The Association Between Uric Acid Levels and GRACE Score in Acute Coronary Syndrome Patients at H. Adam Malik Medan Central General Hospital

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DOI: 10.29322/IJSRP.12.08.2022.p12822
http://dx.doi.org/10.29322/IJSRP.12.08.2022.p12822

Paper Received Date: 11th July 2022
Paper Acceptance Date: 27th July 2022
Paper Publication Date: 6th August 2022

ABSTRACT

Background: Acute coronary syndrome (ACS) is a combination of clinical symptoms that indicate acute myocardial ischemia, consisting of unstable angina pectoris (unstable angina pectoris = UAP), ST-Segment Elevation Myocardial Infarction (STEMI), and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI). Various factors are considered to be related to the incidence of ACS, one of the predisposing factors which is still being debated about its effect on ACS, namely uric acid levels. A previous study showed that adding serum uric acid values to the GRACE score may be better at identifying patients in the low-risk group.

Objective: To determine the relationship between uric acid levels and GRACE scores in ACS patients at H. Adam Malik Hospital, Medan.

Methods: This study is a retrospective analytic study. The study population was patients with acute coronary syndrome who were treated at H. Adam Malik Hospital Medan and the research subjects were 65 people who met the inclusion and exclusion criteria. Data analysis was performed using univariate and bivariate analysis. The correlation test was carried out using the Spearman correlation test to see the relationship between uric acid levels and the GRACE score in ACS patients.

Results: There were 65 samples who participated in this study. There was a significant difference ($p = 0.008$) in the mean uric acid levels in subjects with UAP, NSTEMI, and STEMI, while the GRACE score did not show a significant difference between the three ACS diagnoses. For the relationship between uric acid levels and GRACE scores for all subjects, the Spearman correlation test showed that there was a significant correlation between uric acid levels and GRACE scores ($p < 0.001$) with a correlation value (r) of 0,634.

Conclusion: From the results of this study, it can be concluded that there is a significant relationship between serum uric acid levels and the GRACE score and the higher the uric acid level, the higher the GRACE score will be.

Keywords: Acute coronary syndrome, GRACE score, Gout

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death worldwide, resulting in more than 17 million deaths each year. This disease shows various manifestations such ascoronary heart disease, heart failure, hypertension, stroke, and coronary artery disease (CAD). Coronary artery disease, which can cause acute coronary syndrome (ACS), is responsible for nearly half of the total deaths worldwide due to CVD.[1]

Acute coronary syndrome (ACS) is a combination of clinical symptoms that indicate acute myocardial ischemia, consisting of unstable angina pectoris (UAP), ST-Segment Elevation Myocardial Infarction (STEMI), and Non-ST- Segment Elevation Myocardial Infarction (NSTEMI).). The typical presentation of chest pain in ACS is a feeling of pressure or heaviness in the retrosternal area (angina) that radiates to the left arm, neck, or jaw, may occur intermittently or persist. Thesecomplaints can also be accompanied by diaphoresis, nausea, abdominal pain, dyspnoea and fainting (Lefrandt et al., 2016). UAP is defined by the presence of ischemic symptoms without elevated biomarkers and typically transient, also may be accompanied by ECG changes. The term myocardial infarction (MI) is used when there is evidence of myocardial necrosis in acute myocardial ischemia. STEMI is distinguished from NSTEMI by the ECG, which is characterized by persistent ST-segment elevation.[2,3]

Various factors are related to the incidence of ACS, one of the predisposing factors which is still being debated about its effect on ACS, is patient's uric acid levels. According to a study by It was found that about 33.3% of patients with ACS also had hyperuricemia. High uric acid levels are also associated with metabolic syndrome and the risk of cardiovascular disease. Hyperuricemia is found in about 39% of all deaths from cardiovascular disease. Uric acid serum is produced by the enzymatic activity of xanthine oxidase and is the main end

product of purine metabolism, most of which comes from food, biosynthesis, and breakdown of nucleic acids. Uric acid serum levels reflect the degree of xanthine oxidase activation. During uric acid production, oxygen free radicals are generated and therefore uric acid is a simple and useful clinical indicator of excessive oxidative stress. In humans, one of the tissues with the highest xanthine oxidase activity is the capillary endothelium and small arterial endothelium, important sources of oxygen free radical production in the endothelium. One of the main factors responsible for impaired regulation of vascular tone is increased oxidative stress. Nitric oxide synthesis is impaired, and its degradation is accelerated by excessive free radical activity leading to endothelial dysfunction. Thus, increased levels of uric acid can lead to the formation of oxygen free radicals and indirectly can cause endothelial dysfunction.[4]

High serum uric acid levels also promotes LDL-C oxidation and lipid peroxidation. It also increases the formation of oxygen radicals in inflammatory reactions. In addition, high levels of serum uric acid also increase platelet aggregation and formation of uric acid crystals. The deposition of uric acid in the arterial walls can damage the tunica intima of arteries, promoting coronary thrombosis. Based on the above description, we can conclude that uric acid serum level can be used as a variable for cardiovascular disease risk stratification and risk stratification system for patients with MI. One such scoring system is the Global Registry of Acute Coronary Events (GRACE) risk score.[5]

