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The impact of serum uric acid levels on the clinical prognosis and severity of coronary lesions in patients with acute coronary syndrome and hypertension after percutaneous coronary intervention: a prospective cohort study

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Abstract

Objective. The impact of serum uric acid (sUA) levels on the clinical prognosis and severity of coronary lesions in patients with acute coronary syndrome (ACS) and hypertension after percutaneous coronary intervention (PCI) is not fully clear. Our objective was to investigate the associations among sUA levels, clinical prognosis and severity of coronary lesions of patients with ACS and hypertension after PCI.

Design. By designing prospective cohort study, we followed up patients with ACS and hypertension after PCI for one year to explore the risk factors for one-year total major adverse cardiovascular events (MACE) and multivessel coronary lesions, the dose-effect relationship associations and correlation analysis among sUA levels, total MACE events and severity of coronary lesions.

Setting/participants. Several Chinese internists followed up 422 patients hospitalized for ACS and hypertension after PCI between June 2019 and December 2019 at a large tertiary hospital of Qingdao, Shandong, China.

Outcome measures. One-year follow-up major adverse cardiovascular events (MACEs events) results and coronary angiography results.

Results. Multivessel coronary lesions and noncriminal vessel occlusion were more common and the Gensini score was higher in the hyperuricaemia group. The incidence of all-cause death, PCI or coronary artery bypass grafting (CABG) therapy due to myocardial infarction or angina pectoris, medication conservative therapy in the hospital due to myocardial infarction or angina pectoris and total MACE events were higher in the hyperuricaemia group. Univariate and multivariable logistic regression analysis models showed that hyperuricaemia was an independent risk factor for one-year total MACE events and multivessel coronary lesions after adjustment for confounding variables. As the levels of sUA increased, the severity of coronary lesions and the incidence of total MACE events significantly increased.

Conclusions. Hyperuricaemia is an independent risk factor for one-year total MACE events and multivessel coronary lesions in patients with ACS and hypertension after PCI.

Strengths and limitations of this study

The present study was unique prospective study related hyperuricaemia in specific patients with ACS and hypertension after PCI.

The present study was a prospective, single-centre study with a small sample number which affected the representation of patients.

The present study did not fully adjust for other potentially unknown confounding factors, which may have impacted the results.

The present study did not yet rule out the effect of the patient's current medication such as hydrochlorothiazide diuretics on uric acid levels.

The present study was an observational study, and related treatment measures such as uric acid intervention, were not implemented for these patients.

1. INTRODUCTION

At present, cardiovascular diseases have a high incidence and high fatality rate worldwide. ACS is one of the main cardiovascular diseases and includes unstable angina pectoris (UA), non-STsegment elevation myocardial infarction (NSTEMI) and STsegment elevation myocardial infarction (STEMI).[1] Although the current treatment strategies for ACS are continuously optimized and upgraded, its incidence has remained extremely high in recent years.[2] In the treatment and prevention of ACS, it is urgent to discover and control the risk factors for ACS in a timely manner, and the interrelation and predictive value for the prognosis of

ACS-related risk factors require further research and discussion. Hypertension is one of the most important risk factors for ACS. Hypertension is characterized by a high prevalence, high morbidity, and high fatality rate, causing damage to important organs such as the heart, brain and kidney, seriously threatening human health, and increasing the burden on families and society.[3, 4] Therefore, patients with acute coronary syndrome and hypertension need to pay more attention to the risk factors to improve prognosis. Numerous studies have shown that sUA is an independent risk factor for hypertension and ACS and that sUA has a complex relationship with hypertension and ACS.[5-12] High sUA levels not only are closely related to the severity of coronary lesions of coronary heart disease [13] but also affect its prognosis. Relevant clinical studies have shown that hyperuricaemia is an independent risk factor for poor prognosis in patients with chronic heart failure.[14] In addition, hyperuricaemia is highly correlated with the occurrence of future cardiovascular events after PCI in patients with coronary heart disease.[15, 16] However, the impact of sUA levels on the clinical prognosis and severity of coronary lesions in patients with ACS and hypertension after PCI has not been determined. Therefore this study aimed to further explore the relationship among sUA levels, clinical prognosis and severity of coronary lesions in patients with ACS and hypertension after PCI.

2. METHODS

2.1 Study Design and Patients

The present study was a prospective cohort study with 422 patients hospitalized for ACS and hypertension after PCI between June 2019 and December 2019 at the Affiliated Hospital of Qingdao University, Qingdao, Shandong, China. Several Chinese internists followed up them for one year. The 27 participants were excluded due to missing date during follow-up. The flow diagram is shown in Figure 1.The prospective study complied with the Declaration of Helsinki and was approved. The need for individual consent was waived by the Ethical Review Board of the Affiliated Hospital of Qingdao University. And every participants gave informed consent.

2.2. Grouping and Definitions.

The study population was divided into two groups according to the presence or absence of hyperuricaemia.

Hyperuricaemia was defined as sUA levels of >416 μmol/l (>7 mg/dl) in men and >357 μmol/l (>6 mg/dl) in women.[17]

Hypertension diagnosis was made according to the standard definitions of the 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[18]

ACS diagnosis was made according to the standard definitions of the American College of Cardiology.[19]

MACE events were defined as all-cause death, PCI or CABG therapy due to myocardial infarction or angina pectoris as well as medication conservative therapy in the hospital due to myocardial infarction or angina pectoris.

Multivessel coronary lesions referred to coronary angiography showing that coronary stenosis of two or more vessels was ≥ 75%, and left main coronary lesions were defined as multivessel coronary lesions.

Noncriminal vessel occlusion referred to the occurrence of calcification and chronic occlusive disease of coronary arteries that were not related to the disease.

The Gensini score was calculated using the scoring schema previously defined by Gensini et al.[20]

2.3. Data Collection.

The following information was collected: demographic characteristics; heart rate, systolic blood pressure and diastolic blood pressure measured during hospitalization; body weight and height measured during hospitalization; calculated body mass index (BMI); history of smoking, drinking or diabetes; laboratory parameters(total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase, alanine aminotransferase, creatinine, N-terminal prohormone of brain natriuretic peptide (NT-Pro BNP) and troponin I (TnI); echocardiography results; coronary

angiography results during hospitalization; MACE results during the one-year follow-up period.

2.4. Follow-up

Participant follow-up was carried out by means of outpatient visits and telephone calls up to one year.

2.5. Statistical Analysis

SPSS 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Continuous variables are presented as means ± standard deviation or as medians and interquartile ranges according to their distribution as determined by the Kolmogorov-Smirnov test. Comparisons between groups were performed with Student's t-test or nonparametric tests when as appropriate. Categorical variables are reported as percentages and were compared with the chi-square test. Univariate and multivariable logistic regression models were used to explore the risk factors for one-year total MACE events and multivessel coronary lesions. Multivariable logistic regression analysis was applied with the risk factors defined by univariable analyses with P<0.05.Estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) were reported. Correlation analysis adopted Pearson correlation analysis. P <0.05 was considered statistically significant.

