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ORIGINAL RESEARCH

Uric Acid Levels, Number of Standard Modifiable Cardiovascular Risk Factors, and Prognosis in Patients With Coronary Artery Disease: A Large Cohort Study in Asia

Kongyong Cui, MD*; Yanjun Song, MD*; Dong Yin, MD; Weihua Song, MD; Hongjian Wang, MD; Chenggang Zhu, MD; Lei Feng, MD; Rui Fu, MD; Lei Jia, MD; Ye Lu, MD; Dong Zhang, MD; Chenxi Song, MD; Yuejin Yang, MD; Qiuting Dong, MD; Kefei Dou, MD

BACKGROUND: Serum uric acid (UA) is correlated closely with traditional cardiovascular risk factors, which might interfere with the action of UA, in patients with coronary artery disease. We performed this study to evaluate the prognostic effect of UA levels in individuals with different numbers of standard modifiable cardiovascular risk factors (SMuRFs).

METHODS AND RESULTS: In this prospective study, we consecutively enrolled 10 486 patients with coronary artery disease. They were stratified into 3 groups according to the tertiles of UA concentrations and, within each UA tertile, further classified into 3 groups by the number of SMuRFs (0–1 versus 2–3 versus 4). The primary end point was major adverse cardiovascular and cerebrovascular events (MACCEs), including death, myocardial infarction, stroke, and unplanned revascularization. Over a median follow-up of 2.4 years, 1233 (11.8%) MACCEs were recorded. Patients with high UA levels developed significantly higher risk of MACCEs than those with low UA levels. In addition, UA levels were positively associated with MACCEs as a continuous variable. More importantly, in patients with 0 to 1 SMuRF, the risks of MACCEs were significantly higher in the high-UA-level group (adjusted hazard ratio [HR], 1.469 [95% CI, 1.197–1.804]) and medium-UA-level group (adjusted HR, 1.478 [95% CI, 1.012–2.160]), compared with the low-UA-level group, whereas no significant association was found between UA levels and the risk of MACCEs in participants with 2 to 3 or 4 SMuRFs.

CONCLUSIONS: In patients with coronary artery disease who received evidence-based secondary prevention therapies, elevated UA levels might affect the prognosis of individuals with 0 to 1 SMuRF but not that of individuals with ≥2 SMuRFs.

Key Words: cardiovascular events ■ coronary artery disease ■ standard modifiable cardiovascular risk factors ■ uric acid

Uric acid (UA) is an end product of purine metabolism functioning as a vehicle eliminating purine waste from human body.[1–3] It is generally believed that accumulation of UA causes monosodium urate crystal deposition in the joints and kidneys, leading to gout and nephrolithiasis.[4] Given that hyperuricemia provokes endothelial dysfunction via increasing oxidative stress and inflammation, the roles of UA in the incidence of coronary artery disease (CAD) have raised great interest in the past 2 decades. Although mounting evidence from epidemiological studies have demonstrated a positive association between UA levels

Correspondence to: Qiuting Dong, MD and Kefei Dou, MD, Cardiometabolic Medicine Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167A Beilishi Road, Xi Cheng District, Beijing 100037, China. Email: blue1005dqt@163.com, drdoukefei@126.com

*K. Cui and Y. Song contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- The prognostic effect of serum uric acid levels in patients with coronary artery disease with different numbers of standard modifiable cardiovascular risk factor (SMuRFs) has never been evaluated.
- This study, for the first time, indicated that elevated uric acid levels might affect the prognosis of individuals with 0 to 1 SMuRF but not that of individuals with ≥2 SMuRFs.

What Are the Clinical Implications?

- This study provides convincing evidence for the role of elevated UA levels for patients with coronary artery disease with no or few SMuRFs who received evidence-based secondary prevention therapies.
- Further randomized trials are needed to specify the effect of UA-lowering therapy on prognosis in individuals with coronary artery disease and hyperuricemia, especially in those with no or few SMuRFs.

Nonstandard Abbreviations and Acronyms

CAMI	China Acute Myocardial Infarction
LURIC	Ludwigshafen Risk and Cardiovascular Health
MACCE	major adverse cardiovascular and cerebrovascular event
SMuRF	standard modifiable cardiovascular risk factor
UA	uric acid
URRAH	Uric Acid Right for Heart Health

and CAD,[2,3] medical societies have not recognized elevated serum UA as an independent cardiovascular risk factor,[1–3] with a large number of observational studies and Mendelian randomization studies showing conflicting results.[5–10] Regarding individuals with established CAD, evidence for the positive association of high serum UA levels with poor prognosis seems to be stronger than that in the general population,[11–19] yet there were still some studies reporting inconsistent results.[20–23]

Actually, elevated UA levels are often associated with various cardiovascular risk factors such as abnormal glucose regulation, hypertension, lipid disorder, and obesity, which might interfere with the action of serum UA.[1–3] Therefore, it is important to effectively eliminate or reduce the influence of traditional risk factors when exploring the relationship between UA and cardiovascular events. Standard modifiable cardiovascular risk factors (SMuRFs), which include diabetes, hypertension, dyslipidemia, and smoking, were considered as pivotal drivers triggering the pathogenesis and development of CAD.[24,25] To better specify the roles of UA in the secondary prevention population, we performed this study to evaluate the prognostic effect of serum UA levels in patients with CAD with different numbers of SMuRFs from a large prospective study in Asia.

