International Journal of Cardiology 226 (2017) 26–33

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Relationship of serum uric acid and Killip class on mortality after acute ST-segment elevation myocardial infarction and primary percutaneous coronary intervention

Cheng-Wei Liu [a,b,c], Pen-Chih Liao [a], Kuo-Chin Chen [a], Yu-Wei Chiu [a,d], Yuan-Hung Liu [a], Shin-Rong Ke [a,*], Yen-Wen Wu [a,e,f,g,h]

[a] Cardiology Division of Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[b] Department of Internal Medicine, Tri-service General Hospital, Songshan Branch, National Defense Medical Center, Taipei, Taiwan
[c] Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taiwan
[d] Department of Computer Science & Engineering, Yuan Ze University, Taiwan
[e] Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[f] Department of Nuclear Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[g] Department of Nuclear Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[h] National Yang-Ming University School of Medicine, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 13 June 2016
Received in revised form 6 October 2016
Accepted 9 October 2016
Available online 11 October 2016

Keywords:
Serum uric acid
Killip class
Myocardial infarction
Percutaneous coronary intervention
Inflammation

ABSTRACT

Background: There is conflicting information regarding the association between hyperuricemia and survival in STEMI patients. Our study examined the interaction between hyperuricemia and Killip class on mortality of STEMI patients.
Methods: We analyzed 951 consecutive STEMI patients between February 2006 and September 2012. Hyperuricemia was defined as SUA of at least 7 mg/dL in males and 6 mg/dL in females. Killip class I patients were divided into hyperuricemia and normouricemia groups.
Results: The Killip class I hyperuricemia and normouricemia groups had similar baseline and procedural characteristics, but the hyperuricemia group had significantly greater BMI, serum creatinine, and SUA, and a lower TIMI risk score (2, IQR: 1–4 *vs.* 3, IQR: 2–4, $p = 0.019$). The hyperuricemia group also had greater 30-day and 1-year mortality rates (2.9% *vs.* 0.3%, $p = 0.022$; 6.5% *vs.* 1.1%, $p = 0.002$, respectively). However, hyperuricemia was not associated with mortality of patients in Killip classes II–IV or in the overall study population. Hyperuricemia was associated with increased mortality in subgroups of patients who were at least 65 years-old, male, had BMI of 25 kg/m^2 or less, were in Killip class I, without diabetes, and who did not receive intra-aortic balloon pump support. Hyperuricemia interacted with Killip class I in increasing the risk for 1-year mortality (p for interaction $= 0.038$).
Conclusions: Hyperuricemia increased the 1-year mortality of STEMI patients in Killip class I, but not of patients in Killip classes II–IV. An interaction of hyperuricemia and Killip class significantly affects the mortality of STEMI patients.

1. Introduction

Serum uric acid (SUA) is a metabolite of purines that clinicians often use as a biomarker for inflammation [1]. Hyperuricemia is associated with diverse cardiovascular diseases such as stroke, chronic kidney disease, and hypertension [2], and is also associated with increased mortality in the general population [3–5]. However, there are conflicting reports regarding the relationships of SUA, coronary heart disease, and mortality.

In the 1970s, the Framingham Heart Study concluded that SUA did not have a casual role in coronary heart disease [6]. A subsequent meta-analysis suggested that SUA was unlikely to be a major determinant of coronary heart disease [7]. In contrast, other meta-analyses demonstrated that SUA was an independent predictor of mortality in patients with coronary heart disease or acute myocardial infarction [8,9] In addition, some epidemiologic studies indicated that elevated SUA was associated with high mortality in patients with ST-segment elevation myocardial infarction (STEMI) [10–16], although other studies showed conflicting results [17–19]. It is noteworthy that most studies

Abbreviations: SUA, serum uric acid; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CK, creatine kinase (CK); CK-MB, creatine kinase-myocardial band; TRS, thrombolysis in myocardial infarction (TIMI) risk score; IQRs, interquartile ranges; IABP, intra-aortic balloon pump; IL-6, interlukin-6; CRP, C-reactive protein; XO, xanthine oxidase.