A study showed that adding serum uric acid values to the GRACE score may be better at identifying patients in the low-risk group. In patients with the entire spectrum of ACS, elevated uric acid scores were an independent factor associated with all other causes of death at short-term patient follow-up and adding uric acid values had a predictive value above the GRACE risk score where for each increase in uric acid 1 mg/dL, the risk of 1-year mortality increased by 26%. There are two categories of GRACE scores, GRACE scores less than or equal to one hundred (≤100) and GRACE scores greater than one hundred (>100). The GRACE score was associated with prediction of early and late death in ACS patients. Therefore, this study aims to explain the relationship between uric acid levels and GRACE scores in ACS patients. Thus, it is expected to be one of the considerations in determining the prognosis in ACS patients. [4]

ACUTE CORONARY SYNDROME

Definition

Acute coronary syndrome is a group of clinical symptoms caused by acute myocardial ischemia and includes Unstable Angina Pectoris (UAP), Non-ST-Segment Elevation Myocard Infarction (NSTEMI), and ST-Segment Elevation Myocard Infarction (STEMI). UAP is defined as angina pectoris or ischemic-type chest discomfort that (1) occurs at rest and lasts more than 20 minutes; (2) the pain is severe and usually clear;
(3) the pain is getting heavier or more frequent than before. STEAM and NSTEMI are basically almost the same based on the pathophysiology and clinical symptoms but differ in severity. In NSTEMI there has been necrosis or myocardial damage, whereas in UAP there has been no myocardial damage. STEMI is a clinical syndrome characterized by electrocardiography (ECG) in the form of persistent ST elevation and the release of biomarkers of myocardial necrosis. STEMI and NSTEMI differ in terms of the ECG appearance and are both accompanied by the release of biomarkers of myocardial necrosis.[6]

Epidemiology

Acute coronary syndrome is the cause of 7.7 deaths worldwide each year. There are 1.1 million hospital patients in America who are diagnosed with acute coronary syndrome and 74% of them have acute myocardial infarction. The incidence of acute coronary syndrome almost always persists every year, although currently the management of risk factors for acute coronary syndrome has been improved drastically. ACS is currently the leading cause of death in the Asia Pacific region.[7]

Based on the study of the Global Registry of Acute Coronary Events (GRACE) in a patient population in the United States, it was found that 38% of patients diagnosed with ACS had STEMI. Based on data from Jakarta Acute Coronary Syndrome (JAC) in 2008–2009 there were 2013 people diagnosed with acute coronary syndrome, and 654 of them experienced STEMI.[8]

Risk Factors

Risk factors for ACS include modifiable and non-modifiable risk factors. Modifiable risk factors are hypertension, cholesterol, smoking, obesity, diabetes mellitus, hyperuricemia, lifestyle, lack of physical activity, and stress levels. While the non-modifiable risk factors are age, gender, and family history of disease.[9]

Patophysiology

The myocardial ischemia and angina symptoms occur due to an imbalance between oxygen supply and myocardial oxygen demand. Normally for every oxygen demand, myocardial cells can control the amount of oxygen supply to prevent hypoperfusion and myocardial ischemia. Adequate oxygen supply is determined by coronary blood flow, amount of oxygen, lung function, and hemoglobin count. Coronary blood flow is controlled by the ability of the coronary blood vessel walls to dilate and constrict in accordance with the demand for oxygen by myocardial cells. One of the causes of disruption of the ability to dilate and constrict coronary blood vessels is atherosclerotic plaque.[10]

The process of atherosclerosis is a process that underlies the occurrence of ACS. It is a multifactorial process with interrelated mechanisms (Figure 1). Atherosclerosis is initially characterized by early abnormalities in the endothelial layer, formation of foam cells and fatty streaks, formation of fibrous plaque (connective tissue lesions) and unstable atherosclerotic plaque rupture process. Atherosclerosis is a chronic inflammatory process. Inflammation plays an important role in every stage of atherosclerosis, from the early development of plaque-to-plaque rupture which can lead to thrombosis. Endothelial dysfunction is caused by traditional risk factors such as dyslipidemia, hypertension, diabetes mellitus, obesity, smoking and other risk factors such as homocysteine and hemostatic disorders.[11]

