Uric acid levels are associated with severity and mortality in patients with acute coronary syndrome

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Abstract

Acute coronary syndrome (ACS) causes a serious of coronary artery diseases that associated with sudden and reduced blood flow to the heart. The aim of this study was to assess the potential of serum uric acid (SUA) to predict severity and mortality in patients with ACS. According to their SUA levels, eligible participants were assigned into the Hyperuricemia group and the Normouricemia group (control group). All the patients were requested to enroll into a 1-year follow-up, and the final clinical outcomes included the SYNTAX and Gensini scores, major adverse cardiovascular events (MACEs), and cardiovascular mortality. In total, 874 participants were followed-up. Individuals with high levels of uric acid bore more disease vessels exhibited higher SYNTAX and Gensini scores. Besides, patients in the Hyperuricemia group showed elevated rates of MACE and cardiovascular mortality. High SUA level is positively associated with severity and mortality of patients with ACS. SUA might be a novel ACS prediction marker and risk factor in clinical diagnosis.

Keywords: *uric acid*; *acute coronary syndromes*; *prediction marker*; *risk factor*

Acute coronary syndrome (ACS) causes a serious of coronary artery diseases (CADs) that associated with sudden and reduced blood flow to the heart (1). Coronary arteries are in charge of delivering oxygen and nutrients to the heart muscles to ensure the normal function of heart. However, when fatty deposits on the vessel walls, the blood flow will be blocked, causing cardiac hypoxia and even myocardial infarction. In general, the classification of ACS is based on the electrocardiographic pattern, which causes the clinical manifestations of ACS range widely, including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina (2). Therefore, ACS is still a major health risk, with growing incident and high mortality (3–5). In recent years, with the development of medical treatment, a great effort has been invested in the prediction of ACS and the identification of prognostic markers. However, it is still a long way to go to make them clear.

Uric acid (UA), the final product of purine catabolism, could be detected easily in routine clinical inspection (6). It is well documented in the literature that uric acid participated in inflammation, vascular conditions, endothelial dysfunction, metabolic syndrome, and many other disease progressions (7–9). In addition, a plenty of evidence have shown that the serum uric acid (SUA) level is correlated with cardiovascular risk (2, 10, 11). However, the role of SUA in ACS and the potential of SUA being a new prognostic marker for ACS are still elusive.

In this study, to evaluate the prediction role of UA in ACS, we discussed the relationship between the SUA level and the severity and mortality of ACS patients. We found that patients who had high UA levels in serum were accompanied by higher syntax scores, Gensini scores, and more diseased vessels. Moreover, in 1-year follow-up, the mortality of cardiovascular disease and major adverse cardiovascular events (MACEs) were also significantly elevated in patients with increased SUA levels. Our results provide a new reference for using SUA as an ACS predicator in clinical applications.

