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Original article

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

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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

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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

Table 1
Baseline characteristics in women.

	Quartile1 $n=81$	Quartile2 $n=82$	Quartile3 $n=74$	Quartile4 $n=93$	p-value
Uric acid (mg/dl)	<3.9	3.9–4.9	4.9–6.2	>6.2	
Age, years	68.5 ± 10.8	70.8 ± 10.9	73.0 ± 9.9	76.7 ± 9.0	<0.001
BMI (kg/m^2)	23.2 ± 4.1	23.9 ± 3.7	23.1 ± 3.8	23.8 ± 4.4	0.535
SBP (mmHg)	137.1 ± 26.3	133.8 ± 26.1	138.2 ± 31.0	126.0 ± 32.8	0.045
DBP (mmHg)	74.5 ± 17.0	73.6 ± 15.7	73.7 ± 17.4	68.9 ± 18.8	0.168
HR (bpm)	80.1 ± 17.6	76.7 ± 16.5	78.7 ± 19.4	79.0 ± 23.4	0.732
BUN (mg/dl)	15.1 ± 6.2	16.5 ± 7.0	23.5 ± 17.7	24.4 ± 11.8	<0.001
eGFR (mL/min/1.73 m^2)	79.8 ± 29.2	71.1 ± 25.0	58.1 ± 25.1	45.4 ± 21.5	<0.001
CRP (mg/dl)	1.42 ± 3.25	1.27 ± 3.22	1.61 ± 3.94	1.45 ± 3.48	0.948
Hb (g/dl)	12.7 ± 1.9	12.5 ± 1.3	12.1 ± 2.1	11.9 ± 2.3	0.057
Glucose (mg/dl)	192.5 ± 90.8	155.1 ± 64.8	184.5 ± 117.5	179.8 ± 86.3	0.069
WBC (10^3/μg)	8945 ± 3141	7963 ± 2570	9150 ± 4579	9346 ± 4147	0.082
STEMI	47 (58.0)	53 (64.6)	47 (63.5)	40 (52.6)	0.407
EF (%)	56.4 ± 11.1	56.8 ± 12.7	54.7 ± 12.2	52.2 ± 13.9	0.124
HDL cholesterol (mg/dl)	52.0 ± 12.2	51.1 ± 12.6	54.4 ± 32.3	45.5 ± 14.6	0.063
Triglycerides (mg/dl)	119.8 ± 80.9	112.4 ± 71.1	122.3 ± 99.0	129.2 ± 142.9	0.785
LDL cholesterol (mg/dl)	138.2 ± 39.9	119.3 ± 36.5	117.6 ± 29.9	106.5 ± 32.3	<0.001
Medication on admission					
Allopurinolol	3 (3.7)	1 (1.2)	1 (1.4)	4 (5.3)	0.398
ACE-I or ARB	46 (56.8)	51 (62.2)	39 (52.7)	54 (71.1)	0.110
Beta blockers	36 (44.4)	40 (48.8)	25 (33.8)	23 (30.3)	0.057
Statin	58 (71.6)	62 (75.6)	48 (64.9)	40 (52.6)	0.015
History of HT	51 (63.0)	66 (80.5)	51 (68.9)	57 (75.0)	0.076
History of DM	33 (40.7)	27 (32.9)	33 (44.6)	23 (30.3)	0.225
History of HF	0 (0.0)	1 (1.2)	0 (0.0)	10 (13.2)	<0.001
History of MI	7 (8.6)	8 (9.8)	8 (10.8)	13 (17.1)	0.394
History of PCI	15 (18.5)	11 (13.4)	9 (12.2)	14 (18.4)	0.605
History of CABG	0 (0.0)	2 (2.4)	1 (1.4)	3 (3.9)	0.291
History of stroke	4 (4.9)	3 (3.7)	6 (8.1)	10 (13.2)	0.120
Multivessel disease (%)	22 (28.6)	17 (23.3)	19 (27.5)	28 (40.6)	0.147

Values are expressed as the mean ± SD, or n (%).
ACE-I, angiotensin-converting inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL, high-density lipoprotein; HF, heart failure; HL, hyperlipidemia; HR, heart rate; HT, hypertension; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; WBC, white blood cell count.

women with a higher quartile of UA ($p = 0.007$), whereas statins were used less frequently in women with a higher quartile of UA ($p = 0.015$).