3. RESULTS

3.1. Baseline Characteristics of the Patients

A total of 422 participants were included, and there were 208 (49.3%) patients in the hyperuricaemia group and 214 (50.7%) patients in the normal sUA group. The characteristics of each group are shown in Table 1.In the general clinical data, the proportion of females (61.5% vs 26.2%, *P*=0.000), current smoking (46.6% vs 33.6%, *P*=0.006), unstable angina pectoris (86.9% vs 72.6%, *P*=0.001), STsegment elevation myocardial infarction (13.5% vs 7.5%, *P*=0.001), non-STsegment elevation myocardial infarction (13.9% vs 5.6%, *P*=0.001), body mass index (26.73±3.66 vs 25.44±3.35, *P*=0.000), diastolic blood pressure (85.75±11.42 vs 83.02±11.15, *P*=0.013), triglycerides (1.87±1.26 vs 1.56±1,11, *P*=0.009), high density lipoprotein-cholesterol (1.23±0.31vs 1.16±0.29, *P*=0.007), alanine aminotransferase (30.60±21.80 vs 26.31±16.87, *P*=0.024), creatinine (84.70±88.26 vs 67.27±41.99, *P*=0.010) and troponin I (0.23±0.70 vs 0.04±0.16, *P*=0.001) were higher in patients with hyperuricaemia than in patients with normal sUA levels.

Table1: Baseline characteristics of patients with normal sUA levels or hyperuricaemia

Parameters	sUA normal (n=214)	Hyperuricaemia (n=208)	*P*
Female sex, n (%)	56(26.2%)	128(61.5%)	0.000
Age, years (mean ± SD)	65.21±10.00	67.55±8.42	0.051
Body mass index (mean ± SD)	25.44±3.35	26.73±3.66	0.000
Heart rate, beats/min (mean ± SD)	70.75±10.56	70.60±12.89	0.895
SBP, mmHg (mean ± SD)	155.21±16.14	155.31±16.30	0.948
DBP, mmHg (mean ± SD)	83.02±11.15	85.75±11.42	0.013
Current smoking, n (%)	72(33.6%)	97(46.6%)	0.006
Current drinking, n (%)	54(25.3%)	63(30.3%)	0.246
Diabetes mellitus, n (%)	68(31.8%)	52(25%)	0.123
Total cholesterol, mmol/l (mean ± SD)	4.26±1.06	4.29±1.16	0.735
Triglycerides, mmol/l (mean ± SD)	1.56±1,11	1.87±1.26	0.009
LDL-cholesterol, mmol/l (mean ± SD)	2.39±0.83	2.49±0.89	0.228
HDL-cholesterol, mmol/l (mean ± SD)	1.16±0.29	1.23±0.31	0.007
AST, U/l (mean ± SD)	26.58±56.41	26.63±18.56	0.990
ALT, U/l (mean ± SD)	26.31±16.87	30.60±21.80	0.024
Creatinine, μmol/l (mean ± SD)	67.27±41.99	84.70±88.26	0.010
NT-proBNP, pg/ml (mean ± SD)	424.67±1234.04	624.64±2450.35	0.288

TnI, pg/ml (mean ± SD)	0.04±0.16	0.23±0.70	0.000
LVEF% (mean ± SD)	59.12±4.71	58.32±5.61	0.112
UA, n (%)	186(86.9%)	151(72.6%)	0.001
STEMI, n (%)	16(7.5%)	28(13.5%)	0.001
NSTEMI, n (%)	12(5.6%)	29(13.9%)	0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein; HDL: high density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; NT-pro BNP: N-terminal prohormone of brain natriuretic peptide; TNI: troponin I; LVEF: left ventricular ejection fraction; UA: unstable angina pectoris; STEMI: STsegment elevation myocardial infarction; NSTEMI: non-STsegment elevation myocardial infarction;

3.2. Coronary Angiography Results of the Patients

The results of coronary angiography of each group are shown in Table 2. Multivessel coronary lesions (33.7% vs 19.2%, *P*=0.001) and noncriminal vessel occlusion(12.9% vs 6.5%, *P*=0.026) were more common in the hyperuricaemia group, and the Gensini score (29.71±13.47 vs 18.22±10.39 *P*=0.000) was higher in the hyperuricaemia group.

Table2: Coronary angiography and one-year follow-up MACE events results of patients with normal sUA levels or hyperuricaemia

	sUA normal (n=214)	hyperuricaemia (n=208)	*p*
Coronary angiography			
Number of patients	214	208	
Noncriminal vessel occlusion, n (%)	14(6.5%)	27(12.9%)	0.026
Multivessel coronary lesions, n (%)	41(19.2%)	70(33.7%)	0.001
Gensini score, (mean ± SD)	18.22±10.39	29.71±13.47	0.000
One-year follow-up MACE events			
Number of patients	200	195	
All-cause mortality, n (%)	3(1.5%)	10(5.1%)	0.043
PCI or CABG therapy due to myocardial infarction or angina pectoris, n (%)	17(8.5%)	34(17.4%)	0.008
Medication conservative therapy in hospital due to myocardial infarction or angina pectoris, n (%)	16(8%)	28(14.3%)	0.044
Total MACE events, n (%)	36(18%)	72(36.9%)	0.000

sUA: serum uric acid; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; MACE: major adverse cardiovascular events.

3.3. One-year Follow-up for Patient MACE Events

The results of the one-year follow-up for the MACE events of each group are shown in Table 2. The 27 participants were excluded due to missing date during follow-up. The 108 participants happend MACE events (sUA normal (n=36) hyperuricaemia (n=72)). The incidence of all-cause death(5.1% vs 1.5%, P=0.043), PCI or CABG therapy due to myocardial infarction or angina pectoris(17.4% vs 8.5%, P=0.008), medication conservative therapy in hospital due to myocardial infarction or angina pectoris (14.3% vs 8%, P=0.044) and total MACE events (36.9% vs 18%, P=0.000) were higher in patients with hyperuricaemia than in patients with normal sUA levels.

3.4. Univariate and Multivariable Logistic Regression Analyses of One-year Follow-up MACE Events

The univariate and multivariable logistic regression analyses of the one-year follow-up MACE events models are shown in Table 3. Hyperuricemia was an independent risk factor for one-year total MACE events (all-cause death, PCI or CABG therapy due to myocardial infarction or angina pectoris or medication conservative therapy in the hospital due to myocardial infarction or angina pectoris) (OR=2.618, 95% CI

1.656-4.139, P=0.000; OR=1.920, 95% CI 1.158-3.183, P=0.011, respectively) after adjustment for confounding variables.

Table3: Logistic regression analysis of related risk factors for total MACE events during one-year follow-up

	Univariable analysis		Multivariable analysis	
	OR(95%CI)	*P* value	OR*(95%CI)	*P* value
hyperuricaemia	2.618(1.656-4.139)	0.000	1.920(1.158-3.183)	0.011
TNI	1.564(1.038-2.358)	0.032	1.116(0.738-1.689)	0.602
LVEF	0.957(0.920-0.994)	0.023	0.971(0.932-1.012)	0.161
Gensini score	1.038(1.021-1.056)	0.000	1.018(0.998-1.039)	0.080
Multivessel coronary lesions	2.393(1.496-3.828)	0.000	1.681(0.993-2.847)	0.053

OR: odds ratio; OR*: adjusted odds ratio; CI: confidence interval; MACE: major adverse cardiovascular events; TNI: troponin I; LVEF: left ventricular ejection fraction.

3.5. Univariate and Multivariable Logistic Regression Analyses of the Multivessel Coronary Lesions

The univariate and multivariable logistic regression analyses of the multivessel coronary lesion models are shown in Table 4. Hyperuricemia was an independent risk factor for multivessel coronary lesions (OR=2.140, 95% CI 1.371-3.342, P=0.001; OR=1.688, 95% CI 1.051-2.710, P=0.030, respectively) after adjustment for confounding variables.