METHODS

We will make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

This was a single-center prospective cohort study, and the details of the study design were reported previously.[26–28] Briefly, 10 724 patients with CAD who underwent percutaneous coronary intervention (PCI) were consecutively enrolled between January 2013 and December 2013 from Fuwai Hospital, National Center for Cardiovascular Diseases. This study complied with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Fuai Hospital. All participants provided written informed consent before enrollment. Of note, 66 participants with missing UA data before PCI; 4 participants with severe renal insufficiency; and 128 participants with left ventricular ejection fraction ≤40%, having a history of heart failure, or using diuretics due to heart failure were excluded. In addition, we also excluded 41 participants who suffered major adverse events during hospitalization (death, myocardial infarction [MI], stroke, or urgent revascularization). Eventually, a total of 10 486 participants were analyzed (Figure S1).

Study Procedures and Biochemical Analysis

After fasting for ≥12 hours before angiography, laboratory samples were obtained from each of the participants, and all tests were conducted through the clinical chemistry department at Fuwai Hospital. Concentrations of serum UA, creatinine, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were analyzed by an automated biochemical analyzer (Hitachi 7150,

Tokyo, Japan). UA was measured using a UA Assay Kit (uricase–peroxidase method). A validated standard of UA was used for calibration, and the coefficient of variation of repetitive measurements was <10%. Angiographic and procedural data were collected from catheter laboratory records by 3 experienced interventional cardiologists.[28] During hospitalization, all procedures and medical therapies were performed according to guideline recommendations and cardiologist's discretion. Demographics, cardiovascular risk factors, clinical parameters, laboratory results, coronary angiographic and procedural details, and medications were prospectively collected with standardized questionnaires by independent research personnel.

All patients were stratified into 3 groups according to the tertiles of UA concentrations. Consistent with previous studies, the SMuRFs refers to 4 traditional risk factors including diabetes, hypertension, dyslipidemia, and current smoking.[24,25] Participants who had a history of diabetes, received hypoglycemic therapy, or had a fasting blood glucose ≥7.0 mmol/L, hemoglobin A_{1c} ≥6.5%, or 2-hour plasma glucose ≥11.1 mmol/L in an oral glucose tolerance test were regarded as having diabetes.[29] Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive treatment.[30] Dyslipidemia was defined as an increase in triglyceride (≥150 mg/dL), total cholesterol (≥200 mg/dL), or low-density lipoprotein cholesterol (≥130 mg/dL); a decrease in high-density lipoprotein cholesterol (<40 mg/dL); or use of cholesterol-lowering medication.[31] Current smoking was defined as smoking regularly within the last month before admission. We classified patients into 3 groups on the basis of the number of SMuRFs (ie, 0–1, 2–3, and 4) to avoid a small sample size within groups and permit evaluation of trends according to SMuRF numbers.[32,33] Finally, patients were divided into 9 groups according to UA levels and SMuRF numbers.

Follow-Up and End Points

After discharge, patients were followed up at 6-month intervals until January 31, 2016. Data for end points were collected from medical records, clinical visit, or telephone interviews by trained investigators who were blind to the clinical data. The primary end point was major adverse cardiovascular and cerebrovascular events (MACCEs), including all-cause death, nonfatal MI, stroke, or unplanned revascularization. Secondary end points consisted of cardiac death and the components of the primary end point. Death was considered cardiac unless an unequivocal noncardiac cause could be established. MI was defined in compliance with the Third Universal Definition of MI.[34] Stroke was defined as a new focal neurological deficit lasting >24 hours and confirmed by imaging evidence. Unplanned revascularization was repeat PCI or surgery after discharge excluding staged PCI. All events must be validated by source documents.

Statistical Analysis

Continuous variables were expressed as mean±SD if they conformed to the normal distribution; otherwise, they were shown as median (interquartile range), while categorical variables were expressed as frequencies (percentages). Differences between groups were compared using 1-way ANOVA, the Kruskal–Wallis H test, Pearson's chi-square test, or Fisher's exact test, as appropriate. The cumulative incidence of clinical events was estimated using Kaplan–Meier curves, and differences were assessed with the log-rank test. Univariable and multivariable Cox regression analyses were performed to calculate hazard ratios (HRs) and 95% CIs. The optimal cutoff value of UA for predicting MACCEs were identified by the Youden Index with receiver operating characteristic curve analysis. On a continuous scale, restricted cubic splines were also used to examine the potential nonlinear relationships between UA levels and MACCEs.[35] Of note, most variables have no missing values, with a few exceptions. Missing information on covariates for statistical adjustment, that is, for systolic blood pressure (5.1%), triglyceride (2.2%), low-density lipoprotein cholesterol (2.2%), minimum stent diameter (4.3%), and total stent length (4.3%), were imputed with a sequential regression multiple imputation method. All statistical analyses were conducted in SPSS 23.0 (SPSS Inc., Chicago, IL) and STATA 12.0 (StataCorp, College Station, TX). A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Of the 10 486 participants, 77.2% were men, the median age was 59 years, and the median UA level was 5.6 mg/dL, while 417 (4.0%), 1860 (17.7%), 3494 (33.3%), 3451 (32.9%), and 1264 (12.1%) patients combined with 0, 1, 2, 3, and 4 SMuRFs, respectively. Based on the tertiles of UA levels, participants were divided into 3 groups: <5.1 mg/dL (n=3495), 5.1 to 6.2 mg/dL (n=3497), and ≥6.2 mg/dL (n=3494). In addition, participants were also classified into 1 of 3 groups: 0 to 1 SMuRF (n=2277), 2 to 3 SMuRFs (n=6945), and 4 SMuRFs (n=1264).