We evaluated the possible selection bias by comparing the patient's backgrounds between the enrolled patients ($n = 1380$) and patients with missing UA value ($n = 488$). As shown in Supplemental Table 1, there were no significant differences between the enrolled patients and patients with missing UA value, except for the history of PCI and multivessel disease.

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.jjcc.2015.05.009.

UA levels and clinical events

The mean UA level in women was significantly lower than that in men (4.9 mg/dl vs 5.9 mg/dl, $p < 0.001$) (Figs. 1 and 2). After a median duration of follow-up of 437 days (interquartile range 222–801 days) and 2081 person-years (interquartile range 791–7755 person-years), 186 (13%; 8.93 per 100 person-years) patients experienced MACE [56 (17%; 12.5 per 100 person-years) events in women and 130 (12%; 8.24 per 100 person-years) events in men], all-cause death occurred in 98 (7%; 4.71 per 100 person-years) patients [31 (9%; 6.91 per 100 person-years) events in women; 67 (6%; 4.24 per 100 person-years) events in men]. In both genders, all-cause death (women, $p = 0.002$; men, $p = 0.043$) and incidence of MACE (women, $p < 0.001$; men, $p = 0.003$) were higher in patients with a higher quartile of UA. Cardiac death and occurrence of heart failure were significantly higher only in women with a higher quartile of UA ($p < 0.001$ and $p = 0.041$, respectively), but not in men ($p = 0.055$ and $p = 0.329$, respectively) (Table 3). Kaplan-Meier analysis for MACE-free survival showed that a higher UA quartile was associated with MACE in all patients ($p < 0.001$) (Fig. 3). Kaplan-Meier curves for MACE stratified by women and men showed that a higher quartile was associated with MACE in both women and men ($p < 0.001$, $p = 0.002$, respectively) (Fig. 4).

Predictors of clinical events according to multivariate analysis

In univariate analysis, the highest UA quartile (>6.2 mg/dl in women; >6.9 mg/dl in men), as compared with the lowest UA quartile (<3.9 mg/dl in women; <4.9 mg/dl in men), was associated with MACE in both women [hazard ratio (HR), 4.60; 95% confidence interval (CI), 2.09–10.12; $p < 0.001$] and men (HR, 1.90; 95% CI, 1.15–3.13; $p = 0.011$) (Table 4). However, in multivariate analysis, the highest quartile of UA was independently associated with MACE only in the women (HR, 2.84; 95% CI, 1.19–6.77; $p = 0.018$) but not in the men (HR, 1.32; 95% CI, 0.66–2.64; $p = 0.422$).

Discussion

In this study with subjects from a multicenter registry of patients with ACS undergoing PCI, the impact of UA levels on MACE remained independent in women, but not in men, even after adjustment for traditional cardiovascular risk factors. The effect of gender differences in the role of UA on the long-term prognosis of patients with ACS has not previously been fully explored. To our knowledge, this is the first study to elucidate gender differences in UA for the prognosis of patients with ACS.

Table 2
Baseline characteristics in men.

