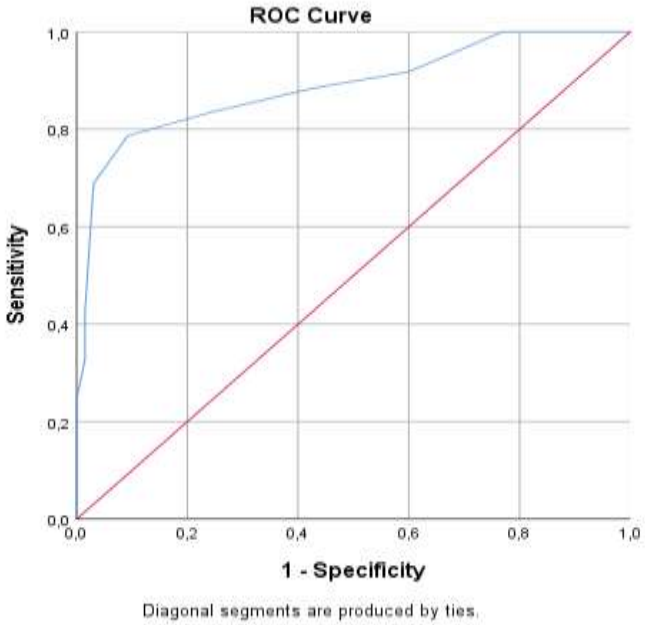

Figure 1 ROC Curve of Acute/Chronic Glycemic Ratio

Tabel 5. Multivariate Analysis of MACE Predictor in ACS and DM Patients

Variables	Coeficient (OR)	P Value	CI 95%	
			Min	Mak
Systolic Blood Pressure (mmHg)	**7.838**	**0.035**	**1.152**	**53.335**
Heart Rate (x/i)	1.721	0.261	0.668	4.436
LVEF (%)	1.365	0.593	0.436	4.274
Acute/chronic Glycemic Ratio	**15.781**	**<0.001**	**6.154**	**40.467**

The final results of multivariate analysis showed that there were two independent factors predicting MACE, namely systolic blood pressure and acute/chronic glycemic ratio ratio. Where the acute/chronic glycemic ratio is the strongest predictor with an OR value of 15,781 (p value <0.001).

Discussion

Hyperglycemia is common and has a poor prognostic value in patients with ACS. But the acute increase of BG is related to proinflammatory and protrombotic conditions, suppressing cardiac contractility, thereby increasing the risk of both short and long-term complications and mortality in ACS patients. [7] The presence of acute fluctuations in BG results in greater oxidative stress compared with chronic and persistent hyperglycemia. [8, 9]

Of the 126 sample in this study, there were 61 people (48.4%) experiencing MACE. The most common was acute heart failure, 25.2% (32 people). Previous study in NSTEMI patients by Vakili et al assessed in hospital and 6 months follow up of MACE of 27%, including number of deaths, re-hospitalization and reinfarction. [10] In addition, the study conducted by Haque et al, the most complications of acute myocardial infarction was heart failure around 53% and arrhythmias around 27%. [11]

There is a linear relationship between the increase in BG and mortality regardless of the presence or absence of diabetes. There are 3 hypotheses related to hyperglycemia as a predictor of mortality in acute medical

conditions, first an increase in BG as a physiological response to stressors. Second, hyperglycemia as an indicator of organ metabolic dysregulation. Third, hyperglycemia causes pro-inflammatory, pro-thrombotic, and worsening endothelial dysfunction. [12]

Admission hyperglycemia is significantly associated with 30-day mortality, especially in the group without a history of diabetes. Threshold values and linear relationships are not seen in groups with a history of diabetes, so in determining hyperglycemia it is very important to pay attention to the status of diabetes. [13] Hyperglycemia in DM patients should be considered whether an event is acute or chronic. Patients with the same hyperglycemia have a different risk of outcome based on their estimated status of chronic BG. This shows the acute increase in BG compared to absolute values is more associated with poor outcomes. The HbA1c value represents the average BG for the past 3 months, and is not affected by acute stress conditions, and can be converted to an estimate of chronic BG. By using a formula to convert the HbA1c value, the comparison of BG admission with estimated chronic BG can show the actual stress condition of hyperglycemia. [7-8]

Marenzi et al found the ability of the admission BG value in predicting morbidity, mortality, and infarct size in IMA patients increases significantly when including the estimation of chronic BG. By comparing the acute BG value and the estimation of chronic BG, the values of the acute/chronic glycemic ratio are obtained, values above 1.3 have a prognostic value in patients with ACS, especially in the DM group because admission hyperglycemia does not always show an actual high value. The same thing was found in the study of Roberts et al, using a comparison of admission BG and estimated mean BG, there was a strong association with acute medical conditions compared to admission BG alone. [8, 14]

In present study, the highest acute/chronic glycemic ratio values were found in the MACE group with a median value of 1.3, then using the ROC curve obtained a cut off of 1.05 with a sensitivity of 83.6% and a specificity of 75.4%. In bivariate analysis using cut-off values, the group of high acute/chronic glycemic ratio are more at risk for MACE. Previous study by Marenzi et al stated that : (1) the acute/chronic glycemic ratio is a better predictor of morbidity and mortality in IMA patients with DM compared to the BG at admission alone. (2) Prognostic value of acute/chronic glycemic ratio is stronger in the group of patients with DM than patients without DM with net reclassification values of 30% and 10%, respectively.[8] This is consistent in this study where the acute/chronic glycemic ratio is the strongest dependent variable in multivariate analysis with an OR value of 15,781 (p value <0.001).

In diabetic patients, hyperglycemia at admission (increase in BG values) does not necessarily reflect acute fluctuations of BG, so the assessment of acute/chronic glycemic ratio can identify true hyperglycemic stress and assist clinicians in risk stratification and deciding insulin therapy in ACS patients with hyperglycemia. Kosiborod et al mentioned BG normalization in IMA patients at admission associated with better survival. [15] In contrast, study by Umpierez et al stated that diabetic patients undergoing CABG with strict glycemic control did not show good results. [16] This has led to debate over the role of glycemic control in ACS. ESC recommendation for glycemic control below 200 mg/dl is also still based on expert opinion and not derived from large studies. In DM, there is cellular adaptation to chronic hyperglycemia, a sudden decrease in BG has an adverse effect. Intensive glycemic regulation does not reduce the extent of infarction and is associated with harm in ACS patients treated with percutaneous intervention.[7] Patient with DM often presents with hyperglycemia at presentations, but do not always show an acute increase, so a decrease in BG is not useful, this is in line with previous studies where glycemic variability in DM patients is more likely to produce effects of oxidative stress, platelet activation, and vascular complications rather than an increase in Chronic BG. [17]

Limitiations of this study are single center with clinical presentation of ACS and revascularization strategies that vary although statistically not significant between the MACE and non-MACE groups. This research is an observational analytic study so the causal relationship cannot be ascertained. The management of hyperglycemia is still very varied and not included in this study so that it can affect the incidence of MACE in each group.

Future studies are expected to be carried out by involving many hospitals and can be focused on the AMI or STEMI patient and with a more uniform revascularization strategy so as to reduce the existing bias. In addition,

with the results of this study, it is expected that further research will use the acute/chronic glycemic ratio as a basis for insulin therapy decisions in ACS patients with hyperglycemia and see their effects on long-term complications such as reduction in infarct area and MACE after 6 months or 1 year later.

Conclusions

Acute/chronic glycemic ratio can predict in-hospital MACE in ACS patients with the cut-off value obtained is 1.05.

Conflict of Interest

The authors declare that there is no conflict of interest.

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