Table4: Logistic regression analysis of related risk factors for multivessel coronary lesions

	Univariable analysis		Multivariable analysis	
	OR(95%CI)	*P* value	OR*(95%CI)	*P* value
hyperuricaemia	2.140(1.371-3.342)	0.001	1.688(1.051-2.710)	0.030
SBP	1.020(1.006-1.035)	0.005	1.025(1.010-1.040)	0.001
Current smoking	1.748(1.151-2.765)	0.010	1.941(1.218-3.094)	0.005
Creatinine	1.006(1.001-1.012)	0.023	1.006(1.001-1.011)	0.021
TNI	1.905(1.203-3.016)	0.006	1.768(1.061-2.946)	0.029

OR: odds ratio; OR*: adjusted odds ratio; CI: confidence interval; SBP: systolic blood pressure; TNI: troponin I.

3.6. Dose-effect Relationship among sUA levels, Clinical Prognosis and Severity of Coronary Lesions

The sUA levels of all patients were grouped according to the interquartile range to investigate the dose-effect relationship associations among sUA levels, clinical prognosis and severity of coronary lesions (Table5). As the levels of sUA increased, the severity of coronary lesions (noncriminal vessel occlusion, 4.7% vs 8.4% vs 9.6% vs 16.2%, P=0.041; multi-vessel coronary lesions, 17.9% vs 22.4% vs 29.8% vs 35.2%,P=0.022; and Gensini score, 16.96±10.35 vs 19.31±10.63 vs 26.12±11.48 vs 33.33±14.01, P=0.000) increased. Further, the Gensini score was positively correlated with uric acid levels(r=0.515, *P*=0.000) (Figure 2). In addition, the incidence of one-year follow-up of total MACE events (13.2% vs 14.2% vs 34.6% vs 41%, P=0.000) also increased significantly with increasing sUA levels.

Table5: Coronary angiography results of sUA levels grouped by interquartile range

	137～315μmol/l	316～387μmol/l	388～446μmol/l	347～659μmol/l	*P*

Coronary angiography					
Noncriminal vessel occlusion, n (%)	5(4.7%)	9(8.4%)	10(9.6%)	17(16.2%)	0.041
Multivessel coronary lesions, n (%)	19(17.9%)	24(22.4%)	31(29.8%)	37(35.2%)	0.022
Gensini score, (mean ± SD)	16.96±10.35	19.31±10.63	26.12±11.48	33.33±14.01	0.000
One-year follow-up total MACE events					
Total MACE events, n (%)	14(13.2%)	15(14.2%)	36(34.6%)	43(41%)	0.000

sUA: serum uric acid. MACE: major adverse cardiovascular events.

4. DISCUSSION

The present study demonstrated that hyperuricaemia was closely related to the incidence of one-year MACE events and was an independent risk factor for one-year total MACE events in patients with ACS and hypertension after PCI. To a certain extent, high sUA levels can reflect the clinical prognosis of these patients. In addition, we found that hyperuricaemia was closely related to the severity of coronary lesions, and was an independent risk factor for multivessel coronary lesions in patients with ACS and hypertension after PCI. Therefore, to a certain extent, high sUA level can also reflect the severity of coronary lesions. As the levels of sUA increased, the incidence of one-year follow-up total MACE events increased significantly and severity of coronary lesions (noncriminal vessel occlusion, multivessel coronary lesions and Gensini score) increased. Further, the Gensini score was positively correlated with uric acid levels.

To date, the impact of sUA levels on the clinical prognosis and severity of coronary lesions in patients with ACS and hypertension after PCI has not been determined. Therefore this study aimed to further explore the relationship among sUA levels, clinical prognosis and severity of coronary lesions in patients with ACS and hypertension after PCI to provide a basis for reducing future cardiovascular events in patients with ACS. Of course, the present study still had some limitations. First, the present study was a prospective, single-centre study with a small sample number which affected the representation of patients. The number and scope of the included study population were relatively limited. Whether the study results can be equally suitable for patients in other regions is not yet known. Second, the present study did not fully adjust for other potentially unknown confounding factors, which may have impacted the results. Third, the present study did not yet rule out the effect of the patient's current medication such as hydrochlorothiazide diuretics on uric acid levels. Fourth, the present study was an observational study, and related treatment measures such as uric acid intervention, were not implemented for these patients. Therefore, the relationship between the reduction in uric acid levels and the prognosis of patients with acute coronary syndrome and hypertension after PCI was not explored.

Cardiovascular diseases have the characteristics of a high fatality rate and high disability rate, especially coronary heart disease (CHD). It is of great significance to reduce the incidence of cardiovascular disease and improve its prognosis. In recent years, hyperuricaemia has been increasingly suggested to be closely related to cardiovascular disease.[21, 22] Clinical studies on related physiological and biochemical mechanisms have suggested that high sUA levels may increase oxidative stress, promote systemic inflammation, promote local inflammation, increase insulin resistance and increase other mechanisms to cause endothelial dysfunction and lead to the occurrence of cardiovascular diseases (CVDs), such as ACS.[23-25]There are many clinical studies related to the effect of uric acid on the prognosis of patients with coronary heart disease. A retrospective prognostic study showed that high sUA levels at admission indicate the inpatient mortality rate, 30-day mortality rate and poor long-term prognosis of patients with acute myocardial infarction (AMI).[26] A meta-analysis of prognostic studies showed that high sUA levels at admission independently predict worse short-term and medium/long-term outcomes after AMI.[27] The Third National Health and Nutrition Examination Survey showed that serum uric acid is independently associated with total mortality and cardiovascular mortality. As the levels of sUA increase, these risks significantly increase.[28] Another retrospective cohort study also showed that hyperuricaemia is an independent risk factor for one-year

all-cause mortality in elderly female patients with ACS.[29] Although these studies and others have shown that uric acid is closely related to the prognosis of coronary heart disease, there are some studies that have not reached these conclusions, which may be due to the poor sample size of the selected population, short follow-up time or selection of statistical methods. Therefore, although the number of related studies is large, the association between uric acid and the prognosis of coronary heart disease is still unclear, indicating the need for similar studies to be conducted. In addition, most of the subjects of these studies were patients with hyperuricaemia and ACS in the past, and the selected population type was relatively fixed. Further, it is necessary to pay particular attention to the prognosis of patients with ACS undergoing PCI. After PCI therapy, preventing coronary restenosis and myocardial infarction becomes more important, and these patients should pay more attention to the secondary prevention of the disease, control of cardiovascular risk factors, delay of disease progression and increase of life expectancy to further improve the prognosis. A retrospective analysis of 213 young adult patients (⩽40 years old) undergoing PCI has shown that UA levels are correlated with MACE events during long-term(930 days) follow-up in young patients with NSTEMI undergoing PCI.[30] Another retrospective study has shown that a high serum sUA level (>5.6 mg/dl) is associated with all-cause mortality in ACS patients after PCI.[31] The present study population was composed of mainly patients with ACS undergoing PCI, and the results of the present study were similar to the above research results.