* Corresponding author.
E-mail address: ksrung@yahoo.com.tw (S.-R. Ke).

http://dx.doi.org/10.1016/j.ijcard.2016.10.025
0167-5273/

which reported positive associations of SUA and mortality examined patients with low risk of STEMI, namely Killip class I and Killip class II [10,12–15], and one study ignored the impact of Killip class on mortality in STEMI patients [11]. Therefore, the uncertain association between SUA and post-STEMI mortality might be affected by disease severity, as indicated by Killip classification. Hence, the present study investigates the associations of SUA, Killip class, and mortality in STEMI patients undergoing primary percutaneous coronary intervention (PCI).

2. Methods

2.1. Study population

All patients with acute coronary syndrome were constitutively registered, and we retrospectively reviewed the records of patients who presented to the emergency department between February 2006 and September 2012. The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Far Eastern Memorial Hospital, New Taipei City, Taiwan. Each patient signed an informed consent agreement before enrollment. Our hospital is a medical center in northern Taiwan that performs a high volume of PCI procedures [20]. The mean number of primary PCI procedures performed ± SD was 194 ± 26 annually and a total of 450 ± 50 PCI procedures was also performed annually. The present study enrolled the patients who presented to our ED directly and excluded those patients without definite door-to-balloon time, mainly those who were transferred from another hospital, those who were transferred from our out-patient department, and those who had in-hospital STEMI. As shown in Supplemental Fig. 1, there were 1156 patients STEMI patient undergoing primary PCI during the study period, and the details of the study population were given previously [21]. We divided analyzable patients into a hyperuricemia group and a normal SUA group. To investigate associations of hyperuricemia, Killip class, and mortality, we compared patients classified as Killip class I *vs.* Killip classes II–IV.

2.2. Study protocol

When any patient presented with ischemic chest pain in our emergency department during the study period, an electrocardiography was performed immediately. If a diagnosis of STEMI was confirmed by a 24-h on-site cardiologist, preparation for primary PCI began as soon as possible. Dual anti-platelet therapy with aspirin (300 mg), clopidogrel (300 mg), and heparin (60 U/kg) was routinely given to these STEMI patients at the emergency department. Intravenous nitroglycerin, a beta-blocker, and an angiotensin converting enzyme inhibitor (or angiotension receptor blocker) were also prescribed unless contraindicated. Blood examinations, including complete blood count, differential count, prothrombin time, activated partial thromboplastin time, creatinine, creatine kinase (CK), CK-myocardial band (MB), and cardiac troponin were measured at the emergency department before the patient was sent to the catheterization laboratory.

Blood samples were taken for measurement of uric acid, lipid profile, and glucose at the intensive care unit on the next morning. CK and CK-MB were monitored every 6 h until peak values were reached. The main therapeutic strategies underlying primary PCI at our hospital were: thrombus aspiration if the culprit vessel was totally occluded; and administration of a glycoprotein IIb/IIIa inhibitor if there was no tendency for bleeding. We enrolled all STEMI patients undergoing primary PCI except those who had missing data for SUA or for door-to-balloon time. For patients who were included, we obtained the following data from their medical records: baseline demographics, angiographic and procedural characteristics, and medication use at discharge. All patients received standard care that adhered to contemporary guidelines [22,23].

2.3. Study definitions

According to contemporary guidelines, we defined STEMI as the presence of: new ST-segment elevation at the J point in at least two contiguous leads of at least 2 mm (0.2 mV) in men and at least 1.5 mm (0.15 mV) in women in leads V2–V3 or at least 1 mm (0.1 mV) in other contiguous chest leads or limb leads; or new or presumably new left bundle branch block [22,23]. Hyperuricemia was defined as a SUA level >7 mg/dL in males and 6 mg/dL in females. We also used the thrombolysis in myocardial infarction (TIMI) risk score (TRS), a well-established and validated prognostic model of 30-day and 1-year mortality in STEMI patients [24]. This score (range: 0 to 14) considers the following variables: (1) age between 65 and 74 years-old (2 points) or >75 years-old (3 points); (2) systolic blood pressure of 100 mm Hg or less (3 points); (3) heart rate of 100 beats per min or more (2 points); (4) Killip classes II–IV (2 points); (5) anterior STEMI or left bundle branch block (1 point); (6) diabetes, or history of hypertension or angina (1 point); (7) body weight of 67 kg or less (1 point); and (8) ischemic time to treatment >4 h (1 point).

