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Original article

Gender differences in the association between serum uric acid and prognosis in patients with acute coronary syndrome

Masayuki Kawabe (MD)[a], Akira Sato (MD, FJCC)[a,*], Tomoya Hoshi (MD)[a], Shunsuke Sakai (MD)[a], Daigo Hiraya (MD)[a], Hiroaki Watabe (MD)[b], Yuki Kakefuda (MD)[b], Mayu Ishibashi (MD)[a], Daisuke Abe (MD)[c], Noriyuki Takeyasu (MD)[c], Kazutaka Aonuma (MD, PhD, FJCC)[a]

[a] Cardiovascular Division, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
[b] Department of Cardiology, Tsukuba Medical Center Hospital, Tsukuba, Japan
[c] Department of Cardiology, Ibaraki Prefectural Central Hospital, Tomobe, Japan

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ABSTRACT

Background: Increased levels of uric acid (UA) have been associated with cardiovascular disease. This association is generally stronger in women than men. However, gender differences in the prognostic value of UA in patients with acute coronary syndrome (ACS) are unknown. We investigated gender differences in the relationship between UA level and the prognosis in patients with ACS.
Method: This was an observational analysis of patients with ACS undergoing percutaneous coronary intervention enrolled in the Ibaraki Cardiac Assessment Study (ICAS) registry. We analyzed 1380 patients (330 women, 1050 men) with ACS who had information on UA. We assessed the association between UA and the incidence of major cardiovascular adverse events (MACE), defined as all-cause death, congestive heart failure, reinfarction, and stroke. Patients were divided according to gender-specific UA quartile.
Results: The mean UA level in women was significantly lower than that in men (4.9 mg/dl vs 5.9 mg/dl, $p < 0.001$). After a median duration of follow-up period of 437 days (interquartile range 222–801 days), MACE had occurred in 186 (13%) patients [56 (17%) events in women; 130 (12%) events in men]. Kaplan-Meier analysis for MACE-free survival demonstrated that a higher quartile of UA was associated with MACE in both women and men ($p < 0.001$, $p = 0.002$, respectively). Multivariate Cox regression analysis revealed that the highest quartile of UA, as compared with the lowest quartile of UA, was an independent predictor of MACE in women [hazard ratio (HR), 2.84; 95% CI, 1.19–6.77; $p = 0.018$] but not in men (HR, 1.32; 95% CI, 0.66–2.64; $p = 0.422$).
Conclusions: An increased level of UA was associated with MACE more strongly in women than in men with ACS. These results suggest that there are gender differences in the association of UA level with the prognosis in patients with ACS.

Introduction

Many epidemiological studies have suggested that elevation of the serum uric acid (UA) level is a risk factor for hypertension, obesity, dyslipidemia, and diabetes mellitus, all of which are also associated with an increased risk for cardiovascular disease [1–5]. Hyperuricemia is common among patients with heart failure and is associated with poor outcome [6]. UA is an end product of purine metabolism, and an increase in its concentration may reflect increased xanthine oxidase pathway activity, which relates to free radicals that result in increased cytokine production, cell apoptosis, and endothelial dysfunction [7,8]. UA plays a role not only as risk factors for cardiovascular risk but also as scavengers against oxidative stress [7]. There is a gender difference in UA level; women usually have a lower UA level than men. The association between serum UA and cardiovascular events in the general population is reported to be stronger in women than in men [9]. Other studies have demonstrated that serum UA is more closely related with metabolic syndrome in women than in men [10]. In addition, gender differences also exist in the mortality rate

* Corresponding author at: Cardiovascular Division, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. Tel.: +81 29 853 3143; fax: +81 29 853 3143.
E-mail address: asato@md.tsukuba.ac.jp (A. Sato).

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in patients with myocardial infarction, and prognosis after myocardial infarction is worse in women than in men [11,12]. Thus gender differences in cardiovascular risk factors and mortality are being increasingly recognized and have become an important issue. Use of various biomarkers such as renal function, natriuretic peptide, and cardiac troponin has helped to improve risk prediction in patients with acute coronary syndrome (ACS), but risk prediction in patients with ACS remains suboptimal [13–16]. Some studies have shown that UA is an independent predictor of mortality in patients with myocardial infarction [17]. Although there are gender differences in relation to UA level, no study has been conducted to access the association of gender differences with the prognostic value of UA in patients with ACS. We undertook this study to investigate whether UA level predicts clinical outcome in a large cohort of patients with ACS who underwent percutaneous coronary intervention (PCI).

