

# Hyperuricemia as a Risk Factors of Major Adverse Cardiac Events in Patients with Acute Coronary Syndrome: a Retrospective Cohort Study

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## **ABSTRAK**

**Tujuan:** mengetahui proporsi hiperurisemia pada pasien SKA serta kesintasan antara kelompok hiperurisemia dengan kelompok tidak hiperurisemia terhadap kejadian MACE pada pasien SKA selama perawatan di ICCU RS Cipto Mangunkusumo. **Metode:** penelitian dengan disain kohort retrospektif dengan analisis kesintasan, dilakukan terhadap 251 pasien SKA yang dirawat di ICCU RSUPNCM pada kurun waktu Januari 2009 – Desember 2011. Data klinis, laboratorium, elektrokardiografi, ekokardiografi, dan angiografi koroner dikumpulkan. Pasien diamati selama 7 hari perawatan di ICCU untuk melihat kejadian MACE dalam perawatan tersebut. MACE merupakan suatu kumpulan komplikasi yang meliputi syok kardiogenik, gagal jantung, stroke, infark berulang, sudden cardiac death, PCI ulang dalam perawatan, dan tindakan Coronary artery bypass graft (CABG). Perbedaan kesintasan kelompok pasien hiperurisemia dan tidak hiperurisemia ditampilkan dalam kurva Kaplan-Meier dan perbedaan kesintasan antara dua kelompok diuji dengan uji Log-rank. Analisis multivariat dengan Cox proportional hazard regression dilakukan untuk menghitung adjusted hazard ratio (dan interval kepercayaan 95%) antara pasien hiperurisemia dan tidak hiperurisemia untuk terjadinya MACE dengan memasukkan variabel-variabel perancu sebagai kovariat. **Hasil:** terdapat perbedaan kesintasan yang bermakna antara kelompok hiperurisemia dan tidak hiperurisemia pada uji Log-rank ( $p < 0,001$ ) dengan crude HR 2,7 (IK 95% 1,6–4) dan adjusted HR 2,67 (IK 95% 1,6–4,3). Pada analisis kesintasan berdasarkan waktu terjadinya MACE, perbedaan kesintasan yang bermakna antara kelompok hiperurisemia (rerata kesintasan 6,05 hari dengan SE 0,2 (IK 95% 5,6–6,4) dengan kelompok tanpa hiperurisemia (rerata kesintasan 7,33 hari dengan SE 0,1 (IK 95% 7,0–7,6). **Kesimpulan:** kesintasan pasien SKA dengan hiperurisemia lebih buruk dibandingkan tidak hiperurisemia selama perawatan ICCU.

**Kata kunci:** hiperurisemia, Sindrom Koroner Akut, Major Adverse Cardiac Event, kesintasan

## **ABSTRACT**

**Aim:** to investigate the MACE-free survivals difference between hyperuricemic and normouricemic patients and to determine its role as risk factor for MACE occurrence in hospitalized acute coronary syndrome patients. **Methods:** retrospective cohort study with survival analysis approach was conducted in 251 patients with acute coronary syndrome who were treated in ICCU Cipto Mangunkusumo Hospital during period from January 2009 to December 2011. Clinical data, laboratory results, electrocardiography result, echocardiography result, and

coronary angiography were collected. Patients were observed and followed on major adverse cardiac event during 7 days of hospitalization in ICCU. Major adverse Cardiac Event is an event as a complication occur after acute coronary syndrome such as cardiogenic syock, acute heart failure, stoke, reinfarct during early ward treatment, sudden cardiac death, repeat PCI during ward ulang and perform coronary artery bypass graft (CABG) surgery. Difference in survival is shown in Kaplan-meier curve and difference in survival between groups were tested with Log-rank test, and multivariate analysis with Cox proportional hazard regression to calculate adjusted HR on major adverse cardiac event with confounding variables as covariates. **Results:** there was a significant difference in survival between hyperuricemia group and non-hyperuricemia group (Log-rank test ( $p < 0.001$ )) with crude HR 2.7 (CI 95% 1.6–4) and adjusted HR 2.67 (CI 95% 1.6-4.3). There was significant difference in survival between hyperuricemia group (mean survival 6.05 days with SE 0.2 (CI 95% 5.6-6.4) and non-hyperuricemia group (mean survival 7.33 days with SE 0.1 (CI 95% 7.0-7.6). **Conclusion:** survival of patients suffering from ACS with hyperuricemia is worse compared to those without hyperuricemia during ICCU hospitalization.