	Quartile1 $n=265$	Quartile2 $n=274$	Quartile3 $n=264$	Quartile4 $n=247$	p-value
Uric acid (mg/dl)	<4.9	4.9–5.9	5.9–6.9	>6.9	
Age, years	64.9 ± 10.5	65.6 ± 11.9	64.4 ± 11.0	63.1 ± 13.1	0.092
BMI (kg/m^2)	23.5 ± 3.6	24.2 ± 3.7	24.6 ± 4.0	26.1 ± 13.0	0.001
SBP (mmHg)	135.2 ± 26.8	136.0 ± 27.3	134.6 ± 25.3	134.8 ± 30.8	0.937
DBP (mmHg)	79.8 ± 16.2	79.2 ± 16.2	79.9 ± 18.0	79.0 ± 18.7	0.928
HR (bpm)	76.7 ± 18.9	74.6 ± 17.8	75.6 ± 18.4	81.1 ± 21.6	0.001
BUN (mg/dl)	15.1 ± 4.6	16.1 ± 6.4	18.7 ± 16.1	21.6 ± 13.5	<0.001
eGFR (mL/min/1.73 m^2)	76.4 ± 22.9	73.2 ± 20.8	65.8 ± 20.5	60.1 ± 49.8	<0.001
CRP (mg/dl)	1.14 ± 2.73	0.93 ± 2.59	0.97 ± 3.18	1.33 ± 3.43	0.426
Hb (g/dl)	14.3 ± 1.7	14.2 ± 1.7	14.3 ± 1.8	13.9 ± 2.2	0.044
Glucose (mg/dl)	179.4 ± 92.1	157.3 ± 72.1	161.9 ± 83.1	176.7 ± 88.7	0.007
WBC ($10^3/\mu g$)	9084 ± 3142	9136 ± 3260	9171 ± 3223	10,271 ± 3937	<0.001
STEMI	150 (56.6)	152 (55.5)	150 (56.8)	147 (59.5)	0.822
EF (%)	56.3 ± 12.6	56.5 ± 11.5	55.2 ± 12.0	54.9 ± 12.9	0.416
HDL cholesterol (mg/dl)	48.5 ± 13.7	46.6 ± 11.3	46.5 ± 13.0	44.0 ± 12.2	0.002
Triglycerides (mg/dl)	118.5 ± 92.7	135.0 ± 133.0	143.6 ± 131.2	174.8 ± 203.8	<0.001
LDL cholesterol (mg/dl)	117.7 ± 32.1	117.7 ± 35.8	122.7 ± 36.6	119.1 ± 40.6	0.387
Medication on admission					
Allopurinolol	6 (2.3)	9 (3.3)	11 (4.2)	14 (5.7)	0.233
ACE-I or ARB	166 (62.6)	167 (60.9)	177 (67.0)	148 (59.9)	0.344
Beta blockers	117 (44.2)	117 (42.7)	120 (45.5)	117 (47.4)	0.744
Statin	186 (70.2)	201 (73.4)	196 (74.2)	173 (74.2)	0.611
History of HT	154 (58.1)	165 (60.2)	175 (66.3)	151 (61.1)	0.255
History of DM	110 (41.5)	89 (32.5)	82 (31.1)	80 (32.4)	0.046
History of HF	4 (1.5)	4 (1.5)	4 (1.5)	11 (4.5)	0.090
History of MI	35 (13.2)	42 (15.3)	43 (16.3)	37 (15.0)	0.793
History of PCI	43 (16.2)	58 (21.2)	51 (19.3)	42 (17.0)	0.447
History of CABG	6 (2.3)	13 (4.7)	4 (1.5)	5 (2.0)	0.126
History of stroke	17 (6.4)	19 (6.9)	24 (9.1)	20 (8.1)	0.655
Multivessel disease (%)	74 (30.3)	67 (26.5)	77 (31.6)	67 (30.5)	0.618

ACE-I, angiotensin-converting inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL, high-density lipoprotein; HF, heart failure; HL, hyperlipidemia; HR, heart rate; HT, hypertension; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; WBC, white blood cell count.