Materials and methods

Study population

We pooled data from patients enrolled in the Ibaraki Cardiac Assessment Study (ICAS) registry, a multicenter registry involving 12 hospitals in Ibaraki Prefecture, Japan. All traceable personal identifiers were removed from the datasets before analysis to protect patient confidentiality. Written informed consent was obtained from all patients, and data collection for this study was approved by each institution's review board. We enrolled 1828 consecutive patients with ACS who underwent PCI from April 2007 to June 2012. Among them, 448 patients who were missing UA values were excluded. Thus, the study group comprised 1380 patients. In each participant, blood was withdrawn before coronary angiography. Serum UA was determined by the uricase-peroxidase method in each participating hospital. Because serum UA level differs substantially between the sexes, results were analyzed separately. Patients were divided according to gender-specific UA quartile.

ACS was defined as ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina. The diagnosis of ACS was based on the universal definition of myocardial infarction [18]. Coronary artery disease was diagnosed based on the presence of >75% lumen obstruction of at least one of the three major coronary arteries. Hypertension was defined as the presence of current treatment with antihypertensive drugs or otherwise as a systolic blood pressure of >140 mmHg and/or diastolic blood pressure of >90 mmHg. Dyslipidemia was defined as current treatment with cholesterol-lowering medications or a low-density lipoprotein (LDL) cholesterol value of >140 mg/dl and/or a high-density lipoprotein cholesterol value of <40 mg/dl. Diabetes mellitus was defined as a fasting glucose concentration of >126 mg/dl or treatment with oral hypoglycemic agents or insulin. The estimated glomerular filtration rate (eGFR) was calculated with the following equation: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ ($\times 0.739$ if the patient is female) [19].

Coronary angiography and PCI procedure

PCI was performed according to standard techniques. All patients received treatment with aspirin (100 mg/day) and clopidogrel (75 mg/day following a 300 mg loading dose) or ticlopidine (200 mg/day). A glycoprotein IIb/IIIa receptor inhibitor is not yet available in Japan. Operators selected interventional devices and performed PCI through either the radial, brachial, or femoral artery using 6–7 French catheters. Heparin was given intravenously before starting the procedure. The standard of care at discharge for all patients treated with stents was to prescribe clopidogrel for at least 1 year. Aspirin was continued indefinitely unless complications occurred. Informed consent was obtained from all patients, and approval for this study was granted by each institution's ethics committee. All adverse events were confirmed by reviewing the medical records of the patients followed at each institution.

Endpoints and definitions

The primary endpoint of this study was major adverse cardiovascular events (MACE) defined as death from any cause, congestive heart failure, myocardial infarction, or stroke. Congestive heart failure was defined as admission to hospital for worsening heart failure requiring intravenous drug treatment. Stroke was defined as cerebral infarction, intracranial hemorrhage, or subarachnoid hemorrhage diagnosed by computed tomography or magnetic resonance imaging.

Statistical analysis

Continuous variables are expressed as mean ± SD, medians (interquartile range), and categorical variables as numbers and percentages. Comparisons between quartiles were made by analysis of variance test for continuous variables and the Pearson chi-square test for categorical variables. Comparisons between the enrolled patients and the patients with missing UA values were analyzed by the Pearson chi-square statistics for categorical variables and unpaired t test or Mann-Whitney U tests for continuous variables according to the distribution. Survival analysis was performed by applying the Kaplan-Meier method and log-rank test. Univariate and multivariate Cox proportional hazards models were used to assess the association between UA quartile and MACE. Potential confounding factors with regard to baseline characteristics were included in multivariate analysis. The covariates for the multivariate analysis included UA, age, body mass index, diabetes mellitus, left ventricular ejection fraction, eGFR < 60 mL/min/1.73 m^2, history of heart failure, ST-elevation myocardial infarction, hyperlipidemia, and hypertension. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Tochigi, Japan), which is a graphical user interface for the R statistical analysis program (The R Foundation for Statistical Computing, version 2.13.0) [20]. A two-tailed p-value of <0.05 was considered to indicate statistical significance.

Results

Clinical and procedural characteristics

Baseline demographic, clinical, and angiographic characteristics of both women and men stratified by UA quartile are shown in Tables 1 and 2. The subjects included 330 women (24%; age, 72.1 ± 10.6 years) and 1050 men (76%; age, 64.5 ± 11.7 years). Of particular note is the different age distribution by UA quartile between the women and men. The quartile of UA increased with age only in women ($p < 0.001$) but not in men ($p = 0.092$). In contrast, the quartile of UA increased with higher body mass index only in men ($p = 0.001$) and not in women ($p = 0.535$). In women, a higher quartile of UA was associated with decreased LDL cholesterol ($p < 0.001$). Among both women and men, a higher quartile of UA level was associated with increasing blood urea nitrogen (BUN) and eGFR ($p < 0.001$, both). Women with history of heart failure, but not men, had higher UA level than those without history of heart failure (women, $p < 0.001$; men, $p = 0.09$). There were also gender differences in medication on admission. There was no significant difference in the types of medication used in men. On the other hand, angiotensin II receptor blocker was used more frequently in