However, previous studies have identified that uric acid is also closely related to hypertension. The possible mechanisms of uric acid causing hypertension are as follows: sUA damages vascular endothelial cells by promoting oxidative stress reactions and causes vasomotor dysfunction by reducing the synthesis of nitric oxide. The sUA activates the renin-angiotensin-aldosterone system to lead to vascular contraction, vascular remodelling water retention and sodium retention.[8, 32, 33] Hypertension is also the most important risk factor for cardiovascular disease. In view of the inseparable and complex relationship among uric acid, hypertension and coronary heart disease, the effect of uric acid and hypertension on the prognosis of patients with coronary heart disease after PCI is unclear. For studies on the effect of uric acid on the prognosis of patients with coronary heart disease after PCI, it is necessary to consider whether patients also have hypertension. Therefore, the present study population mainly focused on patients with ACS and hypertension after PCI. In the present study, hyperuricaemia was an independent risk factor for one-year total MACE events in these patients. As the levels of sUA increased, the incidence of one-year follow-up total MACE events also significantly increased. These results fill the study gap in the prognosis of these patients and simultaneously provide a basis for further studies on the risk of cardiovascular events in this patient group.

In addition, the present study demonstrated that hyperuricaemia was closely related to the severity of coronary lesions, and was an independent risk factor for multivessel coronary lesions in patients with ACS and hypertension after PCI. As the levels of sUA increased, severity of coronary lesions (noncriminal vessel occlusion, multivessel coronary lesions and Gensini score) increased. Further, the Gensini score was positively correlated with uric acid levels (r=0.515, P=0.000). The potential mechanisms of uric acid causing coronary lesions are as follows: sUA may result in atherosclerosis and blood vessel stenosis by causing LDL-C oxidative modification, promoting the release of inflammatory factors to stimulate vascular smooth muscle hyperplasia, activating platelets to promote intravascular thrombosis.[23] In addition, sUA increases the incidence of slow blood flow and no-reflow of the coronary artery.[34] Previous studies on the relationship between uric acid levels and the severity of coronary lesions found that an increase in sUA levels is closely related to the severity of coronary lesions assessed by coronary angiography and that there is a positive correlation between sUA levels and the Gensini score of the severity of coronary lesions.[35, 36] The present study further showed that the relationship between sUA levels and the Gensini score of the severity of coronary lesions exists in patients with ACS and hypertension after PCI. Therefore, the levels of urc acid still can be used as an indicator to assess the severity of coronary lesions in these specific patients with ACS and hypertension after PCI.

In view of the metabolism levels of uric acid in different populations are different, and the effects on the prognosis of different populations are also discrepant. It is necessary to conduct researches related uric acid in different populations. Therefore this study focuses on specific patients with ACS and hypertension after PCI to explore the impact of uric acid on the clinical prognosis and severity of coronary lesions for the first time, thereby helping to improve the prognosis of these patients. In addition, In view of limitations of present study, multicentre, randomized, controlled, and blinded studies with larger sample numbers and different populations are needed for further discussion.

5. CONCLUSION

Hyperuricaemia is an independent risk factor for total MACE events during one-year follow-up and for multivessel coronary lesions in patients with ACS and hypertension after PCI.

Conflicts of Interest

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Author Statement

Shiyu Zhang contributed to the conception of the study;

Shiyu Zhang and Xin Liu contributed significantly to analysis and manuscript preparation;

Shiyu Zhang performed the data analyses and wrote the manuscript;

All authors helped perform the analysis with constructive discussions.

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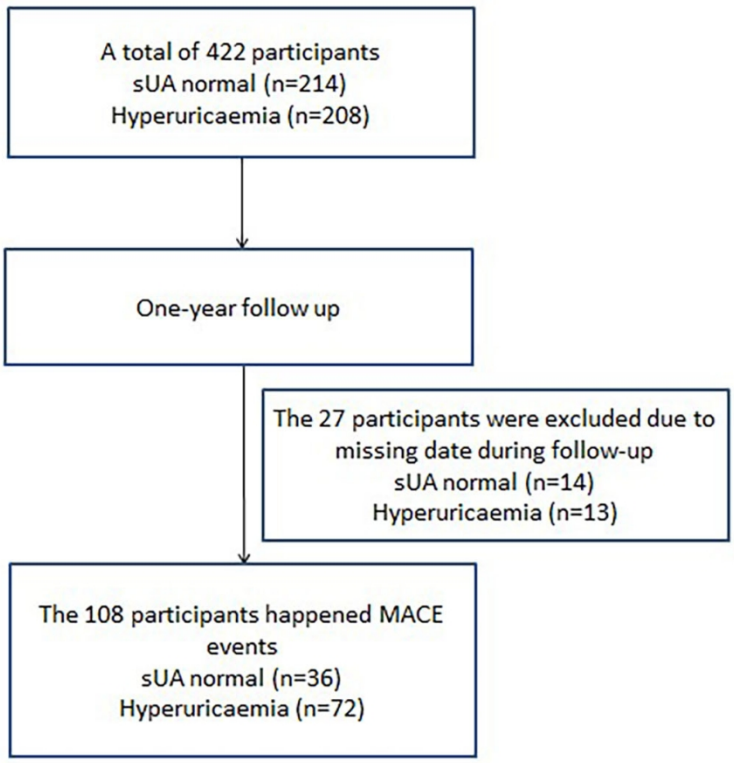
Figure legends/captions:
Figure1：The flow diagram
Figure2：Correlation analysis of uric acid levels and the Gensini score



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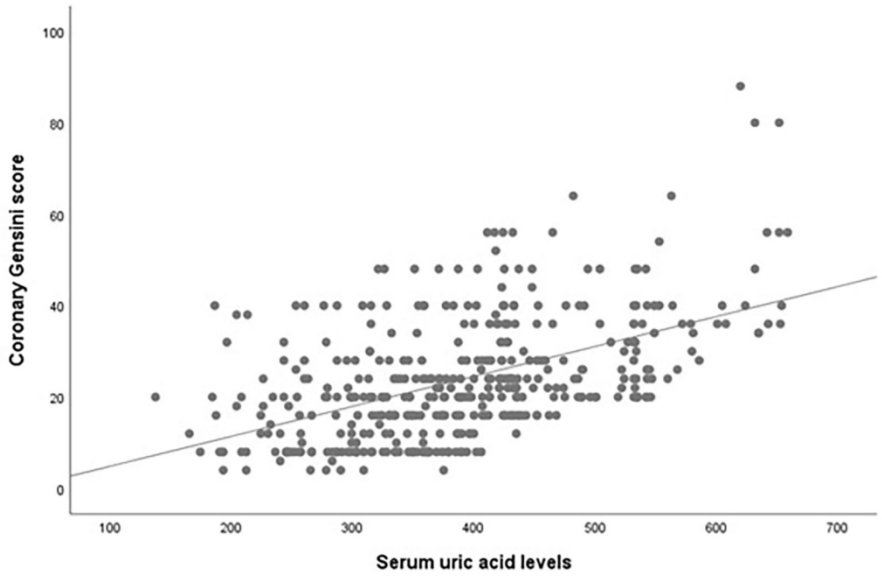

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	4
		(*e*) Describe any sensitivity analyses	4
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	4,5
		(c) Summarise follow-up time (eg, average and total amount)	4,5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5,6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5,6
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7,8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The impact of serum uric acid levels on the clinical prognosis and severity of coronary artery disease in patients with acute coronary syndrome and hypertension after percutaneous coronary intervention: a prospective cohort study

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The impact of serum uric acid levels on the clinical prognosis and severity of coronary artery disease in patients with acute coronary syndrome and hypertension after percutaneous coronary intervention: a prospective cohort study

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Abstract

Objective. The impact of serum uric acid (sUA) levels on the clinical prognosis and severity of coronary artery disease in patients with acute coronary syndrome (ACS) and hypertension after percutaneous coronary intervention (PCI) is not fully clear. This study aimed to assess the association among sUA levels, clinical prognosis and severity of coronary artery disease in patients with ACS and hypertension after PCI.