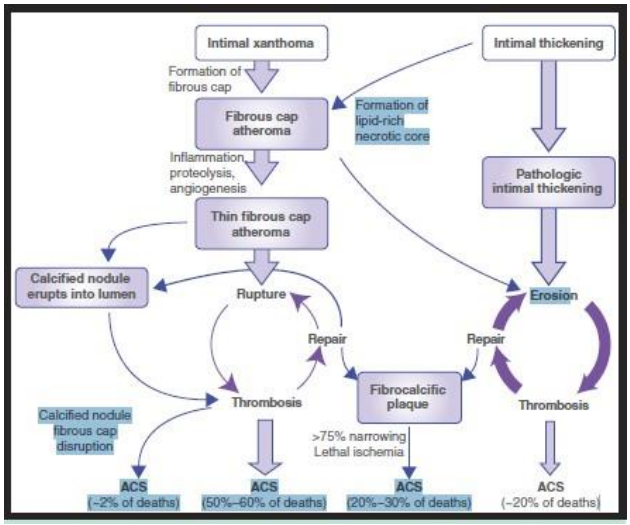

Figure 1. Atherosclerosis formation mechanism

Diagnosis

ACS patient main complaints is discomfort in the chest that is difficult to locate, dull, and usually radiates to the left arm, jaw, or neck. This pain lasts >20 minutes, does not go away with rest or nitroglycerin. If the patient has previously experienced complaints of chest pain or stable angina, the patient will feel the chest pain more severe than before. The pain also which radiates to the two upper extremities or to the right arm was more specific for ACS than pain radiating to the left arm alone with a specificity rate of 96%. The presence of risk factors for ACS from the patient's previous history, such as hypertension, diabetes mellitus, hyperlipidemia, and smoking habits can also help direct the diagnosis of ACS. From several studies, it was also found that 12% of patients with ACS diagnosis did not have ACS risk factors. On physical examination, we will find ACS patients will have cold sweats, wet and cold acral, S3 or S4 heart sounds, systolic murmurs at the apex, wet crackles due to pulmonary edema, and if the patient have severe condition, cardiogenic shock will occur.[12]

The first examination that can be done on a suspect of ACS is an ECG. In UAP and NSTEMI there will be ST segment depression and T wave inversion. T wave inversion is considered significant if the T wave first appears and has an amplitude > 0.2 mV. It is advisable to repeat the ECG every 20 – 30 minutes until the angina symptoms disappear or the ACS diagnosis can be established or ruled out. This is because ischemia can occur in the myocardium that is not detected by a 12-lead ECG. We can also do an ECG examination with the addition of leads V7–V9 to see ischemia in the posterior or V3R-V4R to see ischemia in the right ventricle. In STEMI, an ST segment elevation of 0.2 mV will be found in male patients aged ≥40 years and an ST segment elevation of 0.25 mV in male patients aged <40 years. Meanwhile,

female patients are diagnosed with STEMI if the ST segment elevation is 0.15 mV in leads V2 – V3 and the ST segment elevation is 0.1 Mv in the other leads.[13]

Biomarker examination as a marker of myocardial necrosis can be done by checking troponin and creatinine kinase-MB (CK-MB) levels. Cardiac troponin is a biomarker that is recommended because of its higher sensitivity and specificity compared to CK-MB. The prevalence rate of myocardial infarction increases from 30% to 80% when troponin testing is performed to establish the diagnosis of myocardial infarction. Troponins are detectable in serum 4-10 hours after the onset of angina. Troponin will reach peak levels 12-48 hours after onset and then remain in the serum for 4-10 days. Sensitivity for detecting troponin in serum is almost 100% if serum samples are taken 6-12 hours after onset. Therefore, the troponin test should be repeated 6-12 hours after the first examination to establish the diagnosis of acute myocardial infarction.[14]

Echocardiography can also be performed to assess the presence of left ventricular systolic and diastolic dysfunction, left atrial dilatation, mitral valve regurgitation and TAPSE (Tricuspid Annular Plane Systolic Excursion). If this condition is found, it is usually associated with a poor prognosis. CT angiography with contrast can be performed in patients with suspected ACS to (1) help establish the diagnosis or rule out the presence of epicardial coronary artery occlusion, (2) identify which arteries are atherosclerotic blocked, (3) assist in the assessment of risk stratification and prognosis of ACS patients.[14]

Risk Stratification

After the diagnosis of ACS is established, each ACS patient must be assessed for risk. Several risk stratification systems have been developed that assess several parameters during the acute phase. The Global Registry of Acute Coronary Events (GRACE) Score is recommended for risk assessment of ACS patients. The goal of risk stratification is to determine the next treatment strategy (conservative or immediate intervention) for a person with NSTEMI.[15]

GRACE classification consists of several variables, such age, Killip class, systolic blood pressure, ST segment deviation, cardiac arrest on arrival at the emergency room, serum creatinine, positive heart markers and heart rate (Figure 2). This classification is intended to predict mortality during hospitalization and within 6 months after discharge. For the prediction of in-hospital mortality, patients with a GRACE risk score 108 were considered to have low risk, and score of >140 had medium (1-3%) and high (>3%) mortality risk. For prediction of mortality within 6 months after discharge from hospital, In the hospital, patients with a GRACE risk score 88 were considered to have low risk and score of >118 have medium (3-8%) and high (>8%) mortality risk. Risk stratification based on the Killip class is a risk classification based on clinical indicators of heart failure as a complication of acute myocardial infarction and is intended to estimate the mortality rate within 30 days (Figure 3). [15]

