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Hyperuricemia as predictor of in-hospital major adverse cardiac events in patients with acute myocardial infarction treated at Sanglah General Hospital, Denpasar-Bali

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ABSTRACT

Background: Even though hyperuricemia has been shown to have roles in the formation of atherosclerosis and increasing incidence of coronary heart disease, its role in predicting prognosis in acute myocardial infarction (AMI) patients has not been widely studied.
Objective: This study aimed to investigate the role of hyperuricemia as a predictor of in-hospital major adverse cardiac events (MACE) and to determine the MACE-free survival difference between hyperuricemia and normouricemia patients with AMI who were hospitalized at Sanglah General Hospital.
Methods: Prospective cohort study with consecutive sampling was conducted in AMI patients who were treated at Sanglah General Hospital from November 2016 until February 2017. Uric acid level was measured at the first admission and MACE during hospitalization was observed.
Results: Eighty-seven patients were involved in this study. We found adjusted HR 1.875 (p=0.041; 95% CI 1.026-3.428) for the development of in-hospital MACE. There was a significant difference (log-rank test p=0.03) in MACE-free survival between hyperuricemia (mean survival 17.25 hours) and normouricemia (mean survival 43.389 hours) groups.
Conclusion: Hyperuricemia is an independent predictor of in-hospital MACE in AMI patients hospitalized at Sanglah General Hospital. Event-free survival of hyperuricemic patients is worse compared to normouricemia patients during hospitalization.

Keywords: Hyperuricemia, in-hospital MACE, AMI
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INTRODUCTION

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality in both Western and developing countries despite improvement in diagnostic and therapy.[1] Data from emergency cardiac care Sanglah General Hospital (RSUP Sanglah) from 2015 to 2016 showed that patients diagnosed with AMI reached nearly half of the total patients each year and the majority of those patients were hospitalized in the intensive cardiac care unit (ICCU). The high rate of morbidity and mortality in AMI patients were due to complications such as ischemic and mechanical complications, heart rhythm disorders, embolism, and death. These complications influence patients' survival and thus are called major adverse cardiovascular events (MACE).[2]

Hyperuricemia is elevated uric acid levels in the blood. The prevalence of hyperuricemia in a population was estimated to range from 2.3% to 17.6%, with the average of 5%, and was found to be higher in coronary artery disease (CAD) patients. Several large epidemiological studies have shown that hyperuricemia is associated with an increased incidence of CAD as well as an increased mortality in those with and without preexisting CAD. Data from the First National Health and Nutrition Examination Study (NHANES) suggest that any increase in 1 mg/dL blood uric acid levels leads to increased risk of coronary heart disease by 48% in women.[3] In addition, the mortality rate of AMI patients with hyperuricemia increased by 3.7 times compared to those with normal uric acid level. It is unclear whether hyperuricemia has a direct causal effect or is simply a marker for other known risk factors for CAD, such as hypertension, dyslipidemia, and diabetes. These inconsistent results probably explain why hyperuricemia is currently not listed among conventional cardiovascular risk factors in the guidelines.[4]

Even though hyperuricemia has been shown to have roles in the formation of atherosclerosis and increasing incidence of coronary heart disease, its role in predicting prognosis in acute myocardial infarction (AMI) patients has not been widely studied. Therefore, this study aims to determine the role of hyperuricemia in predicting MACE during hospitalization in patients with AMI who were treated at Sanglah General hospital.

METHODS

This was a single-center prospective cohort study of consecutive patients admitted to integrated cardiac care unit (PJT) RSUP Sanglah with diagnosis of AMI from November 26, 2016 through February 2, 2017, to investigate the role of hyperuricemia as predictor of in-hospital MACE and to determine the MACE-free survival difference between hyperuricemia and normouricemia AMI patients. Patients diagnosed with AMI were observed for development of MACE during hospitalization in the context of the following adverse developments: heart failure (HF), cardiogenic shock, lethal arrhythmias (ventricular arrhythmias or atrioventricular block that caused hemodynamic imbalance), post-infarction angina, and death from a cardiovascular cause. All patients were managed with standard therapy based on clinical pathways from RSUP Sanglah. Exclusion criteria were: patients who have already experienced MACE or acute stroke at initial admission, with the previous history of heart failure, or history of hospitalization more than once due to AMI during the study period. Data were obtained from the patient history of physical and laboratory examinations during hospitalization. Blood uric acid was taken at initial admission.