Baseline characteristics of the participants according to UA levels are listed in Table 1. The percentage of male patients, prevalence of cardiovascular risk factors, and previous MI increased with UA levels. From

Table 1. Baseline Patient, Angiographic, and Procedural Characteristics According to Uric Acid Levels

Variable	Overall (n=10 486)	Low uric acid level (n=3495)	Medium uric acid level (n=3497)	High uric acid level (n=3494)	*P* value
Age, y	59 (51–65)	60 (54–67)	58 (51–65)	56 (49–64)	<0.001
Male, n (%)	8094 (77.2)	2151 (61.5)	2827 (80.8)	3116 (89.2)	<0.001
Body mass index, kg/m^2	25.9 (23.9–27.8)	25.3 (23.2–27.4)	25.8 (23.9–27.7)	26.5 (24.5–28.4)	<0.001
Current smoker, n (%)	5990 (57.1)	1624 (46.5)	2070 (59.2)	2296 (65.7)	<0.001
Diabetes, n (%)	4430 (42.2)	1695 (48.5)	1441 (41.2)	1294 (37.0)	<0.001
Hypertension, n (%)	6755 (64.4)	2185 (62.5)	2210 (63.2)	2360 (67.5)	<0.001
Dyslipidemia, n (%)	7068 (67.4)	2283 (65.3)	2337 (66.8)	2448 (70.1)	<0.001
Previous myocardial infarction, n (%)	1965 (18.7)	571 (16.3)	679 (19.4)	715 (20.5)	<0.001
Previous PCI, n (%)	2553 (24.3)	816 (23.3)	891 (25.5)	846 (24.2)	0.113
Previous CABG, n (%)	423 (4.0)	115 (3.3)	150 (4.3)	158 (4.5)	0.021
Previous stroke, n (%)	1120 (10.7)	390 (11.2)	371 (10.6)	359 (10.3)	0.482
Peripheral vascular disease, n (%)	282 (2.7)	96 (2.7)	100 (2.9)	86 (2.5)	0.570
eGFR <60 mL/min per 1.73 m^2, n (%)	309 (3.1)	56 (1.7)	71 (2.1)	182 (5.4)	<0.001
COPD, n (%)	241 (2.3)	80 (2.3)	78 (2.2)	83 (2.4)	0.920
LVEF <50%, n (%)	410 (4.0)	118 (3.5)	123 (3.6)	169 (5.0)	0.002
Acute coronary syndrome, n (%)	6272 (59.8)	2149 (61.5)	2056 (58.8)	2067 (59.2)	0.045
Systolic blood pressure, mm Hg	125 (120–140)	130 (120–140)	125 (120–140)	122 (115–139)	<0.001
Laboratory data					
Triglyceride, mmol/L	1.53 (1.14–2.10)	1.40 (1.05–1.89)	1.51 (1.13–2.03)	1.72 (1.28–2.37)	<0.001
Total cholesterol, mmol/L	4.05 (3.44–4.81)	4.06 (3.46–4.81)	4.01 (3.40–4.77)	4.09 (3.46–4.84)	0.026
LDL-C, mmol/L	2.35 (1.86–3.01)	2.35 (1.86–2.97)	2.32 (1.83–3.00)	2.38 (1.88–3.06)	0.119
HDL-C, mmol/L	0.99 (0.84–1.18)	1.06 (0.89–1.26)	1.00 (0.84–1.17)	0.94 (0.80–1.10)	<0.001
Hemoglobin A_{1c}, %	6.2 (5.8–7.0)	6.3 (5.9–7.4)	6.2 (5.8–6.9)	6.1 (5.8–6.7)	<0.001
Uric acid, mg/dL	5.64 (4.78–6.58)	4.40 (3.89–4.78)	5.64 (5.36–5.91)	7.04 (6.58–7.73)	<0.001
Radial artery access, n (%)	8853 (91.4)	2957 (90.8)	2948 (91.5)	2948 (91.8)	0.394
3-vessel disease, n (%)	4539 (43.3)	1489 (42.6)	1515 (43.3)	1535 (43.9)	0.608
SYNTAX score	10 (6–17)	10 (6–17)	10 (6–17)	10 (6–17)	0.731
Type B2 or C lesion, n (%)	8063 (76.9)	2685 (76.8)	2679 (76.6)	2699 (77.2)	0.813
No. lesions treated ≥3, n (%)	714 (6.8)	239 (6.8)	235 (6.7)	240 (6.9)	0.967
No. stents ≥3, n (%)	2327 (22.2)	743 (21.3)	776 (22.2)	808 (23.1)	0.172
Use of EES/ZES, n (%)	5477 (52.2)	1818 (52.0)	1841 (52.6)	1818 (52.0)	0.835
Minimum stent diameter, mm	2.75 (2.50–3.00)	2.75 (2.50–3.00)	2.75 (2.50–3.00)	2.75 (2.50–3.00)	<0.001
Total stent length, mm	36 (23–55)	33 (23–54)	35 (23–55)	37 (23–57)	0.001
Medications at discharge					
Aspirin, n (%)	10 348 (98.7)	3444 (98.5)	3453 (98.7)	3451 (98.8)	0.658
$P2Y_{12}$ receptor inhibitor, n (%)	10 326 (98.5)	3438 (98.4)	3443 (98.5)	3445 (98.6)	0.734
β-Blockers, n (%)	9447 (90.1)	3160 (90.4)	3132 (89.6)	3155 (90.3)	0.433
Statins, n (%)	10 056 (95.9)	3335 (95.4)	3371 (96.4)	3350 (95.9)	0.121
Calcium channel blockers, n (%)	5138 (49.0)	1764 (50.5)	1691 (48.4)	1683 (48.2)	0.101

CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; EES, everolimus-eluting stent; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SYNTAX, synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; and ZES, zotarolimus-eluting stent.