Prediktor	Skor
Usia dalam tahun	
<40	0
40-49	18
50-59	36
60-69	55
70-79	73
80	91
Laju denyut jantung (kali per menit)	
<70	0
70-89	7
90-109	13
110-149	23
150-199	36
>200	46
Tekanan darah sistolik (mmHg)	
<80	63
80-99	58
100-119	47
120-139	37
140-159	26
160-199	11
>200	0
Kreatinin (µmol/L)	
0-34	2
35-70	5
71-105	8
106-140	11
141-176	14
177-353	23
≥354	31
Gagal jantung berdasarkan klasifikasi Killip	
I	0
II	21
III	43
IV	64
Henti jantung saat tiba di RS	43
Peningkatan marka jantung	15
Deviasi segmen ST	30

Figure 2. GRACE Score

Kelas Killip	Temuan Klinis	Mortalitas
I	Tidak terdapat gagal jantung (tidak terdapat ronkhi maupun S3)	6%
II	Terdapat gagal jantung ditandai dengan S3 dan ronkhi basah pada setengah lapangan paru	17%
III	Terdapat edema paru ditandai oleh ronkhi basah di seluruh lapangan paru	38%
IV	Terdapat syok kardiogenik ditandai oleh tekanan darah sistolik <90 mmHg dan tanda hipoperfusi jaringan	81%

Figure 3. Killip Score

HYPERURICEMIA

Definition

Hyperuricemia is a condition in which there is an increase in blood uric acid (UA) levels above normal. Hyperuricemia can occur due to increased metabolism of UA (overproduction), decreased urinary UA output (underexcretion), or a combination of both. There are many limits for diagnosing hyperuricemia, in general, AU levels above 2SD of laboratory results in the normal population are said to be hyperuricemia. The pragmatic limit that is often used for hyperuricemia is a condition where there is an increase in UA levels which can reflect pathological abnormalities. From the data, it was found that only 5-10% of normal men had UA levels above 7 mg% and a few of gout had

UA levels below these levels. So UA levels above 7 mg% in men and 6 mg% in women are used as limits for hyperuricemia.[16]

Epidemiology

Globally, the prevalence of gout has doubled between 1990-2010. In adults in the United States, gout is on the rise and affects 8.3 million (4%) Americans. Meanwhile, the prevalence of hyperuricemia is also increasing and affects 43.3 million (21%) adults in the United States.[16]

According to the Riset Kesehatan Dasar (RISKESDAS) in 2013, the prevalence of joint disease in Indonesia based on the diagnosis of medical professional is 11.9% and based on the diagnosis and symptoms is 24.7%. Meanwhile, based on the area, the highest was in Bali (19.3%), followed by Aceh (18.3%), West Java (17.5%) and Papua (15.4%).[17]

Uric Acid Biosynthesis

Abnormalities in the enzyme system that regulates purine metabolism can lead to overproduction of uric acid. Increased activity of Phosphoribosyl Pyrophosphate Synthase (PRPP) causes an increase in the concentration of PRPP, an enzyme that determines purine synthesis and causes uric acid production. Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT) deficiency can also cause uric acid overproduction. HGPRT is responsible for the conversion of guanine to guanylic acid and hypoxanthine to inosinic acid. These two changes require PRPP as a co-substrate and are important utilization reactions involved in nucleic acid synthesis. Deficiency of the HGPRT enzyme results in increased metabolism of guanine and hypoxanthine to uric acid and more PRPP interacting with glutamine in the early stages of the purine pathway. Decreased excretion of uric acid through the urine to be lower than the rate of production causes hyperuricemia and increased sodium urate level.[18]

Free urate crystals can activate several proinflammatory mediators, including Tumor Necrosis Factor α (TNF-α), Interleukin 1 (IL-1), and Interleukin 8 (IL-8). Activation of this mediator signals the chemotactic movement of neutrophils into the joint space, engulfing Monosodium Urate (MSU) crystals by phagocytosis. Neutrophils will lyse and release proteolytic enzymes that trigger acute gout attacks such as pain and swelling. This inflammatory mechanism in gout, especially in untreated disease, can lead to cartilage and joint damage.[18]