Acute myocardial infarction was defined by clinical signs or symptoms, increased cardiac biomarkers {creatine kinase-MB (CK-MB), troponin-I or troponin-T}, and 12-lead electrocardiographic findings. Non-ST segment elevation myocardial infarction[5] was defined as troponin-I levels elevated above 0.05 (units) without an elevated ST segment. Hyperuricemia was defined as blood uric acid levels more than 7 mg/dL in men and more than 6mg/dL in women by reference from RSUP Sanglah laboratory. Specimens were plasma uric acid samples taken from a peripheral vein and examined in the laboratory of clinical pathology RSUP Sanglah with enzymatic colorimetric test method using a Roche Cobas 6000. We considered smoker to represent people who have ever smoked 100 cigarettes in their lifetime, including those who currently smoke and those who used to do so.[6] Hypertension was defined as a blood pressure ≥ 140/90 mmHg based on JNC VII (Seventh Joint National Committee Classification) criteria or the use of antihypertensive medications.[7] Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL, a non-fasting glucose level of ≥200 mg/dL based on American Diabetes Association (ADA) criteria 2010, and a reported history of diabetes or the current use of diabetes medication. Dyslipidemia was defined as disorders of lipid metabolism determined by the ATP III criteria, which consist at least one of the following: LDL cholesterol levels 130 mg/dL, total cholesterol levels 200 mg/dL, triglyceride levels 150 mg/dL, or HDL cholesterol <35 mg/dL in men and <39 mg / dL in women.[8] Obesity was defined as a Body Mass Index (BMI) > 30 kg/m.[9] Reperfusion therapy was defined as therapy to restore patency of coronary artery blood flow in AMI, performed by administering fibrinolytic therapy, percutaneous coronary intervention, or Coronary Artery Bypass Grafting (CABG).[10]

Characteristics of study participants were carried out using univariate analysis. Data were presented using a table that divided the study participants into two groups: subjects who experienced MACE (with MACE) and who did not experience MACE during hospitalization. Numerical data were presented by mean ± standard deviation, and categorical data were presented by percentage and frequency distribution. The association between uric acid levels and MACE occurrence was analyzed using multivariate Cox's proportional hazard model to obtain its hazard ratios (HR) with 95% CI and *p*-value, before and after adjusting for several confounders. The survival difference between hyperuricemia and normouricemia groups was presented by Kaplan–Meier curve and analyzed using log-rank test. Statistical significance was assumed if the null hypothesis could be rejected at the level of $p = 0.05$. All analyses were performed using SPSS software version 23.

RESULTS

A total of 87 patients with AMI were retrospectively studied: 54 (62.1%) patients had STEMI and 33 (37.9%) had NSTEMI. The mean age of the study participants was 57±11 years, of whom 64 (77.6%) were aged below 65 years, and 68 (78.2%) were male. During the observation period, 46 patients (52.9%) experienced MACE, and each patient may experience one or more types of MACE. HF was the most frequent type of MACE experienced by 24 (52.17%) patients, followed by lethal arrhythmias in 21 patients (45.6%), cardiogenic shock in 17 patients (36.95%), cardiovascular mortality in 9 patients (19.56%), and post-infarction angina in 6 patients (13.04%).

Clinical and demographic characteristics between AMI patients who experienced MACE and those who did not during hospitalization are presented in Table 1. AMI patients aged 65 years or above and diagnosed with NSTEMI were experiencing MACE more frequently during hospitalization compared with patients aged below 65 years and diagnosed with STEMI. Patients who received reperfusion therapy experienced fewer incidents of MACE compared with those who didn't receive

Table 1 Clinical and demographic characteristics based on in-hospital MACE

Variable	With MACE (n = 46)	Without MACE (n = 41)
Age		
≥ 65 years old	17 (37)	6 (15)
< 65 years old	29 (63)	35 (85)
Gender		
Male	35 (76)	33 (80)
Female	11 (24)	8 (20)
Hypertension	32 (69)	28 (68)
Dyslipidemia	30 (65)	35 (85)
Diabetes mellitus	19 (41)	12 (29)
Smoker	19 (41)	20 (49)
Reperfusion therapy	19 (41)	27 (66)
Obesity	3 (7)	1 (24)
STEMI	25 (54)	29 (71)
NSTEMI	21 (46)	12 (29)
Onset therapy (hours)	14 18,5	14.530,9
Systolic blood pressure (mmHg)	121.5 33,5	129 22,4
Length of stay in ICCU (hours)	11370,0	101.85 28,3

Values are mean SD or n (%).