Materials and methods

Study design

A total of 1,150 ACS patients who were hospitalized in The Affiliated Jiangning Hospital of Nanjing Medical University were recruited in this trail. The study was
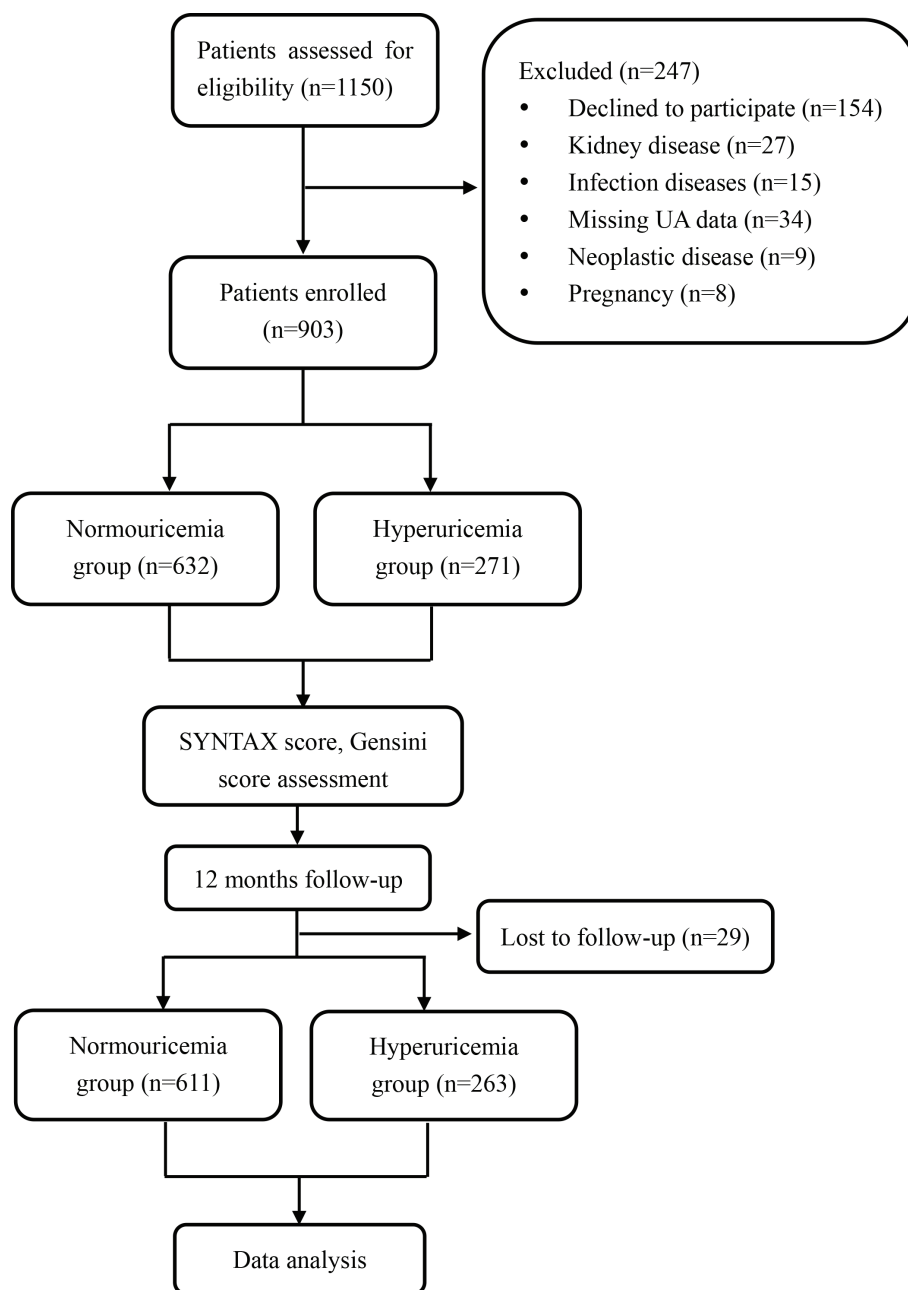
Fig. 1. Participant flow diagram.

approved by Ethics Committee of The Affiliated Jiangning Hospital of Nanjing Medical University. All the participants signed an informed written consent before enrollment.

Exclusion criteria
During the participant recruitment process, 247 patients were excluded after a comprehensive evaluation. Patients who met one of the following six exclusion criteria were eliminated (12): 1) patients who declined to participate in

this study; 2) patients with kidney disease and any other organ dysfunctions; 3) patients with infection diseases; 4) patients who missed their UA data; 5) patients with neoplastic diseases; 6) patients who were pregnant during the follow-up.

Data collection
All the basic information of the participants were collected at the beginning of hospital admission, including demographic characteristics, body weight, previous

Table 1. Baseline characteristics of the participants according to the presence of hyperuricemia

Characteristics	Normouricemia (n = 611)	Hyperuricemia (n = 263)	P
Age (years)	63.3 (12.7)	65.6 (13.2)	0.015
Gender			
Female	182 (29.8)	95 (36.1)	0.065
Male	429 (70.2)	168 (63.9)	
BMI (kg/m²)	24.8 (4.1)	25.5 (4.3)	0.023
Current smoker	193 (31.6)	97 (36.9)	0.127
Hypertension	384 (62.8)	185 (70.3)	0.033
Diabetes mellitus	152 (24.9)	83 (31.6)	0.041
Heart rate (bpm)	73 (65–87)	75 (65–90)	0.051
Number of disease vessels			
1	311 (50.9)	76 (28.9)	
2	183 (30.0)	121 (46.0)	<0.001
3	117 (19.1)	66 (25.1)	
Previous CAD	68 (11.1)	32 (12.2)	0.658
Previous heart failure (HF)	18 (2.9)	5 (1.9)	0.376
LVEF (%)	55.6 (46.0–61.2)	53.2 (41.5–58.8)	0.027
Glucose (mg/dL)	126 (108–159)	134 (108–183)	0.032
Triglycerides (mg/dL)	122 (90–168)	131 (93–178)	0.056
Total cholesterol (mg/dL)	188 (159–216)	192 (161–220)	0.582
HDLc (mg/dL)	43 (30–49)	42 (31–50)	0.711
LDLc (mg/dL)	115 (88–143)	112 (82–146)	0.424
Hemoglobin (g/dL)	13.3 (10.5–14.2)	13.5 (11.0–15.4)	0.531
Creatinine (mg/dL)	0.9 (0.8–1.1)	1.1 (0.9–1.4)	0.015
Uric acid (mg/dL)	5.1 (4.6–5.4)	7.9 (6.7–9.1)	0.008
GFR (mL/min/1.73 m²)	82.9 (64.2–104.5)	64.6 (45.7–90.2)	0.005