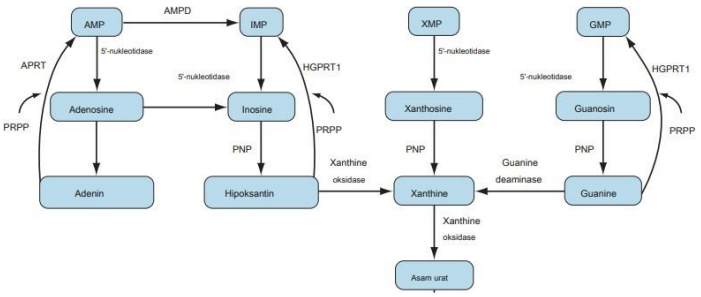

Figure 3. Uric acid biosynthesis

Inflammation and ACS

Research over the last few decades has shown that inflammation is a key factor in the development of CAD and other manifestations of atherosclerosis. Various factors play a role in the pathogenesis of atherosclerosis including endothelial dysfunction, dyslipidemia, inflammatory and immunologic factors, plaque rupture, and smoking. In the process of atherosclerosis, there are key factors involved in the development of endothelial dysfunction, namely oxidation of Low-Density Lipoprotein (ox-LDL) and activation of various cell types and chemoattractant agents. Immune cells predominate in early atherosclerotic lesions, their effector molecules can accelerate the progression of atherosclerotic lesions, and inflammatory activation can lead to ACS.[11]

Hyperuricemia and Endtohelial Dysfunction

Vascular endothelium has a function as a biological barrier to the flow of blood cells and various solutions derived from Vascular Smooth Muscle Cells (VSMC). The endothelium regulates vascular muscle tone and permeability and maintains a balance between coagulation and fibrinolysis. The endothelium is also known to regulate the release of various vascular mediators such as Nitric Oxide (NO), Von Willebrand Factor, Endothelin-1 (ET-1), Angiotensin II (Ang-II), Adhesion Molecules and Cytokines. Nitric oxide is the main mediator produced by the endothelium which is formed from larginine with the help of the Endothelial Nitric Oxide Synthase (eNOS) enzyme. Nitric oxide has vasodilator, anti-platelet, anti-proliferative, anti-atherogenic, anti-inflammatory properties, and also can reduce vascular permeability.[19]

Vascular Endothelial Dysfunction (VED) is a chronic pathological condition in which NO formation and bioavailability are reduced and lead to reduced expression and activation of eNOS. Endothelial dysfunction caused by the production of Reactive Oxygen Species (ROS) and uncoupled eNOS causes a decrease in NO production. Oxidative stress plays an important role in the pathogenesis of VED. Furthermore, there is an increase in the expression of P-selectin, Vascular Cell Adhesion Molecule-1 (VCAM-1), and Monocyte Chemotactic Protein-1 (MCP-1) which results in the attachment of circulating monocytes and lymphocytes, and induces cell death apoptosis, which then together with macrophages and platelets, initiates smooth muscle cell migration and proliferation.[20]

Vascular endothelial dysfunction increases Asymmetric Dimethyl Arginine (ADMA), an endogenous inhibitor of eNOS that decreases NO formation and bioavailability. ADMA can be inactivated by Dimethyl Arginine Dimethylaminohydrolase (DDAH). Decreased DDAH activity leads to accumulation of ADMA, which may be the key to VED, which can inhibit eNOS and trigger the release of proatherogenic mediators. Increased uric acid increases proinflammatory mediators in VSMC. Hyperuricemia can also cause oxygenation of LDL and trigger the formation of lipid peroxidation, which can cause intimal thickening which eventually triggers the formation of atherosclerosis. Several studies have shown a significant role of hyperuricemia in the occurrence of VED which will lead to the formation of atherosclerotic plaques and ultimately lead to AMI compared to individuals with normal uric acid levels.[21]

Inflammation and MI

The relationship between increased uric acid levels with atherosclerosis is endothelial dysfunction and the inflammatory

process. Hyperuricemia causes the formation of platelet

aggregation in blood vessels, which ultimately triggers cardiovascular disease. The value of triglycerides, apolipoprotein B and apolipoprotein E increases and the value of High-Density Lipoprotein (HDL) decreases in hyperuricemia causing atherosclerosis. In fact, hyperuricemia provides the formation of free radicals, which stimulate lipid peroxidation thereby increasing intima thickness. Furthermore, oxidized LDL influences the inhibition of transcription and expression of eNOS. ROS induce lipid peroxidation which can disrupt the structure and viscosity of biological membranes, thereby affecting vascular function.[22]

Hyperuricemia induces arteriolopathy in the preglomerular vessels, which impairs the autoregulatory response of the afferent arteriole, causing glomerular hypertension. Hyperuricemia increases plasma renin values and causes the formation of Angiotensin II, subsequent activation of macrophages and increased production of cytokines resulting in inflammation and increased ROS and lipid peroxidase, which trigger atherosclerosis.[23]

Acceleration of the atherosclerotic process, with increased oxidative stress and underlying ROS, coupled with uncoupled endothelial eNOS and decreased production of naturally occurring local antioxidants lead to the formation of brittle plaques, acidic vascular intima, loss of local antioxidant effects, and endothelial dysfunction occurs. This shows that the increase in uric acid that occurs is an antioxidant response to oxidative stress in patients with traditional risk factors and CAD. Activation of Xanthine Oxidase (XO) will further increase oxidative stress, and with a reduced capacity of serum uric acid as an antioxidant, oxidative stress leads to vascular injury.[23]