Table 2 Life table of MACE-free survivals in AMI patients treated at RSUP Sanglah between November 26, 2016, and February 2, 2017

Time interval (hours)	Number of in-hospital MACE	*Cumulative proportion surviving at the end of interval* (%)
0-20	48	39
21-40	4	29
41-60	5	17
61-80	0	17
81-100	0	17
101-120	1	14
121-140	0	14
141-160	2	0,05

Table 3 Multivariate analysis using cox-proportional hazard model controlling confounding variables on the relationship between hyperuricemia and in-hospital MACE

Variable	Adjusted HR	95% CI	*p*-Value
Hyperuricemia	1.875	1.026-3.428	0.041
Reperfusion therapy	1.557	0.855-2.838	0.148
Age ≥ 65 years	0.689	0.350-1.357	0.282
Female gender	0.859	0.608-1.213	0.388
Smoker	1.487	0.743-2.975	0.263
Obesity	3.137	0.835-11.778	0.090
Hypertension	1.600	0.832-3.077	0.159
Dyslipidemia	1.154	0.621-2.143	0.651
Diabetes mellitus	1.107	0.579-2.118	0.759

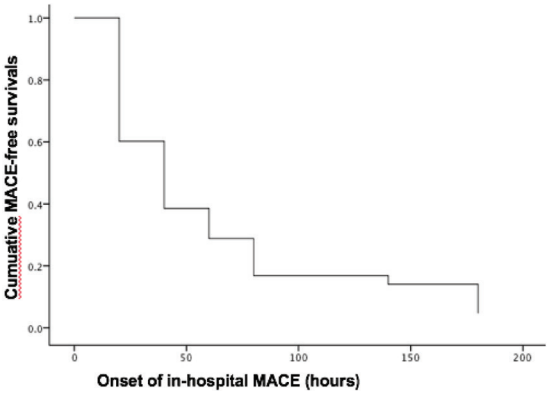

Figure 1 Graph of cumulative MACE-free survival

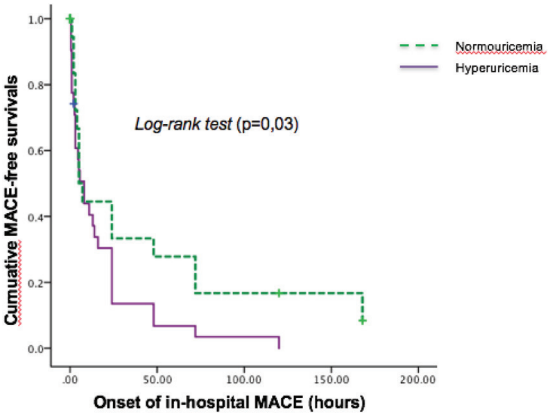

Figure 2 Kaplan–Meier survival analysis in MACE incidence on hyperuricemia and normouricemia group

reperfusion. AMI patients who experienced MACE more frequently have diabetes mellitus but dyslipidemia and obesity less frequently.

MACE-free survival results of AMI patients at RSUP Sanglah are shown in Table 2 and Figure 1. During the observation period, the number of AMI patients who experienced MACE increased and cumulative proportion of AMI patients who were free from MACE decreased. In our study, MACE tended to occur early during the observation period (mostly occurred within the first 20 hours from initial admission).

Figure 2 shows MACE-free survival difference between hyperuricemia and normouricemia groups as presented by Kaplan–Meier curve. There was a significant difference in MACE-free survival (p log-rank = 0.03) between groups of hyperuricemia (mean survival 17.256 hours; 95% CI 7.962-26.550) compared with normouricemia (mean survival 43.389 hours; 95% CI 23.479-63.299). Thus, AMI patients with hyperuricemia experienced MACE more rapidly compared with normouricemia patients during treatment.

Hyperuricemia increased the hazard for in-hospital MACE occurrence both in bivariate

analysis (crude hazard ratio [HR] 1.7; 95% CI 1.6-5.4, p = 0.041) and multivariate analysis after adjusting for reperfusion therapy, older age, female gender, smoker, obesity, hypertension, dyslipidemia, and diabetes mellitus (adjusted HR 1.875; 95% CI 1.026-3.428, p = 0.041) as shown in Table 3.

DISCUSSION

Most AMI patients in this study were diagnosed with STEMI. This is similar to the data from the Global Registry of Acute Coronary Events[1] and French registry of ACS (ONACI) where the highest percentage of AMI in patients with acute coronary syndrome[5] is STEMI. More than half the study participants were male (66.8%). These data were in line with most of the recent studies supporting males face a higher risk of developing AMI. However, given the mean age of the study participants, they were relatively younger (approximately 57 years) when compared to the average age of patients IMA in Western countries (approximately 66 years).