**Key words:** hyperuricemia, acute coronary syndrome, major adverse cardiac event, survival.

## INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in both western and developing countries such as Indonesia. Data from intensive cardiac care unit (ICCU) Cipto Mangunkusumo National General Hospital (RSUPNKM) in 2001-2005 showed that the cases of acute coronary syndrome (ACS) increases from year to year.<sup>1</sup> In addition to the established risk factors of atherosclerosis, such as diabetes, hypertension, smoking and dyslipidemia, other factors such as hyperuricemia also have a significant role for the occurrence of CAD.<sup>2</sup> Prevalence of hyperuricemia in the community is estimated between 2.3% to 17.6% with an average of 5%. The mortality rate of patients with acute myocardial infarction with high uric acid levels increased by 3.7 times compared to patients with normal uric acid levels. Based on data from the First National Health and Nutrition Examination Study (NHANES), Freedman et al<sup>2</sup> showed that increase of 1 mg/dl uric acid levels will follow by increasing risk of ischemic heart disease in women by 48%.<sup>2</sup>

Eventhough 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 coronary syndrome (ACS) patients has not been widely studied. Hyperuricemia can lead to increase risk of major adverse cardiac events (MACE) in ACS patients due to free radical formation, platelet

adhesiveness, and cardiomyocyte dysfunction and hyperptrophy.<sup>3,4</sup> Thus, the information regarding uric acid levels potentially important to predict the clinical course of ACS patients and would help clinicians to stratify patients into their risk of worse outcomes.

The aims of this study are to investigate the MACE-free survivals difference between hyperuricemic and normouricemic patients and to determine its role as risk factor for MACE occurrence in hospitalized acute coronary syndrome patients. The results of this study are expected to enhance our knowledge regarding the role of uric acid level on outcomes of patients with acute coronary syndrome and thus can be use by clinician in determining patient's prognosis.

## METHODS

A retrospective cohort study was conducted among acute coronary syndrome (ACS) patients admitted to intensive cardiac care unit (ICCU) Cipto Mangunkusumo Hospital, Jakarta, between 2007 to 2010 period. Patients were excluded if they have diagnosis of heart failure, acute cerebrovascular accident (CVA) or stroke, cardiogenic shock, as well as died in the first day of admission based on medical record data.

This study was conducted according to Declaration of Helsinki and was obtained ethical clearance from Health Research Ethics Committee, Faculty of Medicine Universitas

Indonesia/Cipto Mangunkusumo Hospital, Jakarta.

### Clinical and Uric Acid Data Collection

Data obtained from the medical records including history taking associated with ischemia symptoms, head to toe physical examination, and laboratory examination. The laboratory examinations include peripheral blood examination, uric acid, blood urea nitrogen (BUN), creatinine, ALT, AST, random blood glucose, electrolyte, lipid profile, cardiac enzyme includes CK-CKMB and troponin T. Other examinations assessed are electrocardiography, chest x-ray, echocardiography, and coronary angiography.

### Outcome Measure

Primary outcome of this study was major adverse cardiac events (MACE), defined as as a complication which occurs after acute coronary syndrome such as cardiogenic shock, acute heart failure, stroke, reinfarct during early hospitalization, sudden cardiac death, repeat PCI during hospitalization, and coronary artery bypass graft (CABG) surgery. Occurrence and timing of these events were collected from medical records.

### Statistical Analysis

Based on an assumption 10% MACE will be occurred in normourisemic group, with type 1 error of 5% and power of 20%, this study needs at least 250 subjects to significantly detect hazards difference of 7% between normourisemic and hyperuricemic groups.

The survivals difference between hyperuricemic and normouricemic groups was presented by Kaplan-Meier Curve and analyzed using log-rank test. The association between uric acid levels and MACE occurrence was analyzed using multivariate Cox's regression model to obtained its hazard ratios (HR), before and after adjusted for several confounders, i.e. decrease of renal function, dyslipidemia, diabetes mellitus, and hypertension.

All analysis performed using satatistical package for social solution (SPSS) software version 17.

## RESULTS

### Recruitment of Subjects and Baseline Characteristics

During Januari 2009 to December 2011 period, there were 360 patients admitted to ICCU ward Cipto Mangunkusumo Hospital with identified medical record and among these 109 patients were excluded due to MACE occurrence before the observation period. Of 251 subjects included in this study, the mean age was 56,24 (standard deviation 11.18) years old and 87 (67.3%) of subjects were male. Demographic, clinical, and cardiovascular-related characteristics according to uric acid levels were shown in **Table 1**.