UA and cardiovascular events

A number of studies have suggested that the elevation of UA in patients with cardiovascular disease could simply be a result of the common presence of high-risk factors such as reduced eGFR, history of heart failure, and hypertension, all of which are associated with worse prognosis [6,7]. However, after adjustment for these risk factors in our multivariate model, we still found that a highest quartile of UA was an independent predictor of MACE in female patients with ACS not in male patients. In the general population, UA is an independent risk factor for hypertension, dyslipidemia, metabolic syndrome, and renal disease [1,3,10,21]. In patients with severe coronary artery disease, an elevated UA level was a strong independent predictor of adverse outcome and mortality [22]. This prognostic value of UA was also shown in patients with ACS. Kojima et al. showed that the combination of Killip's class and UA was significantly associated with mortality in patients with acute myocardial infarction [23]. Kaya et al. showed that a high UA level on admission was independently associated with MACE in patients with ST-elevation myocardial infarction who undergo PCI [17]. The meta-analysis by Trkulja et al. reported a significant association between UA level

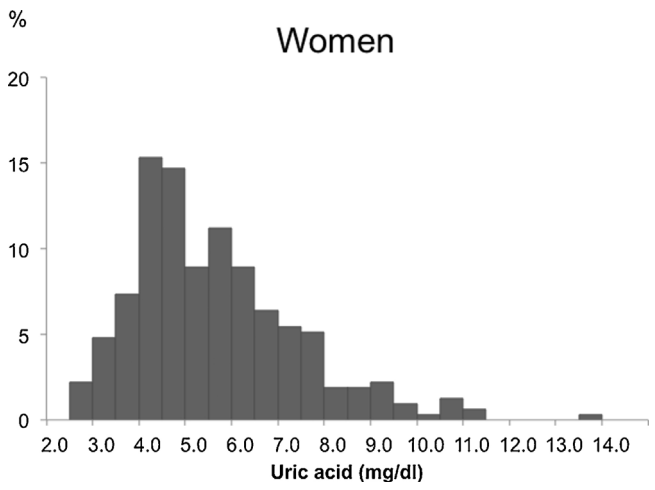

Fig. 1. Histogram of uric acid concentrations in women.

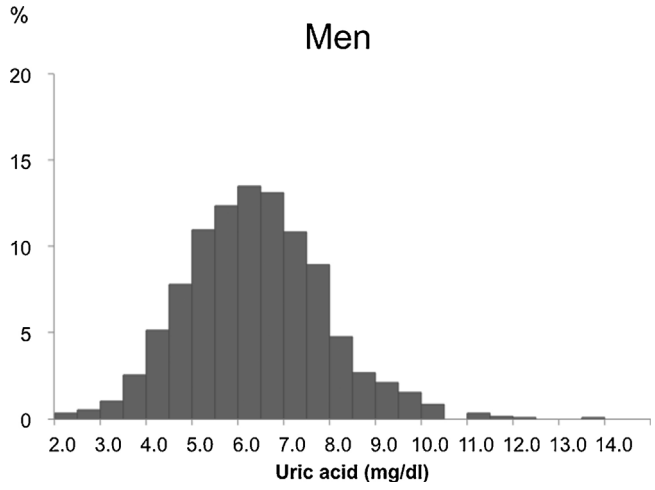

Fig. 2. Histogram of uric acid concentrations in men.

Table 3
Proportion of event occurrence in the patients according to gender and quartile of uric acid.