Data are presented as mean ± SD, median (IQR), or n (%).

medical history, such as diabetes mellitus, and cardiovascular risks like hypertension. The follow-up started after discharge with a phone interview once a month.

Laboratory parameters
The serum levels of UA, left ventricle ejection fraction (LVEF), glucose, triglycerides, high- and low-density lipoprotein cholesterol (HDLc and LDLc), hemoglobin, creatinine, and glomerular filtration rate (GFR) were measured in the morning after overnight fasting in hospital admission. Serum creatinine and GFR were regarded as indicators of kidney failure.

Clinical outcomes
SYNTAX and Gensini scores are widely utilized in predicting the prognosis of CADs (13, 14). To define complexity and severity of ACS, SYNTAX and Gensini scores were used in this study to represent the angiographic characteristics and revascularization conditions. To further reveal the relationship between UA and ACS severity, the correlation of serum uric acid level and the number of diseased vessels were also analyzed. In the 1 year follow-up, cardiovascular mortality and MACE were assessed as two major endpoint factors, and hospital mortality was excluded (15).

Statistical analysis
Data, expressed as mean and standard deviation (SD), were analyzed with Student's *t*-test and χ^2-test using SPSS. $P < 0.05$ was considered as statistically significant.

Results
A flow diagram of this study is shown in Fig. 1. A total of 1,150 patients were assessed for eligibility, and 247 were excluded due to several conditions, such as declined to participate (*n* = 154), missing UA data (*n* = 34), pregnancy (*n* = 8), and diseases. The remaining 903 patients were enrolled in this study and were assigned into the Hyperuricemia group (*n* = 271) and the Normouricemia group (*n* = 632), which served as the control group (Fig. 1). During the 1-year follow-up, only 29 participants were lost. Ultimately, the clinical data of 611 patients in
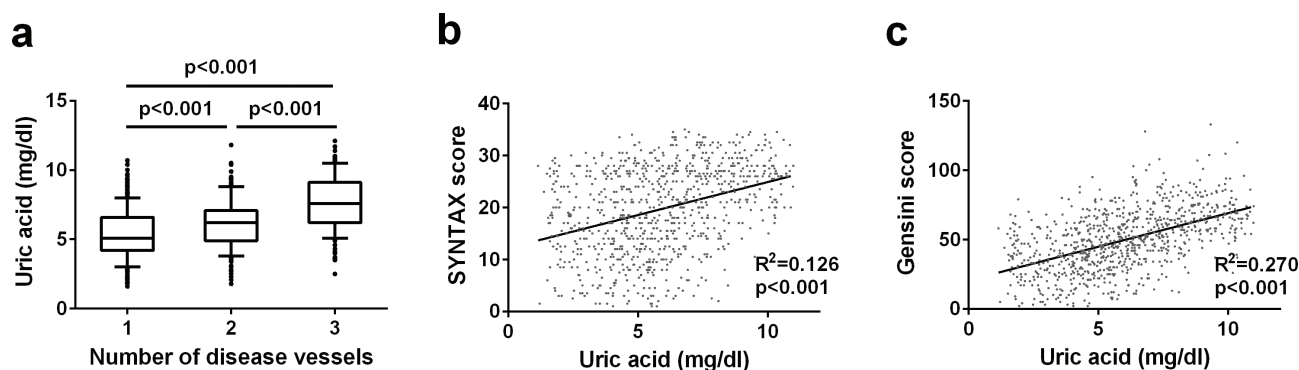
Fig. 2. Relationship between the UA level and severity of ACS patients. (a) UA levels in patients with different number of diseased vessels. Solid black line indicates median, box indicates interquartile range, and lower and upper whiskers indicate 10–90% range. (b) Relationship between the UA level and the SYNTAX score. (c) Relationship between the UA level and the Gensini score.

the Normouricemia group and 263 in the Hyperuricemia group were adopted for the analysis at the end of the trial.