Data were presented as median (interquartile range), mean±SD or frequencies (percentages).

the low-UA-level group to the high-UA-level group, there was an ascending gradient regarding body mass index, triglyceride concentrations, minimum stent diameter, and total stent length, whereas there was a descending gradient with respect to age, systolic blood pressure, high-density lipoprotein cholesterol levels, and hemoglobin A_{1c} levels. In Table S1, the prevalence of male patients, previous MI, previous stroke, peripheral vascular disease, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, 3-vessel disease, and total stent length increased with the number of SMuRFs. In addition, there was an ascending gradient

regarding body mass index, systolic blood pressure, triglyceride levels, hemoglobin A_{1c} levels, and total stent length, whereas there was a descending gradient with respect to minimum stent diameter and the concentrations of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

UA Levels and 2.4-Year Clinical Outcomes

Over a median follow-up of 2.4 (interquartile range, 2.2–2.6) years, 1233 (11.8%) MACCEs were recorded, including 121 (1.2%) deaths, 95 (0.9%) nonfatal MIs, 171 (1.6%) strokes, and 948 (9.0%) unplanned revascularizations. As shown in Table S2 and Figure 1A, participants with high UA levels had significantly higher risk of MACCEs than those with low UA levels in univariable and multivariable Cox regression analyses (13.1% versus 10.7%; adjusted HR, 1.103 [95% CI, 1.016–1.198]), whereas the incidence of MACCEs did not significantly differ between patients with medium UA levels and low UA levels. In addition, UA levels were positively associated with MACCEs as a continuous variable even after adjusting for potential confounders (adjusted HR, 1.057 [95% CI, 1.011–1.106]). In restricted cubic spline analysis, a linear positive association was seen between UA levels and MACCEs in the overall population (Figure S2). Based on receiver operating characteristic curve analysis, the optimal cutoff value of UA for predicting MACCEs was 6.17 mg/dL (Figure S3). With respect to cardiac death, MI, and unplanned revascularization, the results were in line with that of MACCEs (Table S2 and Figure S4).

Subgroup analysis showed that the high-UA-level group presented an elevated incidence of MACCEs compared with that in the low-UA-level group in participants without diabetes (adjusted HR, 1.122 [95% CI, 1.001–1.257]). Similar results were obtained in participants without hypertension (adjusted HR, 1.190 [95% CI, 1.025–1.381]), dyslipidemia (adjusted HR, 1.307 [95% CI, 1.127–1.516]), current smoking (adjusted HR, 1.188 [95% CI, 1.042–1.354]), and metabolic syndrome (adjusted HR, 1.208 [95% CI, 1.060–1.377]). Nevertheless, the incidence of MACCEs did not significantly differ among low-, medium-, and high-UA-level groups in patients with diabetes, hypertension, dyslipidemia, current smoking (Tables S3 through S6 and Figure 2), and metabolic syndrome (Table S7). In addition, female patients in the high-UA-level group had a significantly higher incidence of MACCEs than those in the low-UA-level group, whereas there was a statistically nonsignificantly increased incidence of MACCEs in the high-UA-level group compared with the low-UA-level group in male patients (Table S8).

SMuRFs and 2.4-Year Clinical Outcomes

In Figure 1B and Table S9, the incidence of MACCEs was significantly higher in participants with 4 SMuRFs than that in participants with 0 to 1 SMuRF (HR, 1.227 [95% CI, 1.112–1.353]). Additional adjustment for other variables in Cox regression analysis obtained similar results (adjusted HR, 1.159 [95% CI, 1.027–1.308]). In addition, this significant association was also observed