Design. In this prospective cohort study, we followed up patients with ACS and hypertension after PCI for one year to explore the risk factors for one-year total major adverse cardiovascular events (MACEs) and multi-vessel coronary artery disease, the dose-effect relationship among sUA levels, MACEs and severity of coronary artery disease and correlation between serum uric acid levels and severity of coronary artery disease (Gensini score).

Setting/ patients. Several Chinese internists followed up 422 patients who were diagnosed with ACS and hypertension after PCI in a large tertiary hospital of Qingdao during the period from June, 1 2019 and December, 1 2019.

Outcome measures. One-year follow-up MACEs results and coronary angiography results.

Results. In the coronary angiography results, multi-vessel coronary artery disease (28.5% vs 21.4%, P=0.006) and non-culprit lesion vascular occlusion (11.7% vs 5.3%, P=0.042) were more common in the hyperuricemia group, and the Gensini score (26.69±13.46 vs 17.66±10.57 P<0.001) was also higher. In the results of one-year MACEs, the incidence of all-cause mortality (3.5% vs 2.5%, P=0.037), PCI or coronary artery bypass grafting (CABG) therapy due to myocardial infarction or angina pectoris(15.1% vs 7.6%, P=0.027), medication conservative therapy in hospital due to myocardial infarction or angina pectoris(12.9% vs 6.7%, P=0.041) and total MACEs (31.8% vs 16.9%, P=0.001) were higher in patients with hyperuricemia. Univariate and multivariate logistic regression analysis models showed that hyperuricemia was still an independent risk factor for total MACEs within one year (OR=2.618, 95% CI 1.656-4.139, P<0.001; OR=1.920, 95% CI 1.158-3.183, P=0.011, respectively) and multi-vessel coronary artery disease (OR=2.140, 95% CI 1.371-3.342, P=0.001; OR=1.688, 95% CI 1.051-2.710, P=0.030, respectively) after adjusting for confounding factors. The severity of coronary artery disease [non-culprit lesion vascular occlusion(4.7% vs 8.4% vs 9.6% vs 16.2%, P=0.041); multi-vessel coronary artery disease (17.9% vs 22.4% vs 29.8% vs 35.2%, P=0.022); Gensini score(16.96±10.35 vs 19.31±10.63 vs 26.12±11.48 vs 33.33±14.01, P<0.001)] and the incidence of total MACEs (13.2% vs 14.2% vs 34.6% vs 41%, P<0.001) increased significantly with the sUA levels increasing. Further, the Gensini score was positively correlated with uric acid levels(r=0.515，P<0.001).

Conclusions. Hyperuricemia is an independent risk factor for one-year total MACEs and multi-vessel coronary artery disease in patients with ACS and hypertension after PCI.

Strengths and limitations of this study

The present study was unique prospective study related to hyperuricemia in specific patients with ACS and hypertension after PCI.

The present study was a prospective, single-center study with a small sample number which affected the representation of patients.

The present study did not fully adjust for other potentially unknown confounding factors, which may have impacted the results.

The present study did not rule out the effect of the patient's current medication such as hydrochlorothiazide diuretics on uric acid levels.

The present study was an observational study, and related treatment such as sUA-lowering therapy, was not implemented for these patients.

1. INTRODUCTION

At present, cardiovascular diseases have a high incidence and high fatality rate worldwide. ACS is one of the main cardiovascular diseases, which includes unstable angina pectoris (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI).[1] Although the current treatment strategies of ACS are continuously optimized and upgraded, its incidence has remained extremely high in recent years.[2] In the treatment and prevention of ACS, it is urgent to discover and control the risk factors for ACS in a timely manner, and the interrelation and predictive value for the prognosis of ACS-related risk factors require further research and discussion. Hypertension is one of the most important risk factors for ACS. Hypertension is characterized by a high prevalence, high morbidity, and high fatality rate, causing damage to important organs such as the heart, brain and kidney, seriously threatening human health, and increasing the burden on families and society.[3, 4] Therefore, patients with acute coronary syndrome and hypertension need to pay more attention to the risk factors to improve prognosis. Numerous studies presented that sUA was an independent risk factor for hypertension and ACS and that sUA had a complex relationship with hypertension and ACS.[5-12] But the association among sUA levels, coronary heart disease and hypertension is still controversial. A cross-sectional population-based study showed hyperuricemia was closely related to coronary heart disease-related mortality irrespective of sex. Another relative study showed that the risk of non-fatal myocardial infarction increased significantly with the levels of uric acid increasing. And subgroup analysis suggested that uric acid was more closely related to myocardial infarction in female patients than male patients.[13] However, several studies failed to show that relative association. A recent study which included 231 patients with chronic coronary syndromes showed the absence of correlation between sUA and coronary arteries disease.[14] And Framingham Study which included 6763 patients followed up for 117376 person-years showed sUA was no longer associated with coronary heart disease events and cardiovascular mortality after adjustment for related risk factors.[15] In addition, the relationship between uric acid and hypertension has always been a hot topic of discussion. Previous studies showed that hyperuricemia was common in patients with primary hypertension. And they influenced each other during the development process.[16] Even uric acid-lowering drugs can be used to prevent the increase of blood pressure in patients with primary hypertension.[17] Other studies suggested high sUA levels not only were closely related to the severity of coronary artery disease, [18] but also affected its prognosis. Relevant clinical studies presented that hyperuricemia was an independent risk factor for poor prognosis in patients with chronic heart failure.[19] In addition, hyperuricemia was highly correlated with the occurrence of future cardiovascular events after PCI in patients with coronary heart disease.[20, 21] In view of the contradictory role of sUA in coronary heart disease and hypertension, when clinical research related to sUA are conducted, it is necessary to consider mutual potential impact among sUA, coronary heart disease and hypertension. However, there are few studies commonly involving uric acid, coronary heart disease and hypertension currently. Therefore this study included patients with ACS and hypertension after PCI to further explore the relationship among sUA levels, clinical prognosis and severity of coronary artery disease.

2. METHODS

2.1 Study Design and Patients

The present study was a prospective cohort study with 422 patients who were diagnosed with ACS and hypertension after PCI in the Affiliated Hospital of Qingdao University during the period from June, 1 2019 and December, 1 2019. Several Chinese internists followed up them for one year. The prospective study complied with the Declaration of Helsinki and was approved. Ethics approval was provided by the Ethical Review Board of

Affiliated Hospital of Qingdao University(QYFYWZLL26229).

2.2. Patient and Public Involvement

No patient involved.

2.3. Grouping and Definitions

The study population was divided into two groups according to the presence or absence of hyperuricemia. Hyperuricemia was defined as sUA levels of >333 μmol/l (>5.6 mg/dl).[22]

Hypertension diagnosis was made according to the standard definitions of the 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[23]

ACS diagnosis was made according to the standard definitions of the American College of Cardiology.[24]

MACEs were defined as all-cause death, PCI or CABG therapy due to myocardial infarction or angina pectoris as well as medication conservative therapy in hospital due to myocardial infarction or angina pectoris.

Multi-vessel coronary artery disease referred to coronary angiography showing that coronary stenosis of two or more vessels was ≥ 75%, and left main coronary artery disease was defined as multi-vessel coronary artery disease.

Non-culprit lesion vessel occlusion referred to the occurrence of calcification and chronic occlusive disease of coronary arteries that were not related to the disease.