2.4. Study endpoints

The study end points were 30-day and 1-year all-cause mortality. All outcome data were collected from medical records and telephone surveys.

2.5. Statistical analysis

Categorical and continuous variables are expressed as numbers and percentages and as medians and interquartile ranges (IQRs), respectively. We used the Chi-square test to compare categorical variables and the Mann–Whitney *U* test to compare continuous variables. We assessed the significance of the relationships of different variables with the primary end points by univariate and multivariate Cox-proportional logistic regression analysis. The multivariate analyses adjusted for potential confounders within the present study or TRS. The cumulative incidence of survival was assessed by comparing Kaplan–Meier survival curves of patients with and without hyperuricemia. All *p* values were two-tailed and a *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software, version 20.0.

3. Results

A total of 951 STEMI patients undergoing primary PCI were screened during the study period, 7 of whom were excluded due to missing data for SUA. The study population ($n = 944$, 88% male) had a median age of 57 years-old and a median SUA level of 6.1 mg/dL.

3.1. Patient characteristics and outcomes according to Killip class and SUA level

Patients with hyperuricemia had higher baseline levels of serum creatinine, received more intra-aortic balloon pump (IABP) support, but received less stent implantation than those with normal SUA (Table 1). There were 511 patients in Killip class I and 433 patients in Killip classes II–IV. A smaller percentage of patients in Killip class I had hyperuricemia ($n = 139$, 27.2%) than in Killip classes II–IV ($n = 162$, 37.4%). However, the 2 groups were similar in all other baseline and angiographic characteristics, as well as medication use at discharge. Analysis of Killip class I patients indicated that those with hyperuricemia had higher serum creatinine levels and body mass index than those without hyperuricemia, but there were no other significant differences. In the overall study population, the TRS was significantly greater in patients with hyperuricemia. However, in Killip class I patients, the TRS was significantly lower in patients with hyperuricemia than in those with normal SUA.

3.2. Effect of hyperuricemia on survival of all patients and Killip class I patients

In the overall study population, univariate analysis indicated that hyperuricemia was associated with greater 1-year mortality (hazard ratio [HR]: 2.439, 95% confidence interval [CI]: 1.510–3.939, $p < 0.001$) and greater 30-day mortality (HR: 2.361, 95% CI: 1.269–4.392, $p = 0.007$) (Table 2). Univariate analysis of Killip class I patients also indicated that hyperuricemia was associated with greater mortality (HR: 6.187, 95% CI: 1.905–20.092, $p = 0.002$ for 1-year mortality; HR: 10.705, 95% CI: 1.197–95.777, $p = 0.034$ for 30-day mortality). Multivariate analysis indicated that these relationships remained significant in Killip class I patients (adjusted HR [aHR]: 5.176, 95% CI: 1.488–18.007, $p = 0.01$ for 1-year mortality; aHR: 11.204, 95% CI: 1.123–111.8, $p = 0.047$ for 30-day mortality), but not in the overall study population.

3.3. Other variables associated with survival in all patients and Killip class I patients

Multivariate Cox-proportional regression analyses (Table 2) showed that the major factors associated with increased 30-day and 1-year mortality in the overall population were IABP support (aHR: 7.837, 95% CI: 2.275–18.755, $p < 0.001$ for 30-day mortality; aHR: 7.951, 95% CI: 3.317–19.508, $p < 0.001$ for 1-year mortality) and advanced Killip class (HR: 1.663, 95% CI: 1.210–2.286, $p = 0.02$ for 30-day mortality; HR: 1.673, 95% CI: 1.217–2.300, $p = 0.002$ for 1-year mortality). Elevated