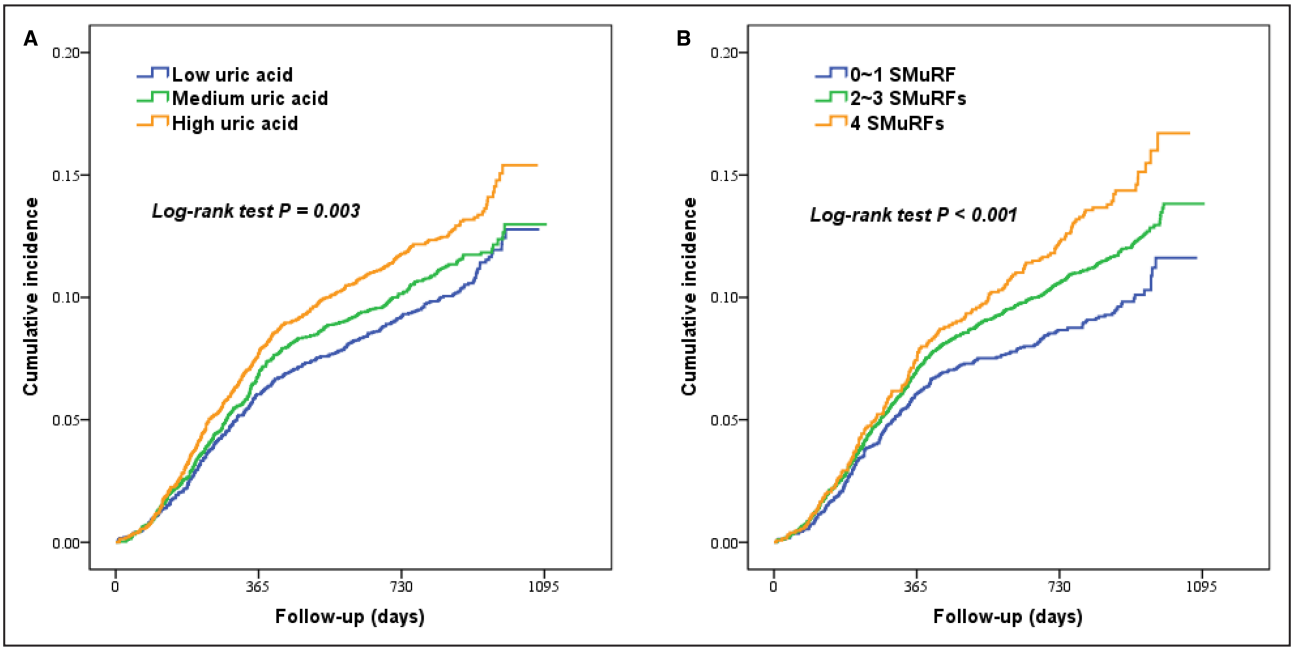

Figure 1. Kaplan–Meier survival curves for major adverse cardiovascular and cerebrovascular events according to uric acid tertiles (A) and number of SMuRFs (B).
SMuRFs indicates standard modifiable cardiovascular risk factors.

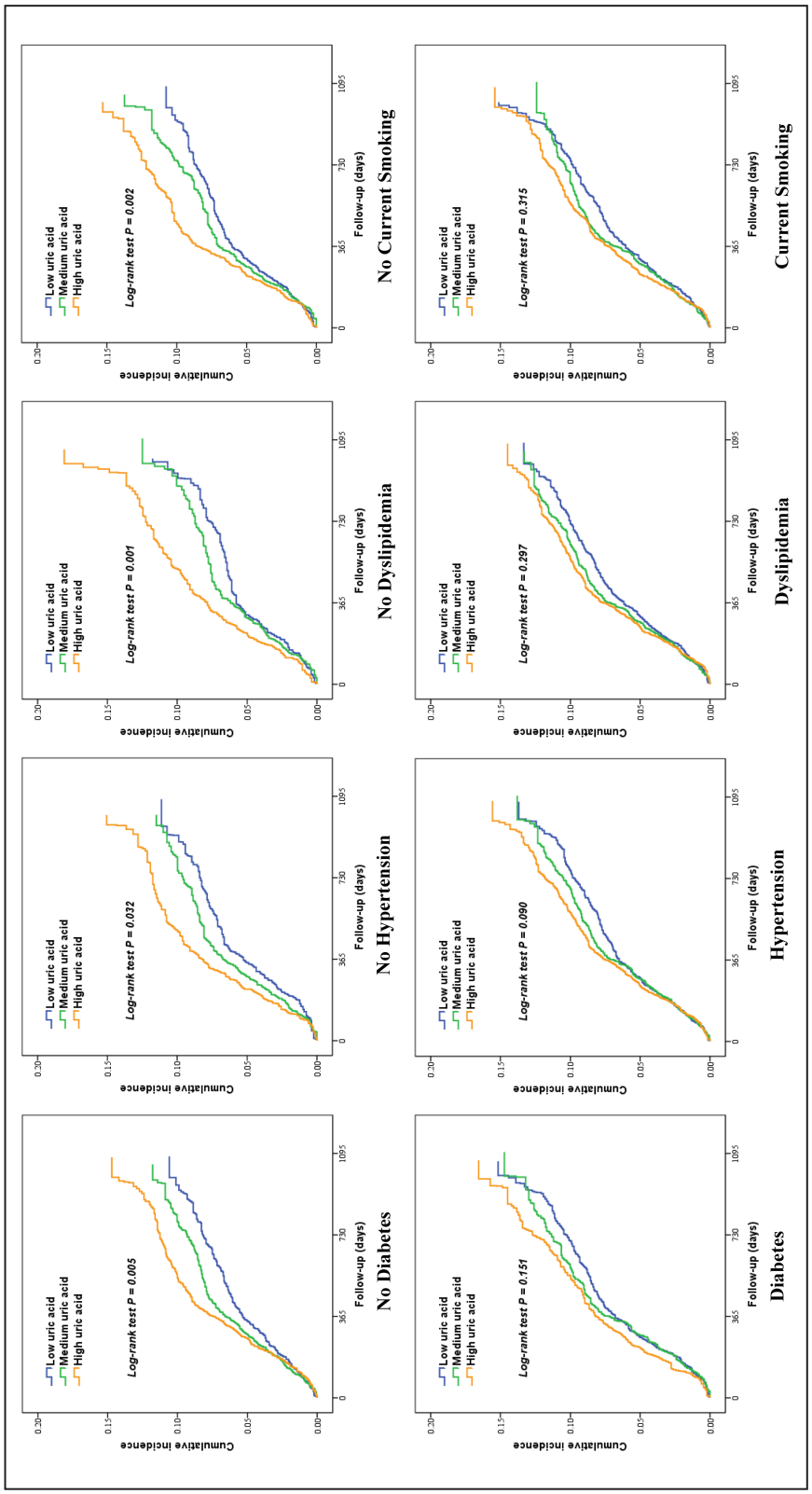

Figure 2. Kaplan–Meier survival curves for major adverse cardiovascular and cerebrovascular events according to uric acid tertiles in individuals with or without diabetes, hypertension, dyslipidemia, and current smoking.

between participants with 2 to 3 SMuRFs and those with 0 to 1 SMuRF. Secondary outcomes according to the number of SMuRFs were shown in Table S9 and Figure S5.