The Gensini score was calculated using the scoring schema previously defined by Gensini et al.[25]

2.4. Data Collection

The following information was collected: demographic characteristics; heart rate, systolic blood pressure and diastolic blood pressure measured during hospitalization; body weight and height measured during hospitalization; calculated body mass index (BMI); history of smoking, drinking or diabetes; laboratory parameters[total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase, alanine aminotransferase, creatinine, calculated glomerular filtration rate(GFR), N-terminal prohormone of brain natriuretic peptide (NT-Pro BNP) and troponin I (TnI)]; drugs using in treatment; echocardiography results; coronary angiography results during hospitalization; MACEs results during the one-year follow-up period.

2.5. Follow-up

Patients were followed up through outpatient clinics and telephone calls for up to 1 year. During the one-year follow-up period, 27 patients (13 patients in the normal sUA group and 14 patients in the hyperuricemia group) were dropped out of the study due to loss of follow-up (changing of mobile phone number, moving due to special reasons and so on) or other reasons.

2.6. Statistical Analysis

SPSS 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Continuous variables are presented as means ± standard deviation or as medians and interquartile ranges according to their distribution as determined by the Kolmogorov-Smirnov test. Comparisons between groups were performed with Student's t-test or nonparametric tests when as appropriate. Categorical variables are reported as percentages and were compared with the chi-square test. Univariate and multivariate logistic regression models were used to explore the risk factors for one-year total MACEs and multi-vessel coronary artery disease. Multivariate logistic regression analysis was applied with the risk factors defined by univariate analysis with $P<0.05$.Estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) were reported. Correlation analysis adopted Spearman correlation analysis. $P<0.05$ was considered statistically significant.

3. RESULTS

3.1. Baseline Characteristics of the Patients

A total of 422 participants were included, and there were 131 (31%) patients in the hyperuricemia group and 291 (69%) patients in the normal sUA group. The characteristics of each group are shown in Table 1.In the general clinical data, the proportion of females, body mass index, current smoking, current drinking, triglycerides, creatinine, GFR, and troponin I were higher in patients with hyperuricemia. Diastolic blood pressure, high density lipoprotein-cholesterol were lower in patients with hyperuricemia. All patients registered took dual antiplatelet drugs. Our results showed no significant difference between two groups in dual antiplatelet therapy, lipid-lowering therapy, vasodilator therapy, heart rate-controlling therapy, diuretic therapy, antihypertensive therapy and so on.

Table1: Baseline characteristics of patients with normal sUA levels or hyperuricemia

Parameters	sUA normal (n=131)	Hyperuricemia (n=291)	*P*
Female sex, n (%)	44(33.6%)	140(48.1%)	0.005
Age, years (mean ± SD)	65.31±9.71	66.84±9.14	0.117
Body mass index (mean ± SD)	25.30±3.27	26.42±3.63	0.002
Heart rate, beats/min (mean ± SD)	70.14±10.44	70.91±12.30	0.530
SBP, mmHg (mean ± SD)	156.40±16.37	154.74±16.12	0.332
DBP, mmHg (mean ± SD)	86.52±11.44	83.45±11.21	0.011
Current smoking, n (%)	30(22.9%)	139(47.8%)	<0.001
Current drinking, n (%)	21(16%)	96(33%)	<0.001
Diabetes mellitus, n (%)	48(36.6%)	72(24.7%)	0.012
Total cholesterol, mmol/l (mean ± SD)	4.30±1.14	4.27±1.10	0.823
Triglycerides, mmol/l (mean ± SD)	1.47±0.97	1.82±1.27	0.002
LDL-cholesterol, mmol/l (mean ± SD)	2.42±0.91	2.46±0.84	0.619
HDL-cholesterol, mmol/l (mean ± SD)	1.28±0.32	1.16±0.28	<0.001
AST, U/l (mean ± SD)	29.29±71.52	25.40±18.89	0.382
ALT, U/l (mean ± SD)	26.90±18.64	29.11±19.94	0.284
Creatinine, μmol/l (mean ± SD)	59.53±17.29	83.21±81.59	<0.001
GFR, mL/(min·1.73m²) (mean ± SD)	123.98±39.64	90.91±31.91	<0.001
NT-pro BNP, pg/ml (mean ± SD)	473.22±1449.33	545.75±2115.55	0.722
TnI, pg/ml (mean ± SD)	0.04±0.14	0.18±0.61	<0.001
LVEF% (mean ± SD)	59.05±4.84	58.58±5.33	0.383
UA, n (%)	112(85.5%)	225(77.3%)	0.132
STEMI, n (%)	11(8.4%)	33(11.3%)	0.132
NSTEMI, n (%)	8(6.1%)	33(11.3%)	0.132
Lipid lowering therapies, n (%)	111(84.7%)	248(85.2%)	0.896
Vasodilator therapies, n (%)	120(91.6%)	256(88%)	0.268
Calcium channel blockers, n (%)	40(30.5%)	114(39.2%)	0.088
ACEI/ARB, n (%)	58(44.3%)	149(51.2%)	0.188
β-receptor blockers, n (%)	71(54.2%)	175(60.1%)	0.252
diuretics, n (%)	74(56.5%)	109(37.5%)	0.128

SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein; HDL: high density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; NT-pro BNP: N-terminal prohormone of brain natriuretic peptide; TNI: troponin I; LVEF: left ventricular ejection fraction; UA: unstable angina pectoris; STEMI: ST segment elevation myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; ACEI: angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor inhibitor; GFR: Glomerular Filtration Rate.

3.2. Coronary Angiography Results of the Patients

The results of coronary angiography of each group are shown in Table 2. Multi-vessel coronary artery disease and non-culprit lesion vessel occlusion were more common in the hyperuricemia group, and the Gensini score was higher in the hyperuricemia group.

Table2: Coronary angiography and one-year follow-up MACEs results of patients with normal sUA levels or hyperuricemia

	sUA normal (n=131)	hyperuricemia (n=291)	*p*
Coronary angiography			
Number of patients	131	291	
Non-culprit lesion vessel occlusion, n (%)	7(5.3%)	34(11.7%)	0.042
Multi-vessel coronary lesions, n (%)	28(21.4%)	83(28.5%)	0.006
Gensini score, (mean ± SD)	17.66±10.57	26.69±13.46	<0.001
One-year follow-up MACEs			
Number of patients	118	277	
All-cause mortality, n (%)	3(2.5%)	10(3.5%)	0.037
PCI or CABG therapy due to myocardial infarction or angina pectoris, n (%)	9(7.6%)	42(15.1%)	0.027
Medication conservative therapy in hospital due to myocardial infarction or angina pectoris, n (%)	8(6.7%)	36(12.9%)	0.041
Total MACEs, n (%)	20(16.9%)	88(31.8%)	0.001

sUA: serum uric acid; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; MACEs: major adverse cardiovascular events.

3.3. One-year Follow-up MACEs

The results of the one-year follow-up MACEs of each group are shown in Table 2. The 27 patients were dropped out of the study due to loss of follow-up or other reasons. The 108 participants happened MACEs (sUA normal (n=20) hyperuricemia (n=88)). The incidence of all-cause mortality, PCI or CABG therapy due to myocardial infarction or angina pectoris, medication conservative therapy in hospital due to myocardial infarction or angina pectoris and total MACEs were higher in patients with hyperuricemia.