	Q1 <3.9 mg/dl *n* = 81; 115 person-years	Q2 3.9–4.9 mg/dl *n* = 82; 137 person-years	Q3 4.9–6.2 mg/dl *n* = 74; 103 person-years	Q4 >6.2 mg/dl *n* = 76; 93 person-years	*p*-value
Women					
All death	3 (2.60)	4 (2.91)	9 (8.73)	15 (16.10)	0.002
Cardiac death	2 (1.73)	1 (0.72)	6 (0.05)	10 (10.75)	<0.001
Heart failure	4 (3.47)	5 (3.64)	3 (2.91)	12 (12.90)	0.041
Stroke	2 (1.73)	1 (0.72)	0 (0.00)	5 (5.37)	0.053
Myocardial infarction	2 (1.73)	2 (1.45)	0 (0.00)	2 (2.15)	0.613
MACE	8 (6.95)	10 (7.29)	10 (9.70)	28 (31.00)	<0.001
	Q1 <4.9 mg/dl *n* = 265; 406 person-years	Q2 4.9–5.9 mg/dl *n* = 274; 421 person-years	Q3 5.9–6.9 mg/dl *n* = 264; 414 person-years	Q4 >6.9 mg/dl *n* = 247; 336 person-years	*p*-value
Men					
All death	16 (3.94)	11 (2.61)	15 (3.62)	25 (7.44)	0.043
Cardiac death	7 (1.72)	5 (1.18)	5 (1.20)	14 (4.16)	0.055
Heart failure	7 (1.72)	8 (1.90)	14 (3.38)	11 (3.27)	0.329
Stroke	4 (0.98)	5 (1.18)	8 (1.93)	8 (2.38)	0.491
Myocardial infarction	3 (0.73)	2 (0.47)	3 (0.72)	5 (1.48)	0.627
MACE	27 (6.65)	22 (5.22)	36 (8.69)	45 (13.39)	0.003

Values are expressed as the *n* (per 100 person-years).
MACE, major adverse cardiac and cerebrovascular event.

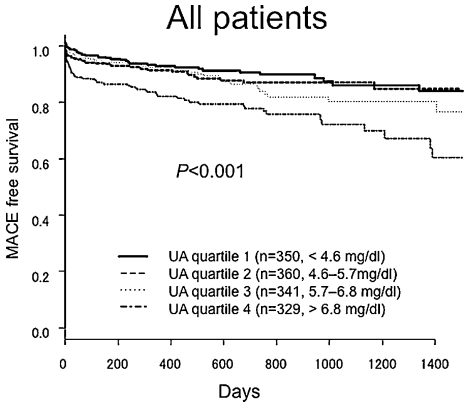

Fig. 3. Kaplan-Meier curves for major adverse cardiovascular event (MACE)-free survival according to quartile of uric acid (UA) in all patients.

and short- and long-term outcomes after acute myocardial infarction [24]. Some studies have demonstrated that there is a significant relationship between UA level and post-primary PCI myocardial perfusion grade [22,25]. UA has been shown to be an indicator of antioxidant activity in serum [26]. Hyperuricemia has been suggested to reflect raised xanthine oxidase activity in patients with heart failure [27]. The xanthine oxidase enzyme system is an important source of oxygen free radicals [28]. High UA levels not only contribute to oxygen free radical generation but also decrease the amount of nitric oxide in vascular endothelial cells, which in turn inhibits vasodilatation [17]. The subsequent generation of oxygen free radicals is one of the underlying causes of impaired coronary flow after primary PCI [29]. Endothelial-derived nitric oxide, a potent vasodilator, plays an important role in the regulation of coronary blood flow [30]. Allopurinol has been found to improve endothelial function in type 2 diabetes, hyperuricemic patients with chronic heart failure, and heavy smokers [31]. Further studies will be needed to determine whether allopurinol affects the prognosis of ACS patients with an elevated UA.

Relationship between UA and gender

Several previous studies have demonstrated that UA level regarding development of hypertension or renal disease was significantly higher in women than in men [32,33]. There also have been gender differences in the association between UA level and atrial fibrillation prevalence [34]. Freedman et al. demonstrated a