The Multiple Risk Factors Intervention Trial (MRFIT) study found that hyperuricemia is an independent risk factor for acute myocardial infarction (AMI). The Apolipoprotein Mortality Risk Study (AMORIS) found that an increase in serum uric acid levels was associated with an increased incidence of AMI in adult patients without a previous history of cardiovascular disease. Other studies, in a systematic review and meta-analysis, have shown that hyperuricemia can marginally increase the incidence of CHD and is independent of other traditional risk factors.[24]

Uric acid can also be used to identify patients in the ACS group. A study showed that adding serum uric acid values to the GRACE risk score may be better at identifying patients in the low-risk group. In patients with the entire spectrum of ACS, elevated uric acid scores were an independent factor associated with all other causes of death at short-term patient follow-up and adding uric acid values had a predictive value above the GRACE risk score where for each increase in uric acid 1 mg/dL, 1-year mortality risk increased by 26%.[25]

MATERIAL AND METHODS

The research design used in this research is descriptive retrospective where data collection is done through medical records. The study was conducted at the Cardiology Division of the Department of Internal Medicine at H. Adam Malik Hospital Medan from November 2020 to March 2021. The target population of the study was patients with acute coronary syndrome, while the reachable population were patients with acute coronary syndrome who were treated at H. Adam Malik

Hospital, Medan. The subjects of this study were taken from the population of patients with acute coronary syndrome who met the inclusion and exclusion criteria, and in writing were willing to participate in this study by signing an informed consent form.

Research subjects with acute coronary syndrome and met the inclusion and exclusion criteria, were given informed consent and filled out a letter of consent to participate in the study. The research subjects then took a history of disease history and risk factors for CAD such as hypertension, diabetes mellitus, dyslipidemia, smoking history and family history of CAD. Then carried out laboratory examinations such as complete blood count, liver function test, kidney function test, lipid profile, blood glucose level, Troponin T, CK-MB, and uric acid level. Each patient was then calculated with a GRACE score based on the results of the physical examination, ECG, and pre-existing supporting laboratory tests. Furthermore, uric acid levels are associated with the GRACE score.

All basic data such as age, sex, risk factors, routine blood, kidney function, uric acid, Troponin T, GRACE score, were tabulated and described. In this study, univariate analysis was carried out to obtain the distribution of the basic characteristics of the research subjects on the independent and dependent variables. Bivariate analysis was conducted to see the relationship between the independent and dependent variables. To see the relationship between uric acid levels and GRACE scores in ACS patients, the Spearman correlation test was used. Data analysis using SPSS withp value <0.05 was considered statistically significant.

RESULT

This study was done on 65 people with acute coronary syndrome (ACS) who were treated at H. Adam Malik Hospital Medan who had met the inclusion criteria. 43 (66.2%) subjects are male, with a mean age of 53.74 years and 22 (33.8%) subjects are female with a mean age of 50.14 years. Subjects who have a smoking habit are 37 people (56.9%). Subjects with a family history of heart diseases are 29 people (44.6%). Hypertension occurred in 34 subjects (52.3%). Subjects with a history of Diabetes Mellitus are 34 people (52.3%). Hyperlipidemia was present in 36 people (55.4%). From the results of cardiac examination, it was found that 29 people (44.6%) had STEMI, 26 people (40%) had NSTEMI and 10 people (15.4%) had UAP.

Subject Characteristics	**N = 65 (%)**
Gender, n (%)	
Male	43 (66,2)
Female	22 (33,8)
Age (years)	52,52 (12,96)
Smoker, n (%)	
Yes	37 (56,9)
No	28 (43,1)
Family History of ACS, n (%)	
Yes	29 (44,6)
No	36 (55,4)
Hypertension, n (%)	
Yes	34 (52,3)
No	31 (47,7)
Diabetes Mellitus, n (%)	
Yes	34 (52,3)
No	31 (47,7)

Hyperlipidemia, n (%)	
Yes	36 (55,4)
No	29 (44,6)
ACS Diagnosis, n (%)	
UAP	10 (15,4)
NSTEMI	26 (40)
STEMI	29 (44,6)
Killip	
I	20 (30,8)
II	42 (64,6)
III	2 (4,6)
Cardiac Arrest	
Yes	10 (15,4)
No	55 (84,6)
ST Segment Deviation	
Yes	57 (87,7)
No	8 (12,3)
GRACE score (Median, Min-Max)	101 (55-163)

Table 1. Subject characteristics

Table 2 shows the results of blood tests of the subjects which includes complete blood counts, cardiac enzymes, lipid profiles, ad random blood glucose level, and kidney function of 65 research subjects.