**Table 1.** Demographic, clinical, and cardiovascular-related characteristic

Characteristics	Hyperuricemia (n=125)	non-hyperuricemia (n=126)
Sex (male), n (%)	87 (69,6)	82 (65,1)
Age (year), mean (SD)	58 (9,90)	56.2 (11.18)
Age category, n (%)		
- <45 years old	10 (8)	16 (12.7)
- 45-60 years old	71 (56.8)	67 (53.2)
- > 60 years old	44 (35.2)	43 (34.1)
Occupation, n (%)		
- Civil servant	39 (31.2)	38 (30.2)
- Retired	27 (21.6)	26 (20.6)
- Private employee	22 (17.6)	30 (23.8)
- Housewife	17 (13.6)	24 (19.0)
- Unemployed	19 (15.2)	8 (6.3)
- Others	1 (0.8)	0 (0.0)
Risk factors, n (%)		
- Hypertension	85 (68.0)	78 (61.9)
- Smoking	71 (56.8)	71 (56.3)
- DM	45 (36.0)	42 (33.3)
- Dyslipidemia	45 (36.0)	44 (34.9)
- History of CV disease	33 (14.4)	15 (11.9)
ACS category, n (%)		
- STEMI	42 (33.6)	58 (46.0)
- NSTEMI	41 (32.8)	19 (15.1)
- UAP	42 (33.6)	49 (38.4)
Infarct size, n (%)		
- Extensive	79 (63.2)	83 (65.9)
- Non-extensive	46 (36.8)	43 (34.1)

**Table 1.** Demographic, clinical, and cardiovascular-related characteristic

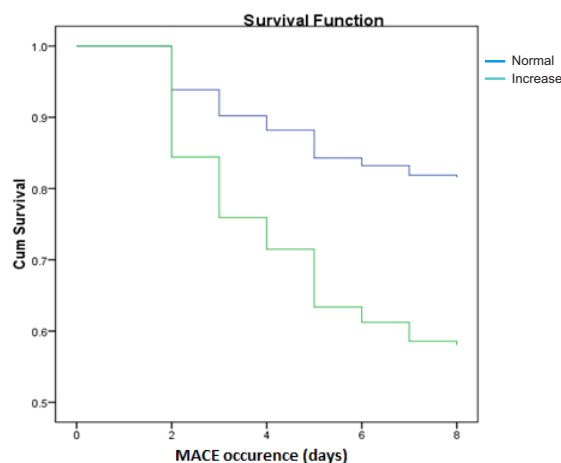
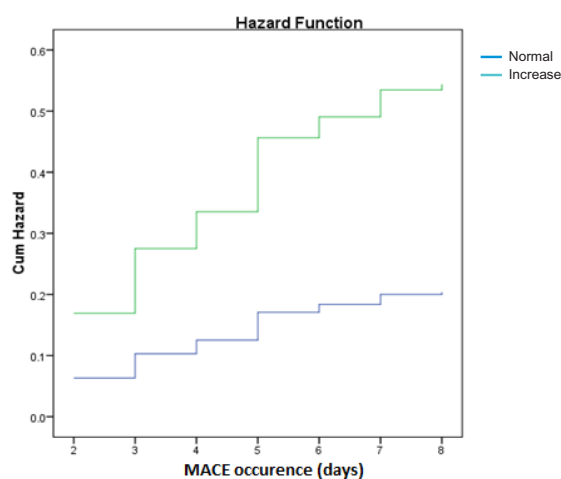
Characteristics	Hyperuricemia (n=125)	non-hyperuricemia (n=126)
Infarct location, n (%)		
- Ext. anterior	56 (44.8)	50 (39.7)
- Inferior	26 (20.8)	34 (27.0)
- Anterioseptal	18 (14.4)	26 (20.6)
- Lateral	15 (12.0)	3 (2.4)
- Anterior	5 (4.0)	7 (5.6)
- Others	5 (4.0)	6 (4.8)
Revascularization, n (%)	28 (22.4)	44 (34.9)
LVEF, mean (SD)	45.8 (13.62)	48.9 (11.43)
LVEF, n (%)		
- >40	75 (60.0)	97 (77.0)
- ≤40	50 (40.0)	29 (23.0)
Kidney function (eGFR), mean (SD)	66.3 (30.66)	72.1 (36.97)
Kidney function (eGFR), n (%)		
- <60	54 (43.2)	46 (36.5)
- ≥60	71 (56.8)	80 (63.5)
Diuretic consumption, n (%)	9 (7.2)	3 (2.4)
MACE, n (%)	52 (41.6)	23 (18.3)

According to **Table 1**, there were no differences regarding demographic and clinical characteristics between hyperuricemic and normouricemic patients, as well as on cardiovascular risk factors. Some differences were found on types of ACS (more ST-elevation myocardial infarction in normouricemic patients) and more revascularization done in normouricemic patients.