Demographic information and baseline characteristics of the participants

The basic information of the participants in both groups was summarized in Table 1. There were no significant differences in some baseline characteristics between the two groups, with respect to gender ratio (F182/M429 in the Normouricemia group and F95/M168 in the Hyperuricemia group) and current smoker (193 in the Normouricemia group and 97 in the Hyperuricemia group). However, the participants in the Hyperuricemia group were a little older than those in the Normouricemia group (65.6 vs. 63.3, $P = 0.015$), and the body mass index (BMI) of the patients in the Hyperuricemia group (25.5) was also slightly higher than those in the Normouricemia group (24.8, $P = 0.23$). The serum content of the uric acid was markedly higher in the Hyperuricemia group (7.9 vs. 5.1 [mg/dL], $P = 0.008$) as well as the levels of creatinine (1.1 vs. 0.9 [mg/dL], $P = 0.015$) and glucose (134 vs. 126 [mg/dL], $P = 0.032$). On the contrary, the GFR in the Hyperuricemia group was dramatically lower than those in the Normouricemia group (64.6 vs. 82.9 [mg/min/1.73 m²], $P = 0.005$), which indicated a kidney dysfunction. In addition, the proportions of patients with hypertension (70.3% vs. 62.8%, $P = 0.033$) and diabetes mellitus (31.6% vs. 24.9%, $P = 0.041$) in the Hyperuricemia group were significantly higher than those in the Normouricemia group. Observably, patients in the Hyperuricemia group tended to bear more diseased vessels ($P < 0.001$) and lower LVEF. Besides, other blood biochemical indexes of the patients like hemoglobin, triglycerides, lipoprotein cholesterol, and total cholesterol were at the same level in two groups. There were also no differences between the two groups in the proportion of patients with previous history of heart diseases and heart risks.

Serum uric acid level and angiographic findings

To demonstrate the relationship between uric acid and ACS severity, we first analyzed the serum contents of uric acid according to the number of diseased vessels. We found that with the increase of diseased vessel numbers, the level of uric acid in serum was also markedly elevated (Fig. 2a). In addition, we assessed angiographic characteristics of the participants using both the SYNTAX and Gensini scoring systems, and the results were shown in Fig. 2b, c. Both SYNTAX and Gensini scores were positively associated with uric acid contents ($P < 0.001$), which suggested that the higher UA level indicated more complexity and severity of ACS.

Cardiovascular mortality and MACE of the patients with normouricemia and hyperuricemia

A total of 874 patients were remained after 1-year of follow-up, and 29 patients were deceased during the process. Participants with normal level of uric acid showed ~5% cardiovascular mortality at the end of follow-up, while patients with hyperuricemia exhibited ~10% cardiovascular mortality in the Kaplan–Meier curves (Fig. 3a). Consistently, the MACE rate (~18%) in the Hyperuricemia group was significantly higher than those (~12%) in the Normouricemia group (Fig. 3b). Taken together, elevated uric acid levels were associated with higher mortality and the MACE rate.

Discussion

Accumulating evidence has demonstrated that the main molecular mechanisms that cause ACS include inflammatory immune response, oxidative stress, neurohumoral factors, microvascular and thrombosis, abnormal lipid metabolism, matrix degradation, hemodynamics, and myocardial injury (16–18). Previous studies have shown that active and effective antiplatelet therapy can significantly improve the clinical prognosis of ACS patients.
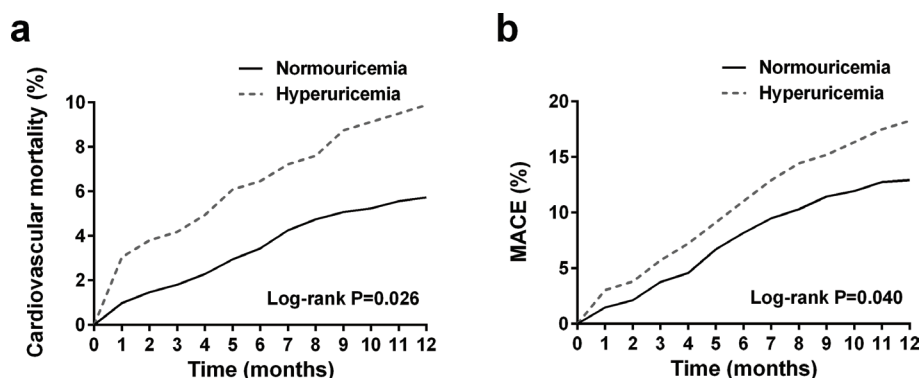
Fig. 3. Kaplan–Meier curves of 1-year cardiovascular mortality (a) and major adverse cardiovascular events (MACEs) according to the presence of hyperuricemia.