Laboratory Findings	
Complete Blood Count	
Haemoglobin (gr/dl)	13,90 ± 1,51
Leukocyte (/µl)	8932 (4209-15000)
Thrombocyte (µl)	298 (103-424)
Carbohydrate Metabolism	
Ad random blood glucose level (mg/dl)	175 (80-361)
Renal Function	41,80 (13 – 184,9)
Ureum (mg/dl)	0,7258 ± 0,13102
Creatinine (mg/dl)	
Lipid Profile	209 (111 - 284)
Total Cholesterol (mg/dl)	140 (44 – 220)
LDL (mg/dl)	41 (20 – 70)
HDL (mg/dl)	151,63 ± 44,751
Triglyceride (mg/dl)	
Cardiac Enzyme	4,50 (0,02 – 27,50)
Troponin I (ng/ml)	56 (15 – 531)
CKMB (U/L)	

Table 2. Subject laboratory findings

Table 3 shows the mean and median of all laboratory characteristics based on the diagnosis of ACS. There were significant differences in mean creatinine levels in subjects with UAP, NSTEMI, and STEMI. The same thing was also found in hemoglobin and triglyceride levels, there were significant differences in the mean levels of troponin I and CKMB in subjects with STE, NSTEMI, and STEMI.

Laboratory Findings	UAP	NSTEMI	STEMI	P
Complete Blood Count				
Haemoglobin (gr/dL)	13,89 ± 1,26	14,31 ± 1,48	13,55 ± 1,58	0,200^
Leukocyte (/µl)	9476 (4674-12776)	8469 (5821-15000)	9340 (4209-11303)	**0,022***
Thrombocyte (/µl)	311 (103-424)	264 (165-411)	266 (145-421)	**0,006***
Carbohydrate Metabolism				
Ad random blood glucose level (mg/dL)	180 (87-298)	178 (80-361)	169 (89-283)	**0,008***
Renal Function				
Ureum (mg/dL)	34,75 (20,5-184,9)	33,50 (13-172,5)	38,40 (13-112,6)	**0,010***
Creatinine (mg/dL)	0,6870 ± 0,13022	0,7223 ± 0,10305	0,7424 ± 0,15320	0,200^
Lipid Profile				
Total Cholesterol (mg/dL)	173,50 (124-272)	170 (111-265)	235 (142-284)	**0,006***
LDL (mg/dL)	85,50 (44-205)	85,50 (54-201)	165 (49-220)	**0,001***
HDL (mg/dL)	50,50 (33-70)	55 (22-70)	35 (20-70)	**0,018***
Triglyceride (mg/dL)	151 ± 52,60	126,04 ± 39,36	174,79 ± 33,76	0,200^
Cardiac Enzyme				
Troponin I (ng/mL)	1,77 (0,02-7,40)	6,26 (0,02-19,32)	0,04 (0,02-27,50)	**0,000***

CKMB (U/L)	43 (19-79)	59,50 (15-531)	61 (16-125)	**0,000***

Table 3. Subject laboratory findings based on ACS diagnosis

The median uric acid level was 6.1 mg/dL with the lowest level of 2.7 mg/dL and the highest level of 17.1 mg/dL. The results of the GRACE score assessment showed an average of 100.43 (SD = 28.973).

Table 4 shows the characteristics of uric acid and the GRACE score based on the diagnosis of ACS. There was a significant difference in the mean uric acid levels in subjects with UAP, NSTEMI, and STEMI, while the GRACE score did not show a significant difference between the three ACS diagnoses. Based on the ROC curve plot, the cutoff value for the GRACE score is 118.5 with a sensitivity (80%) and specificity (97%).

	UAP	NSTEMI	STEMI	P
Uric Acid (mg/dL)	6 (3,9 – 9,8)	5,9 (2,7 – 17,1)	6,2 (3,8 – 12,6)	**0,008**
GRACE score	98,90 ± 24,32	97,08 ± 30,48	103,97 ± 29,57	0,200

Table 4. Subject uric acid level based on ACS diagnosis

Table 5 shows the correlation of uric acid and GRACE scores in all subjects, then stratified by gender and type of diagnosis of ACS.

		N	GRACE Score	
			r	P
Uric Acid	Whole subject	65	0,634	<0,001
	Male	43	0,606	<0,001
	Female	22	0,750	<0,001
	UAP	10	0,733	0,002
	NSTEMI	26	0,603	<0,001
	STEMI	29	0,712	<0,001

Table 5. Spearman correlation of uric acid level and Grace score

The correlation analysis for all subjects using the Spearman Correlation test showed that there was a significant correlation between uric acid levels and the GRACE score ($p < 0.001$) with a correlation value (r) of 0.634. The correlation value shows that there is a strong and positive correlation between uric acid levels and the GRACE score.

The correlation analysis for male subjects, totaling 43 subjects, also showed that there was a significant correlation between uric acid levels and the GRACE score ($p < 0.001$) with a correlation value (r) of 0.606 while for female subjects in total of 22 subjects. also showed a significant correlation between uric acid levels and the GRACE score ($p < 0.001$) with a correlation value (r) of 0.750. The two correlation values indicate that there is a strong and positive correlation between uric acid levels and GRACE scores in male and female subjects.