#### MACE-free Survival and Association between Uric Acid and MACE Occurrence

Kaplan-Meier survival curve (**Figure 1**) showed there was significant difference of 7-days MACE-free survival between hyperuricemic and normouricemic groups; 60% vs. 82%, respectively ( $p$  log-rank <0.001). There was also mean MACE-free survival difference between groups; 6.05 (SE 0.2) days in hyperuricemic group vs. 7.33 (SE 0.1) days in normouricemic group.

Hyperuricemia increase the hazard for MACE occurrence both in bivariate analysis

**Figure 1.** Kaplan-Meier survival analysis in MACE incidence on hyperuricemia group and non-hyperuricemia group**Figure 2.** Hazard function reflecting the Hazard ratio of both group after adjustment of confounding variable

(crude hazard ratio [HR] 2.67 (95% confidence interval 1.6 to 5.4) and multivariate analysis after adjusted for renal function, dyslipidemia, hypertension, and diabetes mellitus (adjusted HR 2.70 (95% CI 1.60 to 4.50).

#### DISCUSSION

To our knowledge, this is the first study in a cohort acute coronary syndrome patients admitted to ICCU to assess whether high uric acid levels at admission might increase risk for major adverse cardiac events (MACE) during hospitalization, using survival approach to describe and analyze the MACE-free survivals between hyperuricemic and normouricemic groups.

Despite of similar baseline characteristics between hyperuricemic and normouricemic groups, there was different MACE-free survival rates among these groups even after adjustment for several confounders. Patients with hyperuricemia having more than 20% lower of MACE-free survival compared to normouricemic patients, and in average the MACE were occurred 1.25 days earlier during hospitalization in hyperuricemic patients. Using Cox's proportional hazard regression analysis, we showed that the hazard for MACE occurrence was almost 3 times higher in hyperuricemic compared to normouricemic patients. The results were inline with other similar studies from Dunkelgrun et al.<sup>4</sup> and Bickel et al.<sup>5</sup> who also showed that MACE were more common and more rapidly occurred in patients with hyperuricemia.

There are several explanations regarding the findings of this study. First, hyperuricemia can causes free radical formation and fat peroxidation, thus enhanced the endothelial dysfunction.<sup>4</sup> Second, study by Kaya et al.<sup>6</sup> has showed that there is an association between hyperuricemia with poor coronary collateral vascularization, due to inflammation process.

Using cohort design, we could ensure that the exposure (high uric acid level on admission) was precede the outcome (MACE after 24 hours since admission) which is fulfill first Hill's criteria for causation in epidemiologic study. Another Hill's criteria which also met by this study are strong relationship represent by adjusted HR of 2.7 with quite narrow confidence interval and the results are consistent with other studies.<sup>7-10</sup> Biological plausibilities were also can be expected trough the effect of hyperuricemia on oxidative stress and endothelial dysfunction.<sup>11</sup> Unfortunately, we cannot prove dose-response relationship and challenge-dechallenge effect which are also important criteria for causation.

As a retrospective cohort study, we cannot obtain all important information data regarding risk factors, confounding factors, and laboratory tests; thus the analysis was only performed on available data and residual confounding could be expected. Despite this limitation, as the medical record system of ICCU patient's in our hospital is valid as proved in previous studies,<sup>7</sup>

the results of this study could be expected valid as well. Furthermore, Cox's regression as 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.

## CONCLUSION

There was MACE-free survival difference between hyperuricemic and normouricemic patients and hyperuricemia is a risk factor for major adverse cardiac events (MACE) in hospitalized acute coronary syndrome patients.

Doctor should consider the uric acid result data in managing ACS patients to stratify the risk of MACE. The uric acid examination should be taken when patients admitted in the hospital in order to optimal management of ACS patients in reducing morbidity and mortality rate. It is necessary to have research on the relations of hyperuricemia to the MACE event with longer time of investigations in ACS patient after patient discharge from the hospital. It is necessary to have continuing research on prognostic factors MACE events to reduce mortality rate, morbidity rate, and cost. It is necessary to have clinical trial research on the importance of prescribing uric acid lowering drugs to the MACE events in ACS patients during inpatient or outpatient setting.

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