3.4. Univariate and multivariate Logistic Regression Analysis of One-year Follow-up MACEs

The Univariate and multivariate logistic regression analysis of the one-year follow-up MACEs models are shown in Table 3. Hyperuricemia was an independent risk factor for one-year total MACEs after adjustment for confounding variables (Sex, Age, BMI, SBP, GFR, Current smoking, Diabetes mellitus, Total cholesterol, Triglycerides, LDL-cholesterol, NT-pro BNP, TNI, LVEF, Gensini score, Multi-vessel coronary lesions, Non-culprit lesion vessel occlusion). The table 3 only showed the risk factors defined by univariate analysis with P<0.05.

Table3: Logistic regression analysis of related risk factors for total MACEs during one-year follow-up

	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P* value	OR*(95%CI)	*P* value
hyperuricemia	2.618(1.656-4.139)	<0.001	1.920(1.158-3.183)	0.011
TNI	1.564(1.038-2.358)	0.032	1.116(0.738-1.689)	0.602
LVEF	0.957(0.920-0.994)	0.023	0.971(0.932-1.012)	0.161

Gensini score	1.038(1.021-1.056)	<0.001	1.018(0.998-1.039)	0.080
Multi-vessel coronary lesions	2.393(1.496-3.828)	<0.001	1.681(0.993-2.847)	0.053

OR: odds ratio; OR*: adjusted odds ratio; CI: confidence interval; MACEs: major adverse cardiovascular events; TNI: troponin I; LVEF: left ventricular ejection fraction.

3.5. Univariate and multivariate Logistic Regression Analysis of the Multi-vessel Coronary Artery Disease

The Univariate and multivariate logistic regression analysis of the multi-vessel coronary artery disease models are shown in Table 4. Hyperuricemia was an independent risk factor for multi-vessel coronary artery disease after adjustment for confounding variables(Sex, Age, SBP, GFR, BMI, Current smoking, Diabetes mellitus, Total cholesterol, Triglycerides, LDL-cholesterol, TNI, NT-pro BNP, LVEF%, Non-culprit lesion vessel occlusion, Gensini score, Multi-vessel coronary lesions). The table 4 only showed the risk factors defined by univariate analysis with P<0.05.

Table4: Logistic regression analysis of related risk factors for multi-vessel coronary lesions

	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P* value	OR*(95%CI)	*P* value
hyperuricemia	2.140(1.371-3.342)	0.001	1.688(1.051-2.710)	0.030
SBP	1.020(1.006-1.035)	0.005	1.025(1.010-1.040)	0.001
Current smoking	1.748(1.151-2.765)	0.010	1.941(1.218-3.094)	0.005
Creatinine	1.006(1.001-1.012)	0.023	1.006(1.001-1.011)	0.021
TNI	1.905(1.203-3.016)	0.006	1.768(1.061-2.946)	0.029

OR: odds ratio; OR*: adjusted odds ratio; CI: confidence interval; SBP: systolic blood pressure; TNI: troponin I.

3.6. Dose-effect Relationship among sUA levels, Clinical Prognosis and Severity of Coronary Artery Disease

The sUA levels of all patients were grouped according to the interquartile range to investigate the dose-effect relationship associations among sUA levels, clinical prognosis and severity of coronary artery disease (Table5). As the levels of sUA increased, the severity of coronary artery disease (non-culprit lesion vessel occlusion; multi-vessel coronary artery disease; and Gensini score) increased. Further, the Gensini score was positively correlated with uric acid levels (Figure). The figure is provided in online. In addition, the incidence of one-year follow-up total MACEs also increased significantly with the sUA levels increasing.

Table5: Dose-effect Relationship among sUA levels, Clinical Prognosis and Severity of Coronary Artery Disease

	137～315μmol/l	316～387μmol/l	388～446μmol/l	347～659μmol/l	*P*
Coronary angiography					
Non-culprit lesion vessel occlusion, n (%)	5(4.7%)	9(8.4%)	10(9.6%)	17(16.2%)	0.041
Multi-vessel coronary artery disease, n (%)	19(17.9%)	24(22.4%)	31(29.8%)	37(35.2%)	0.022
Gensini score, (mean ± SD)	16.96±10.35	19.31±10.63	26.12±11.48	33.33±14.01	<0.001
One-year follow-up total MACEs					
Total MACEs, n (%)	14(13.2%)	15(14.2%)	36(34.6%)	43(41%)	<0.001

sUA: serum uric acid. MACEs: major adverse cardiovascular events.

4. DISCUSSION

This study demonstrated that hyperuricemia was closely related to the incidence of one-year MACEs and was an independent risk factor for one-year total MACEs in patients with ACS and hypertension after PCI. To a certain extent, high sUA levels can reflect the clinical prognosis of these patients. In addition, we found that hyperuricemia was closely related to the severity of coronary artery disease, and was an independent risk factor for multi-vessel coronary artery disease in patients with ACS and hypertension after PCI. Therefore, to a certain extent, high sUA level can also reflect the severity of coronary artery disease. As the levels of sUA increased, the incidence of one-year follow-up total MACEs increased significantly and severity of coronary artery disease (non-culprit lesion vessel occlusion, multi-vessel coronary artery disease and Gensini score) increased. Further, the Gensini score was positively correlated with uric acid levels.

To date, the impact of sUA levels on the clinical prognosis and severity of coronary artery disease in patients with ACS and hypertension after PCI has not been fully clear. Therefore this study aimed to further explore the relationship among sUA levels, clinical prognosis and severity of coronary artery disease in patients with ACS and hypertension after PCI to provide a basis for reducing future cardiovascular events in patients with ACS and hypertension. Of course, the present study still had some limitations. First, the present study was a prospective, single-center study with a small sample number, which affected the representation of patients. The number and scope of the included study population were relatively limited. Whether the study results can be equally suitable for patients in other region was not yet known. Second, the present study did not fully adjust for other potentially unknown confounding factors, which may have affected the results. Third, the present study did not yet rule out the effect of the patient's current medication such as hydrochlorothiazide diuretics on uric acid levels. Fourth, the present study was an observational study, and related treatment such as sUA-lowering therapy, was not implemented for these patients. Therefore, the relationship between the reduction in uric acid levels and the prognosis of patients with acute coronary syndrome and hypertension after PCI was not explored.

Cardiovascular diseases have the characteristics of a high fatality rate and high disability rate, especially coronary heart disease (CHD). It is of great significance to reduce the incidence of cardiovascular disease and improve its prognosis. In recent years, hyperuricemia has been suggested to be closely related to cardiovascular disease.[26, 27] Clinical studies related physiological and biochemical mechanisms have suggested that high sUA levels may increase oxidative stress, promote systemic inflammation, promote local inflammation, increase insulin resistance and increase other mechanisms to cause endothelial dysfunction and lead to the occurrence of cardiovascular diseases (CVDs), such as ACS.[28-30]There are many clinical studies related to the effect of uric acid on the prognosis of patients with coronary heart disease. A retrospective study showed that high serum uric acid levels at admission were independently correlated with death and other adverse cardiovascular events during hospitalization.[31] Another retrospective prognostic study presented that high sUA levels at admission indicated the higher mortality rate during hospitalization, higher 30-day mortality rate and poor long-term (1 to 6 years) prognosis of patients with acute myocardial infarction (AMI).[32] A meta-analysis of prognostic studies showed that high sUA levels at admission independently predicted worse short-term(during hospitalization and 30 days after the occurrence of AMI) and medium or long-term(1 year or 6 months to 2 years after the occurrence of AMI) outcomes after AMI.[33] Our study also confirmed that the long-term prognosis of ACS patients in high uric acid levels group was worse (the incidence of MACEs increased significantly within 1 year). However, death and MACEs rarely happened during short-term follow-up (during hospitalization and 30 days after AMI) in this study. Therefore, the impact of high uric acid levels on the short-term prognosis was not clear in our study. The Third National Health and Nutrition Examination Survey showed that serum uric acid was independently associated with total mortality and cardiovascular mortality. As the levels of sUA increased, these risks significantly increased[34] Another retrospective cohort study also showed that hyperuricemia was an independent risk factor for one-year all-cause mortality in elderly female patients with ACS.[35] Although these studies and others suggested that uric acid was closely related