UA Levels, SMuRFs and Clinical Outcomes

In participants with 0 to 1 SMuRF, the risks of MACCEs were significantly higher in the high-UA-level group (adjusted HR, 1.469 [95% CI, 1.197–1.804]) and medium UA-level group (adjusted HR, 1.478 [95% CI, 1.012–2.160]) compared with the low-UA-level group in univariable and multivariable Cox regression analyses. Furthermore, UA levels were positively associated with MACCEs as a continuous variable even after adjusting for potential confounders (adjusted HR, 1.207 [95% CI, 1.082–1.347]). In participants with 2 to 3 SMuRFs, the risk of MACCEs was higher in the high-UA-level group than that in the low-UA-level group in the univariable model (HR, 1.087 [95% CI, 1.000–1.180]), whereas this association disappeared after adjusting for other variables in the multivariable model (adjusted HR, 1.057 [95% CI, 0.958–1.167]). Inversely, no significant association was found between UA levels and the incidence of MACCEs in participants with 4 SMuRFs (Table 2, Figure 3, and Figure S6). In addition, restricted cubic spline analysis showed a linear positive association between UA levels and MACCE using smoothed restricted cubic spline plots in participants with 0 to 1 SMuRF and 2 to 3 SMuRFs (Figure S2). The optimal cutoff values of UA for predicting MACCEs were 5.14 mg/dL and 6.18 mg/dL in participants with 0 to 1 SMuRF and 2 to 3 SMuRFs, respectively (Figure S3).

DISCUSSION

This large-scale cohort study confirmed that high UA levels were significantly associated with increased risk of 2.4-year MACCEs, in conjunction with high risk of cardiac death, nonfatal MI, and unplanned revascularization in individuals with CAD who received evidence-based secondary prevention therapies after PCI. Moreover, this study, for the first time, demonstrated that the predictive value of UA levels on MACCEs was more evident in individuals with 0 to 1 SMuRF, whereas no statistically significant association was found between UA levels and MACCEs in individuals with 2 to 3 or 4 SMuRFs.

UA per se exerts a plethora of deleterious effects in cells and it may be directly involved in the pathophysiology of cardiovascular disease through increased oxidative stress and inflammation, reduced availability of nitric oxide, endothelial dysfunction, vasoconstriction, proliferation of vascular smooth muscle cells, insulin resistance, and metabolic dysregulation.[2,3] Moreover, elevated UA levels may be a marker or a consequence of upregulated or increased xanthine oxidoreductase activity and increased oxidative stress.[2] Of note, extracellular UA can also act as an antioxidant, which might be beneficial for people with cardiovascular disease. Though having been extensively discussed, the association between UA levels and cardiovascular events has not been definitely established in primary and secondary prevention populations. For individuals with CAD, plenty of observational studies demonstrated that high UA levels were significantly associated with poor prognosis in individuals with stable CAD[11,12] and acute coronary syndrome[13–16] and in individuals who underwent PCI[15–18] or coronary artery bypass grafting.[19] However,

Table 2. 2.4-Year Major Adverse Cardiovascular and Cerebrovascular Events According to Serum Uric Acid Tertiles in Patients With Different Numbers of SMuRFs

No. SMuRFs	Group	Event, n (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
0–1	Low uric acid	63 (7.2)	1 (reference)	1 (reference)
	Medium uric acid	80 (10.2)	1.444 (1.038–2.009)*	1.478 (1.012–2.160)*
	High uric acid	78 (12.6)	1.359 (1.151–1.604)*	1.469 (1.197–1.804)*
	Per 1 mg/dL increase	221 (9.7)	1.157 (1.056–1.269)*	1.207 (1.082–1.347)*
2–3	Low uric acid	254 (11.4)	1 (reference)	1 (reference)
	Medium uric acid	259 (11.3)	0.998 (0.840–1.187)	0.957 (0.788–1.162)
	High uric acid	317 (13.1)	1.087 (1.000–1.180)*	1.057 (0.958–1.167)
	Per 1 mg/dL increase	830 (12.0)	1.057 (1.008–1.132)*	1.044 (0.988–1.104)
4	Low uric acid	57 (14.6)	1 (reference)	1 (reference)
	Medium uric acid	63 (15.0)	1.038 (0.725–1.485)	0.983 (0.665–1.453)
	High uric acid	62 (13.7)	0.972 (0.812–1.163)	0.971 (0.795–1.185)
	Per 1 mg/dL increase	182 (14.4)	0.980 (0.888–1.082)	0.979 (0.877–1.092)

Adjusted for age, sex, body mass index, previous myocardial infarction, previous stroke, acute coronary syndrome, systolic blood pressure, triglyceride, low-density lipoprotein cholesterol, minimum stent diameter, total stent length, and use of statin at discharge. HR indicates hazard ratio; and SMuRFs, standard modifiable cardiovascular risk factors.

*$P<0.05$.