At present, aspirin with the antagonist dual antiplatelet therapy and P2Y12 receptor antagonist has become the first-line standard treatment for ACS patients (19, 20). However, the side effects of antiplatelet drugs and the influence of genetic factors often limit their clinical application. Excessive use of antiplatelet agglutination drugs including ticagrelor and clopidogrel may cause various side effects, including dyspnea and drug dependence (21, 22). Therefore, predicting the risk of ACS in advance and conducting early intervention are still the top priority for clinical reduction of ACS.

Relevant biomarkers based on the molecular mechanism of the disease play an important role in the diagnosis, risk stratification, treatment, and prognosis prediction of ACS patients. Common cardiac immune markers, including tumor TNF-α, IL-6, etc., have been widely used in various studies to assess the risk of ACS (23, 24). Some neurohumoral markers, such as N-terminal-pro-B-type natriuretic peptide and B-type natriuretic peptide, have also been proven to predict the prognosis of ACS patients (25, 26). Although the relationship between the above multiple markers and ACS has been revealed by multiple studies, the most commonly used clinical prediction is still myocardial injury markers, including myosin light chain and aspartame aminotransferase (27, 28). Cardiac troponin (cTn) has become the only myocardial marker recommended for ACS classification. However, although cTn is highly specific to ACS, its ability to predict and grade ACS is not perfect. Although cTn is highly specific to ACS, its ability to predict and grade ACS is not perfect. The cTn in the blood often increases 4–7 h after myocardial damage. This 'troponin blind zone' prevents cTn from prompting the occurrence of ACS in time. Looking for new biomarkers with high sensitivity and specificity, rapidity can provide more evidence for the prevention and treatment of ACS and reduce the occurrence of adverse cardiovascular events.

In this study, we reported a close relationship between UA and ACS patients' severity and mortality. We separately assessed the condition and mortality of ACS in patients with hyperuricemia and normouricemia. We proved that the UA level in the patients' serum was positively correlated with the SYNTAX score and the Gensini score. We demonstrated that UA could be used as a new biomarker to assist in forecasting and rating ACS.

Numerous studies have shown that high UA level can activate the renin–angiotensin system and cause endothelial cell dysfunction and inflammatory reaction in the cardiovascular system, which is related to the occurrence and development of cardiovascular diseases (7, 12). Hyperuricemia is caused by abnormal purine metabolism in the human body, excessive production, or decreased excretion of blood UA, which leads to increased serum UA concentration. A large number of epidemiology shows that hyperuricemia is an independent risk factor for cardiovascular disease. The molecular mechanism of hyperuricemia inducing ACS may include inflammation, vascular endothelial damage, the activation of platelets and the coagulation system, increased renin activity, and the promotion of thrombosis (29).

Moreover, the accumulation of uric acid in the blood is also inextricably linked to the occurrence and development of hypertension, coronary heart disease, atrial fibrillation, and atherosclerosis, which may lead to coronary disease (30). Related studies have shown that hyperuricemia not only is an independent risk factor for coronary heart disease, but also has important predictive value for the severity and prognosis of coronary heart disease. Patients with hyperuricemia have an increased risk of side effects of antiplatelet drugs and thrombosis and ischemia after PCI (31). The detection of UA is of great significance to the precautions for the PCI treatment of patients with clinical coronary heart disease. Similarly, we reported the prediction and evaluation effect of serum UA levels on another cardiovascular disease-ACS.

Atherosclerosis and vascular plaque formation are important mechanisms for the pathogenesis of ACS. Since elevated UA is closely related to atherosclerosis, it is logical that we use UA to predict the development of ACS and the prognosis of ACS patients. Consistent with the findings of previous studies, we found a positive correlation between UA levels and ACS severity and mortality.

Conclusion

We investigated the relationship between the UA levels and the severity and mortality of ACS patients in this research. We reported that the number of diseased vessels, the SYNTAX score, and the Gensini score all increased in patients with higher UA. We demonstrated that patients with hyperuricemia had a significantly higher cardiovascular mortality rate. Therefore, we believe that UA can be used as an auxiliary biomarker to participate in the prediction and evaluation of ACS.

Conflict of interest and funding

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