to the prognosis of coronary heart disease, there were some studies that failed to draw these conclusions, which may be due to the poor sample size of the selected population, short follow-up time or selection of statistical methods. Therefore, although there are many related studies, the association between uric acid and the prognosis of coronary heart disease is still unclear, indicating the need for similar studies to be conducted. In addition, most of the subjects of these studies were patients with hyperuricemia and ACS in the past, and the selected population type was relatively fixed. Further, it is necessary to pay particular attention to the prognosis of patients with ACS undergoing PCI. After PCI therapy, preventing coronary restenosis and myocardial infarction becomes more important, and these patients should pay more attention to the secondary prevention of the disease, controlling of cardiovascular risk factors, delaying of disease progression and increasing of life expectancy to further improve the prognosis. A retrospective analysis of 213 young adult patients (≤40 years old) undergoing PCI showed that sUA levels were correlated with MACEs during long-term(930 days) follow-up in young patients with NSTEMI undergoing PCI.[36] Another retrospective study presented that a high serum sUA level (>5.6 mg/dl) was associated with all-cause mortality in ACS patients after PCI.[37] Our study population was composed of mainly patients with ACS undergoing PCI, and the results were similar to the above research results.

However, previous studies identified that uric acid was also closely related to hypertension. The possible mechanisms of uric acid causing hypertension are as follows: sUA damages vascular endothelial cells by promoting oxidative stress reactions and causes vasomotor dysfunction by reducing the synthesis of nitric oxide. The sUA activates the renin-angiotensin-aldosterone system to lead to vascular contraction, vascular remodeling, and water or sodium retention.[8, 38, 39] Hypertension is also the most important risk factor for cardiovascular disease. In view of the inseparable and complex relationship among uric acid, hypertension and coronary heart disease, the effects of uric acid and hypertension on the prognosis of patients with coronary heart disease after PCI are unclear. For the studies about effects of uric acid on the prognosis of patients with coronary heart disease after PCI, it is necessary to consider whether patients also have the history of hypertension. Therefore, our study population mainly focused on patients with ACS and hypertension after PCI. In this study, hyperuricemia was an independent risk factor for one-year total MACEs in these patients. As the levels of sUA increased, the incidence of one-year follow-up total MACEs also significantly increased. These results fill the study gap in the prognosis of these patients and simultaneously provide a basis for further studies on the risk of cardiovascular events.

In addition, our study demonstrated that hyperuricemia was closely related to the severity of coronary artery disease, and was an independent risk factor for multi-vessel coronary artery disease in patients with ACS and hypertension after PCI. As the levels of sUA increased, severity of coronary artery disease (non-culprit lesion vessel occlusion, multi-vessel coronary artery disease and Gensini score) increased. Further, the Gensini score was positively correlated with uric acid levels. The potential mechanisms of uric acid causing coronary lesions are as follows: sUA may result in atherosclerosis and blood vessel stenosis by causing LDL-C oxidative modification, promoting the release of inflammatory factors to stimulate vascular smooth muscle hyperplasia, activating platelets to promote intravascular thrombosis.[28] In addition, the incidence of slow blood flow and no-reflow of the coronary artery increases.[40] Previous studies on the relationship between uric acid levels and the severity of coronary artery disease found that the increase in sUA levels was closely related to the severity of coronary artery disease assessed by coronary angiography and that there was a positive correlation between sUA levels and the Gensini score of the severity of coronary artery disease.[41, 42] Our study further showed that the relationship between sUA levels and the Gensini score of the severity of coronary artery disease existed in patients with ACS and hypertension after PCI. Therefore, the levels of sUA still can be used as an indicator to assess the severity of coronary artery disease in these specific patients with ACS and hypertension after PCI.

In view of the metabolism levels of uric acid in different populations are different, and the effects on the prognosis of different populations are also discrepant. It is necessary to conduct researches related uric acid in

different populations. Therefore this study focuses on specific patients with ACS and hypertension after PCI to explore the impact of uric acid on the clinical prognosis and severity of coronary artery disease for the first time, helping to improve the prognosis of these patients. In addition, in view of limitations of the present study, multi-center, randomized, controlled, and blinded studies with larger sample numbers and different populations are needed for further discussion.

5. CONCLUSION

Hyperuricemia is an independent risk factor for one-year total MACEs and multi-vessel coronary artery disease in patients with ACS and hypertension after PCI.

Contributorship Statement

Shiyu Zhang proposed study ideas and designed study plans.
Xiaodong Zhang and Yanming Shao were responsible for collecting data and following up patients for one year.
Xin Liu and Bingxue Song contributed significantly to analysis and manuscript preparation.
Shiyu Zhang performed the data analyses and wrote the manuscript.
Haichu Yu was responsible for the revision of the final version of the article.

Conflicts of Interest

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Data sharing statement

No additional unpublished data are available.

Ethics statement

Patient consent for publication

Not required.

Ethics approval

Ethics approval was provided by the Ethical Review Board of Affiliated Hospital of Qingdao University(QYFYWZLL26229).

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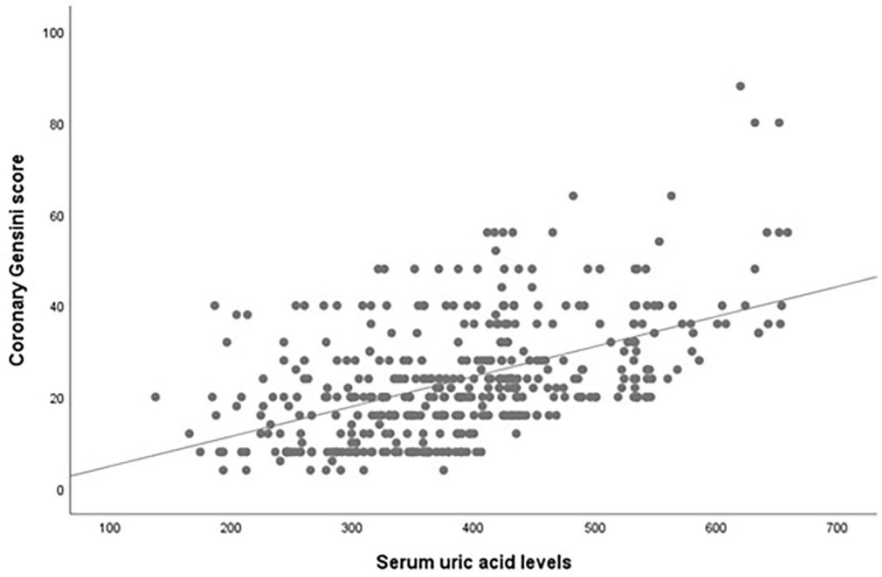
Figure legends/captions:

Figure：Correlation analysis of uric acid levels and the Gensini score

The figure is provided in online.



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3,4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	4
		(*e*) Describe any sensitivity analyses	4
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.