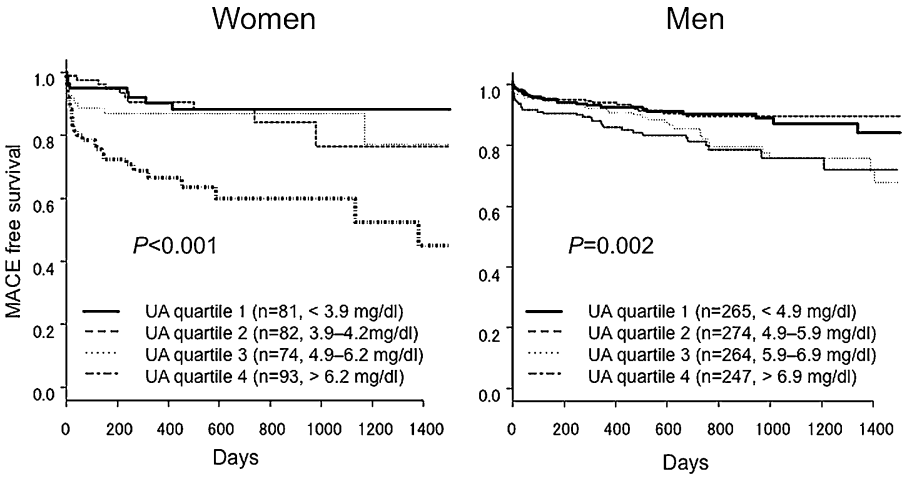

Fig. 4. Kaplan-Meier curves for major adverse cardiovascular event (MACE)-free survival according to quartile of UA stratified by women and men.

Table 4
Cox regression analysis for MACE.

	Non-adjusted model		Adjusted model	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Women				
Quartile1 (<3.9 mg/dl)	Reference		Reference	
Quartile2 (3.9–4.9 mg/dl)	1.24 (0.49–3.16)	0.639	0.86 (0.29–2.51)	0.783
Quartile3 (4.9–6.2 mg/dl)	1.58 (0.62–4.02)	0.331	0.61 (0.18–2.06)	0.430
Quartile4 (>6.2 mg/dl)	4.60 (2.09–10.12)	<0.001	2.84 (1.19–6.77)	0.018
Men				
Quartile1 (<4.9 mg/dl)	Reference		Reference	
Quartile2 (4.9–5.9 mg/dl)	0.80 (0.45–1.42)	0.456	0.69 (0.32–1.45)	0.331
Quartile3 (5.9–6.9 mg/dl)	1.50 (0.90–2.48)	0.114	1.05 (0.54–2.02)	0.874
Quartile4 (>6.9 mg/dl)	1.90 (1.15–3.13)	0.011	1.32 (0.66–2.64)	0.422

HR in adjusted model was adjusted for age, body mass index, diabetes mellitus, ejection fraction, estimated glomerular filtration rate < 60 mL/min/1.73 m^2, history of heart failure, ST-elevation myocardial infarction, hyperlipidemia, and hypertension.
HR, hazard ratio; CI, confidence interval.

stronger association between increased UA level and cardiovascular mortality among women than men in healthy subjects [5]. Meta-analysis showed that an association between hyperuricemia and cardiovascular mortality was significant in women but not in men [35]. Few studies have addressed the association between UA levels and gender differences in the prognosis of patients with ACS. In patients admitted for elective coronary angiography, high UA levels were linearly related to coronary artery disease severity in women, but UA was eliminated from multivariate model because the association of UA to coronary artery disease largely reflects predominance of metabolic risk factors such as hyperinsulinemia, advanced age, hypertension, and dyslipidemia [36]. The present study demonstrates that UA has gender differences on the prognosis in patients with ACS because the association remained even after adjustment for comorbidities in women, but not in men. Postmenopausal women had a higher UA level than premenopausal women [7]. The changing UA level in postmenopausal women suggests that there is an interaction with sex hormones [9]. Some studies have demonstrated a strong association between UA level in healthy populations and cardiovascular mortality, even after adjustment for menopausal status [9,37]. Although increasing UA level after menopause might influence outcomes, it remains a matter for further discussion. The mechanisms that cause UA to be less related to MACE in men than women remain uncertain and providing a potential explanation for this finding would be rather speculative. However, one reason is that men have another strong risk factor influencing the mortality of patients with MACE rather than women. Among patients with established coronary artery disease, lower BMI is an independent predictor of mortality [38]. We found that BMI was increased with quartile of UA only in men (Table 1). This trend would attenuate the excess effect of elevated UA level.