A significant correlation was found between uric acid levels and the GRACE score in 22 female subjects ($p = <0.001$) and 43 male subjects ($p = <0.001$), with 26 NSTEMI diagnoses ($p = <0.001$), 29 people diagnosed with STEMI ($p = <0.001$) and 10 people diagnosed with UAP ($p = 0.002$). The correlation analysis for subjects with STEMI, NSTEMI and UAP showed a significant correlation between uric acid levels and the GRACE score with a correlation value (r) of 0.712, 0.603 and 0.733, respectively. The correlation value shows that there is a strong and positive correlation between uric acid levels and GRACE scores in all ACS diagnoses.

Therefore it can be concluded that the higher the uric acid level, the higher the GRACE score will be.

DISCUSSION

Acute coronary syndrome (ACS) describes a wide range of myocardial ischemia characterized by the presence of atherosclerotic plaques and their rupture. Atherosclerosis is a multifactorial process with interrelated mechanisms. Hyperuricemia often occurs in patients with symptomatic heart failure, acute coronary syndromes, hypertensive arterial disease, and atrial fibrillation. It has been suggested that serum uric acid plays an important role in the pathogenesis of cardiovascular disease affecting the xanthine oxidase pathway that contributes to the production of reactive oxygen species with cell membrane damage. Several previous studies have found that there is a large amount of uric acid in atherosclerotic plaques, which can increase platelet adhesion and promote thrombus formation, thereby affecting patient prognosis and increasing all-cause mortality.[2]

In this study, it was found that most of the subjects with ACS were male, 43 people (66.2%), with an average age of 53.74 years. One of the factors such as smoking can be the reason for ACS in men. It is said that the male sex is more susceptible to the process of atherosclerosis, presumably due to the role of the hormone estrogen which can prevent the formation of atherosclerotic plaques. Estrogen also plays a role in the stabilization of atherosclerotic plaques, so that atherosclerotic plaques in women are less prone to rupture than men. It is also said that atherosclerotic plaques in women experience erosion more often than rupture, so that the clinical symptoms of ACS are felt more slowly.[26]

Based on the risk factors for ACS, this study found 37 (56.9%) subjects is a smoker, 34 (52.3%) subjects with a history of Diabetes Mellitus, 34 (52.3%) subjects with a history of hypertension, 36 (55, 4%) subjects with a history of hyperlipidemia, and 29 (44.6%) subjects with a family history of ACS. Smoking, hypertension, DM, history of hyperlipidemia, and family history of ACS are risk factors for ACS.[27]

In this study, there were 29 (44.6%) subjects with STEMI, 26 (40%) subjects with NSTEMI and 10 (15.4%) subjects with UAP. The ACCESS research group reported that 46% of ACS that occurred in developing countries were STEMI and 54% were NSTEMI/UAP.[28]

Based on laboratory results, the median of Troponin I was 4.5 ng/mL and the median of CKMB was 56 U/L. In this study, the average cholesterol level was 202.31 mg/dl, the mean LDL level was 126.97 mg/dl, the median HDL level was 41 mg/dl, and the median triglyceride level was 145 mg/dl. Another study also reported the results of lipid profiles in ACS patients, where the mean total cholesterol results were 4.96 mmol/l, LDL 3.18 mmol/l, and triglycerides 1.3 mmol/l while the mean HDL was 1.16 mmol/l.[29]

From this study, the mean GRACE score was 100.43 and the mean uric acid level was 6.59 mg/dL. Another study reported results that were not much different from this study, where the mean GRACE score was 133. Another study also reported the

mean uric acid level was 5.7 mg/dL and in a cohort study found

that uric acid was an independent predictor of all other causes of death at short-term patient follow-up and that adding uric acid values had a predictive value above the GRACE risk score where for every 1 mg/dL increase in uric acid, the 1-year mortality risk increased 26%.[30]

Based on the correlation analysis, there was a significant correlation between uric acid levels and the GRACE score ($p < 0.001$) with the correlation value ($r = 0.634$) indicating that there was a strong and positive correlation between uric acid levels and the GRACE score. This indicates that the higher the uric acid level, the higher the GRACE score will be. These results are in accordance with previous studies which showed a correlation between uric acid and the GRACE score with a correlation value (r) of 0.6054 which indicated an excess of oxidative stress production, assessed based on the increase in uric acid levels which would be more severe in patients with high GRACE scores.[4]

CONCLUSION

From the results of this study the following conclusions can be drawn:

1. There is a significant relationship between uric acid levels and the GRACE score.
2. The higher the uric acid level, the higher the GRACE score will be.

Further research is needed with a prospective study design on uric acid levels and GRACE scores to assess the prognosis of ACS patients and recurrent cardiovascular events after percutaneous coronary intervention.

ACKNOWLEDGMENTS

We acknowledgments to all staff and residents of the Department of Internal Medicine, Universitas Sumatera Utara/H. Adam Malik Hospital Medan for all your support andguidance.

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