MACE in our study tended to occur at the beginning of the observation period (mostly occurred within the first 20 hours since entering the hospital). A meta-analysis study on patients with CAD stated that MCE mostly occurred within 30 days after primary PCI; after that, the incidence tended to decrease over time. Furthermore, data from GRACE study and ONACI registry showed that complications during treatment and mortality in STEMI patients are more common in the first 24 hours. The most frequent complications are a heart pump failure (53%) and ventricular fibrillation (27%), and about half of the patients die within the first two hours if not treated. MACE during treatment is more common in STEMI patients compared to NSTEMI. The result of studies on mortality in patients with ACS during treatment varies, as it depends on the sample size, patient characteristics, distribution of cases (frequency of STEMI, NSTEMI, and UAP patients), the number of patients who underwent PCI during treatment, and technical and revascularization status. Mortality of AMI patients during the treatment period is still quite high (around 22%) despite the exclusion of patients who died within the first 24 hours.

Another important finding of our study is with hyperuricemia the risk of MACE during hospitalization nearly doubled, both according to the bivariate analysis (crude HR 1.7; p = 0.05) and multivariate analysis using the Cox proportional hazard regression (adjusted HR 1.875; p=0.041) after adjusting for confounding variables. Although previous studies such as Framingham Heart Study failed to find any association between uric acid serum and CAD and also mortality related to cardiovascular disease, recent studies show the opposite fact, that MACE more frequently and rapidly happens in patients with hyperuricemia. The concentration of uric acid on admission correlated with MACE in patients with ACS. The serum concentration of uric acid significantly correlated with male gender, body mass index, creatinine serum concentration, and hypertension. Studies in Beijing that involved 502 STEMI patients stated that STEMI patients with hyperuricemia tended to experience MACE more frequently (consisting of HF and cardiogenic shock) during hospitalization compared with controls. Another study on patients with coronary heart disease (CHD) concludes that uric acid serum is one of the independent predictors of MACE in CHD patients. A retrospective cohort study in 251 patients with ACS who were hospitalized in the ICCU states that there were significant differences of survivals between hyperuricemia and normouricemia groups.

The exact mechanisms of hyperuricemia for the development of CAD and MACE are not fully understood but might be associated with insulin resistance, endothelial dysfunction, and increased oxidative stress. High levels of uric acid trigger the oxidation of low-density lipoprotein (LDL) cholesterol and lipid peroxidation that causes endothelial dysfunction. Hyperuricaemia also increases the formation of oxygen free radicals, inflammatory reaction, platelet aggregation, and formation of uric acid crystals. The uric acid buildup in the artery walls causes damage to the intima, thus increasing the risk of thrombosis. IMA patients with hyperuricemia are prone to left-ventricular remodeling that leads to systolic or diastolic dysfunction of the left ventricle. Hyperuricemia increases oxidative stress and activation of pro-inflammatory cytokines that stimulate cardiac myocyte apoptosis and myocardial remodeling. Furthermore, the hypoxia and tissue hypoperfusion in AMI increase xanthine oxidase activation and oxidative stress. Hyperactivity of xanthine oxidase increases blood uric acid level and perpetuate the vicious circle that affects the cardiac function even more severely. Hyperuricemia is a predictor of heart failure and mortality in AMI patients.

This study uses a cohort design so that the exposure of hyperuricemia exceeds MACE. In addition, this study confirms a significant relationship between hyperuricemia and MACE with relatively few samples and narrow confidence intervals compared to similar studies. It maybe because of hyperuricemia being a powerful predictor for the occurrence of MACE. This study is prospective, so it has some advantages over a retrospective study wherein important information and data about

the risk factors, confounding factors, and MACE can be used more extensively. In addition, Cox's regression as the basis of multivariate analysis used in this study was able to explore the risks for MACE occurrence in a more representative way compared to logistic regression analysis.

The study also had some limitations: selection of sample conducted using consecutive sampling (non-probability sampling); this is a single-center-based study. In addition, we did not explore the dose–response relationship between uric acid status and MACE. The research was conducted within a relatively short period, so we could not address the long-term effect of hyperuricemia on the development of MACE.

CONCLUSION

Hyperuricemia is an independent predictor of in-hospital MACE in AMI patients hospitalized at Sanglah General Hospital. MACE-free survival of hyperuricemic patients is worse compared to normouricemia patients during hospitalization. Therefore, blood uric acid levels should be considered to perform risk stratification with simple and practical modalities in the management of patients with AMI. It is necessary to have continuing research with longer observation time involving the cooperation of some referral hospitals in order to obtain more representative results to assess the long-term effects of hyperuricemia in predicting prognosis patients with AMI.

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