Study limitations

Our study has several limitations. This was a nonrandomized, retrospective, and observational study, and as with any observational study, it is possible that both unrecognized and recognized confounding factors may influence the data despite adjustment for these factors. There could be a selection bias in the present study as shown in Supplemental Table 1. The study findings are based on a single UA measurement. As a result, time-dependent changes in UA concentration remain unaccounted for. Additional factors that affect UA concentration, such as doses and types of diuretics (e.g. loop diuretics, thiazide, and spironolactone) were also not assessed. Because N-terminal pro B-type natriuretic peptide, brain natriuretic peptide, and high-sensitivity troponin assays were not available for the majority of the patients in this study, we could not adjust for these biomarkers. Finally, menopausal status and history of gout are not available in this study.

Conclusions

In conclusion, among patients with ACS, an increased UA level was associated with MACE in both women and men. The effect of UA level on MACE remained independent even after adjustment for the traditional cardiovascular risk factors in women but not in men. These results suggest that there are gender differences in the association of UA level with the prognosis in patients with ACS.

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Conflict of interest

No conflicts of interest are declared by any of the authors regarding this manuscript.

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References

[1] Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk development of hypertension and impaired fasting glucose or Type 2 diabetes in Japanese male office workers. Eur J Epidemiol 2003;18:523–30.
[2] Burack RC, Keller JB, Higgins MW. Cardiovascular risk factors and obesity: are baseline levels of blood pressure, glucose, cholesterol and uric acid elevated prior to weight gain? J Chronic Dis 1985;38:865–72.
[3] Athyros VG, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Milionis HJ, Mikhailidis DP. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart disease Evaluation (GREACE) study. Am J Kidney Dis 2004;43:589–99.
[4] Vuorinen-Markkola H, Yki-Järvinen H. Hyperuricemia and insulin resistance. J Clin Endocrinol Metab 1994;78:25–9.
[5] Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 1995;141:637–44.