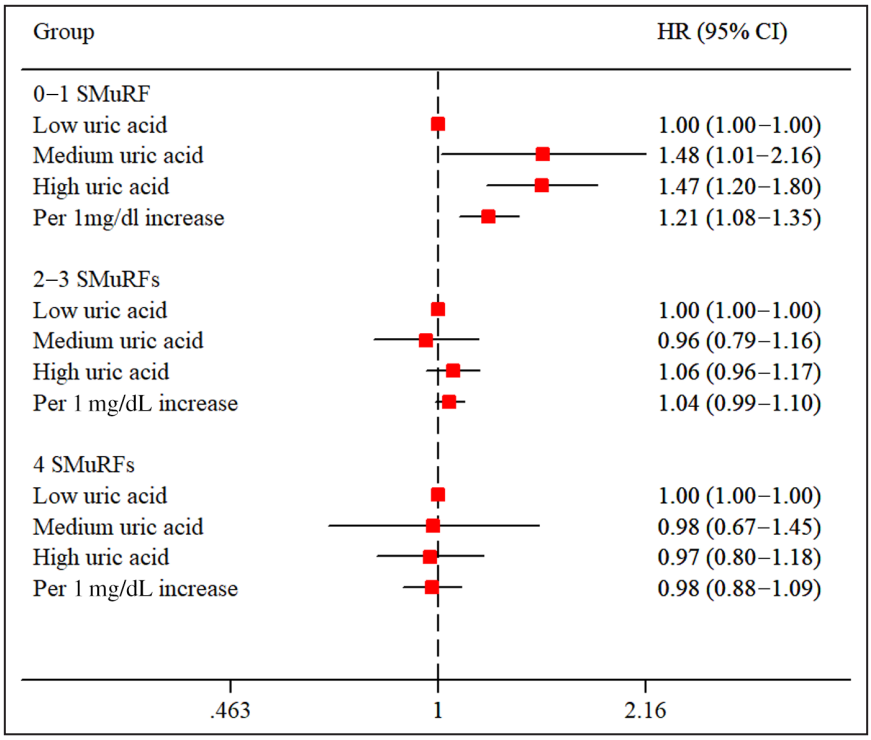

Figure 3. The adjusted HRs for major adverse cardiovascular and cerebrovascular events according to serum uric acid levels in patients with different numbers of SMuRFs.
HR indicates hazard ratio; and SMuRFs, standard modifiable cardiovascular risk factors.

in a recent study involving 5070 patients with chronic coronary syndrome, scholars found that patients with high UA levels did not significantly influence the rate of cardiovascular death and hospitalization of heart failure during 1-year follow-up.[20] Lazzeri et al[21] demonstrated that hyperuricemia was not independently associated with early death in 856 patients with ST-segment–elevation MI. An analysis of the LURIC (Ludwigshafen Risk and Cardiovascular Health) study demonstrated that high UA levels were not significantly associated with a higher risk of 7.3-year all-cause death after adjusting for age, sex, traditional cardiovascular risk factors, the severity of coronary atherosclerosis, and medication use in subjects referred for coronary angiography.[22] In addition, a study with 647 patients with angiographically proven CAD found that UA ≥6.4 mg/dL was not significantly associated with a higher risk of cardiovascular death at 5-year follow-up.[23]

Our study presented a consistent result with most of the studies displayed above, as the increased risk of MACCEs was documented in the high-UA group even after fully adjusting for potential confounders, indicating that hyperuricemia might be a pivotal risk factor for recurrent cardiovascular events. Notably, this study found a linear positive association between UA levels and MACCEs in patients with CAD who underwent PCI. In contrast, Zheng et al[36] indicated a U-shaped relationship between UA and 4.9-year all-cause death in patients with CAD (*P* for nonlinearity <0.05). In a study by Matsumoto et al,[18] patients with UA levels of ≤4.0 mg/dL had a statistically nonsignificantly increased risk of cardiovascular events compared with those with UA levels of 4.0 to 5.1 mg/dL after PCI. Further studies are needed to determine whether excessively low UA levels are associated with increased cardiovascular risk. Moreover, the prognostic effect of high UA levels for MACCE was more evident in women than in men. Consistently, several studies also reported a stronger association between UA levels and cardiovascular events in women than in men or the existence of such an association in women only.[37–40] In addition, we also found that the positive association between UA levels and cardiovascular events was more pronounced in participants without metabolic syndrome compared with that in participants with metabolic syndrome. However, Pugliese et al[41] reported that increasing UA levels were significantly associated with higher 11.8-year cardiovascular death irrespective of the presence of metabolic syndrome. Actually, the follow-up time was relatively short in our study; thus, the prognostic effect of UA for MACCE has not been fully reflected.

The URRAH (Uric Acid Right for Heart Health) study from Italy reported that the optimal cutoff values of UA able to discriminate all-cause death, cardiovascular

death, fatal MI, and stroke were 4.7 mg/dL, 5.6 mg/dL, 5.7 mg/dL, and 4.8 mg/dL, respectively, indicating that individuals with normal UA levels were also associated with a higher risk of cardiovascular events.[40,42,43] The present study identified 6.17 mg/dL as the optimal cutoff value of UA for predicting MACCE. The different optimal cutoff values of UA between the present study and the URRAH study may be due to the different population, follow-up time, and end point. Nonetheless, UA as a predictor of recurrent cardiovascular disease in patients with CAD with moderate to high UA levels would not change the criteria for therapeutic intervention since there is a lack of clear evidence of its benefit.

It is well known that SMuRFs are positively related to the increased risk of cardiovascular events in individuals with CAD, which is confirmed in the present study. However, UA has not been regarded as an independent risk factor for cardiovascular disease. In clinical practice, UA is correlated closely with almost all known cardiovascular risk factors, and teasing out the individual contribution of each factor has proven difficult.[1–3] For example, previous studies revealed that elevated UA levels in metabolic syndrome have been attributed to hyperinsulinemia, as insulin reduces renal excretion of UA.[41,44] Therefore, some expert groups argued that studies indicating UA as an independent risk factor did not sufficiently control for other traditional risk factors. To well elucidate the roles of UA in patients with CAD who underwent PCI, the relationship between high UA levels and prognosis was also analyzed in individuals with different numbers of SMuRFs (0–1, 2–3, and 4), especially in those who had no or few SMuRFs.

Potentially the most important finding of this study is that UA levels were strongly and positively associated with the risk of MACCEs in individuals with 0 to 1 SMuRF, whereas this association was not found in individuals with 2 to 3 or 4 SMuRFs. In addition, elevated UA levels were also significantly associated with higher risk of MACCEs in individuals without diabetes, hypertension, dyslipidemia, and current smoking, other than in those who had these cardiovascular risk factors. Of note, patients with more SMuRFs will attach more medical attention and receive tight evidence-based secondary prevention therapies compared with those with no or few SMuRFs. This action will reduce the overall risk of cardiovascular events and attenuate the effect of UA levels on the prognosis of individuals with more SMuRFs.

In clinical practice, individuals with no or few SMuRFs, who are perceived to be of *low risk*, are often ignored. However, previous studies enrolling individuals with acute coronary syndrome, especially those with ST-segment–elevation MI, reported that patients without SMuRFs presented higher risk of unadjusted in-hospital or 30-day death than those with SMuRFs.[25,32,33] After adjusting for potential confounders including medication use, this association changed. In the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, the increased risk of 30-day death in SMuRF-less patients remained significant after adjusting for age, sex, left ventricular ejection fraction, creatinine, and blood pressure but was attenuated or lost on inclusion of pharmacotherapy prescription (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, or statin) at discharge, while the long-term mortality rate remained increased in individuals without SMuRFs.[25] In the China Acute Myocardial Infarction (CAMI) registry, a higher risk-factor burden with SMuRFs was associated with poor prognosis among patients with ST-segment–elevation MI after multivariate adjustment including evidence-based medications.[33] The potential causes of this paradox might be suboptimal prescription and neglect of nontraditional risk factors. According to the results of the present study, UA was a potential independent predictor for poor prognosis in patients with CAD with no or fewer SMuRFs. Thus, rigorous secondary prevention strategies including UA-lowering therapy might be beneficial for patients with CAD with high UA levels and no or few SMuRFs.

Given that UA is closely related to systemic inflammation, an anti-inflammatory combined with UA-lowering therapy may be an effective method to improve the prognosis of patients.[45] Allopurinol is a xanthine oxidase inhibitor that lowers UA levels and is licensed for the prevention of gout rather than cardiovascular events.[45] Several studies have already suggested a benefit of allopurinol on endothelial function, flow-mediated dilatation, blood pressure, left ventricular mass, carotid intimal thickness, and arterial stiffness.[2,3] Nevertheless, the ALL-HEART (Allopurinol versus usual care in UK patients with ischaemic heart disease) trial involving 5721 individuals with ischemic heart disease reported that the primary outcome of cardiovascular death, nonfatal MI, or stroke was not significantly reduced when treated with allopurinol therapy (HR, 1.04 [95% CI, 0.89–1.21]).[46] It should be noted that most of the participants in that trial had normal UA levels, with a median concentration of 5.7 to 5.9 mg/dL. Thus, UA levels may have a weak effect on cardiovascular events, and the benefit of UA-lowering therapy was not significant in this population. However, whether UA-lowering therapy will provide a beneficial effect on patients with CAD with hyperuricemia, especially those with no or few SMuRFs, remains to be investigated.

There are several limitations that cannot be ignored. First, this is a single-center, observational study that offers extremely low evidence in the evidence hierarchy, given the highly significant baseline imbalances among

different groups. Although multivariable-adjusted analysis was performed, it was difficult to control the unmeasured confounders. The results of the present study should be interpreted as hypothesis generating. Second, the lack of data on UA-lowering therapy and changes of UA levels during follow-up potentially conferred biases to the results. In addition, UA levels might also be affected by lifestyle modifications including diet, exercise habits, and alcohol intake during follow-up. Third, it is not clear whether the increase of UA levels in participants was due to decreased excretion or overproduction. More detailed phenotypic characterization of patients will help to determine the relationship between UA levels and cardiovascular events and identify potential mechanisms accounting for it. Fourth, previous studies have documented a high risk of atrial fibrillation in individuals with hyperuricemia[47,48]; however, the incidence of atrial fibrillation was not collected during follow-up. Fifth, we did not have data on long-term adherence to evidence-based secondary prevention therapies. Last but not least, these findings should be applied with caution to ethnicities other than Chinese.

CONCLUSIONS

This large-scale study of patients with CAD who received evidence-based secondary prevention therapies, for the first time, indicated that elevated UA levels might affect the prognosis of individuals with 0 to 1 SMuRF but not the prognosis of those with ≥2 SMuRFs. Further randomized trials are needed to specify the effect of UA-lowering therapy on prognosis in individuals with CAD and hyperuricemia, especially in those with no or few SMuRFs.

ARTICLE INFORMATION

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Affiliations

Cardiometabolic Medicine Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (K.C., Y.S., D.Y., W.S., H.W., C.Z., L.F., R.F., L.J., D.Z., C.S., Q.D., K.D.); State Key Laboratory of Cardiovascular Disease, Beijing, China (K.C., Y.S., D.Y., W.S., H.W., C.Z., L.F., R.F., L.J., D.Z., C.S., Y.Y., Q.D., K.D.); National Clinical Research Center for Cardiovascular Diseases, Beijing, China (K.C., Y.S., D.Y., W.S., H.W., C.Z., L.F., R.F., L.J., D.Z., C.S., Y.Y., Q.D., K.D.); Medical Research & Biometrics Center, (Y.L.) and Coronary Heart Disease Center (Y.Y.), Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

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Concept and design: Kefei Dou and Qiuting Dong; acquisition, analysis, or interpretation of data: Kongyong Cui, Yanjun Song, Yuejin Yang, Dong Yin, Weihua Song, Hongjian Wang, Chenggang Zhu, Lei Feng, Rui Fu, Lei Jia, Ye Lu, Dong Zhang, and Chenxi Song; drafting of the manuscript: Kongyong Cui and Yanjun Song; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: Ye Lu, Kongyong Cui, and Yanjun Song; administrative, technical, or material support: Kefei Dou and Qiuting Dong; supervision: Kefei Dou and Qiuting Dong.

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Disclosures

None.

Supplemental Material

Tables S1–S9
Figures S1–S6

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