[6] Pascual-Figal DA, Hurtado-Martínez JA, Redondo B, Antolinos MJ, Ruiperez JA, Valdes M. Hyperuricemia and long-term outcome after hospital discharge in acute heart failure patients. Eur J Heart Fail 2007;9:518–24.
[7] Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811–21.
[8] Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840–4.
[9] Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: the NHANES I Epidemiologic Follow-up Study, 1971–1992. JAMA 2000;283: 2404–10.
[10] Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, Lee MH, Park JR, Kim H, Rhee EJ, Lee WY, Kim SW, Ryu SH, Keum DG. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J 2005;69:928–33.
[11] Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med 1999;341:217–25.
[12] Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. Ann Intern Med 2001;134:173–81.
[13] Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–95.
[14] Nagaya N, Nishikimi T, Goto Y, Miyao Y, Kobayashi Y, Morii I, Daikoku S, Matsumoto T, Miyazaki S, Matsuoka H, Takishita S, Kangawa K, Matsuo H, Nonogi H. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. Am Heart J 1998;135:21–8.
[15] Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. Prognostic significance of admission troponin T concentration in patients with myocardial infarction. Circulation 1996;94:1291–7.
[16] Murata N, Kaneko H, Yajima J, Oikawa Y, Oshima T, Tanaka S, Kano H, Matsuno S, Suzuki S, Kato Y, Otsuka T, Uejima T, Nagashima K, Kirigaya H, Sagara K, et al. The prognostic impact of worsening renal function in Japanese patients undergoing percutaneous coronary intervention with acute coronary syndrome. J Cardiol 2015. http://dx.doi.org/10.1016/j.jjcc.2014.12.005.
[17] Kaya MG, Uyarel H, Akpek M, Kalay N, Ergelen M, Ayhan E, Isik T, Cicek G, Elcik D, Sahin O, Cosgun SM, Oguzhan A, Eren M, Gibson CM. Prognostic value of uric acid in patients with ST-elevated myocardial infarction undergoing primary coronary intervention. Am J Cardiol 2012;109:486–91.
[18] Thygesen CK, Alpert JS, White HD. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
[19] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.
[20] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8.
[21] Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002;13:2888–97.
[22] Madsen TE, Muhlestein JB, Carlquist JF, Horne BD, Bair TL, Jackson JD, Lappe JM, Pearson RR, Anderson JL. Serum uric acid independently predicts mortality in patients with significant, angiographically defined coronary disease. Am J Nephrol 2005;25:45–9.
[23] Kojima S, Sakamoto T, Ishihara M, Kimura K, Miyazaki S, Yamagishi M, Tei C, Hiraoka H, Sonoda M, Tsuchihashi K, Shimoyama N, Honda T, Ogata Y, Matsui K, Ogawa H. Prognostic usefulness of serum uric acid after acute myocardial infarction (the Japanese Acute Coronary Syndrome Study). Am J Cardiol 2005;96:489–95.
[24] Trkulja V, Car S. On-admission serum uric acid predicts outcomes after acute myocardial infarction: systematic review and meta-analysis of prognostic studies. Croat Med J 2012;53:162–72.
[25] Akpek M, Kaya MG, Uyarel H, Yarlioglues M, Kalay N, Gunebakmaz O, Dogdu O, Ardic I, Elcik D, Sahin O, Oguzhan A, Ergin A, Gibson CM. The association of serum uric acid levels on coronary flow in patients with STEMI undergoing primary PCI. Atherosclerosis 2011;219:334–41.
[26] Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A 1981;78:6858–62.
[27] Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, Davos CH, Cicoira M, Shamim W, Kemp M, Segal R, Osterziel KJ, Leyva F, Hetzer R, Ponikowski P, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107:1991–7.
[28] Terada LS, Guidot DM, Leff JA, Willingham IR, Hanley ME, Piermattei D, Repine JE. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. Proc Natl Acad Sci U S A 1992;89:3362–6.
[29] Romano M, Buffoli F, Tomasi L, Aroldi M, Lettieri C, Ferrari MR, Zanini R. The no-reflow phenomenon in acute myocardial infarction after primary angioplasty: incidence, predictive factors, and long-term outcomes. J Cardiovasc Med 2008;9:59–63.
[30] Parent R, Paré R, Lavallée M. Contribution of nitric oxide to dilation of resistance coronary vessels in conscious dogs. Am J Physiol 1992;262:10–6.
[31] Puddu P, Puddu GM, Cravero E, Vizioli L, Muscari A. Relationships among hyperuricemia, endothelial dysfunction and cardiovascular disease: molecular mechanisms and clinical implications. J Cardiol 2012;59:235–42.
[32] Zhang W, Sun K, Yang Y, Zhang H, Hu FB, Hui R. Plasma uric acid and hypertension in a Chinese community: prospective study and meta-analysis. Clin Chem 2009;55:2026–34.
[33] Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 2001;24:691–7.
[34] Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Uejima T, Oikawa Y, Koike A, Nagashima K, Kirigaya H, Yajima J, Sawada H, Aizawa T, Yamashita T. Gender-specific relationship between serum uric acid level and atrial fibrillation prevalence. Circ J 2012;76:607–11.
[35] Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2010;62:170–80.
[36] Tuttle KR, Short RA, Johnson RJ. Sex differences in uric acid and risk factors for coronary artery disease. Am J Cardiol 2001;87:1411–4.
[37] Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study. Int J Cardiol 2008;125:232–9.
[38] Kaneko H, Yajima J, Oikawa Y, Tanaka S, Fukamachi D, Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Kano H, Uejima T, Koike A, Nagashima K, Kirigaya H, et al. Obesity paradox in Japanese patients after percutaneous coronary intervention: an observation cohort study. J Cardiol 2013;62:18–24.