Serum Uric Acid Showed U-shaped Relationship with All-Cause Mortality and Cardiovascular Mortality in High Atherosclerosis Risk Patients: ASSURE Study

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Abstract

Background: Previous studys have demonstrated association between hyperuricemia and cardiovascular disease (CVD), and Framingham study has confirmed patients with high atherosclerotic risk (HAR) had worse prognosis. But after controlling other traditional atherosclerotic risks, the association between serum uric acid (SUA) and all-cause mortality, cardiovascular mortality remains controversial, especially in HAR patients.

Objective: The aim of study was to reveal the relationship with SUA and all-cause mortality, cardiovascular mortality in HAR patients.

Methods: The multi-center cohort study comprised 3,640 participants (1927male, 1713 female),whose mean age was 60.2±10.4 years andmean follow-uptimewere 68.85±11.37 months. Factors related to cardiovascular mortality and all-cause mortality, major adverse cardiac events in-hospital during follow-up were tested by multivariate Cox regression analysis and log-rank test. Restricted cubic splines with knots were used to explore theshape of dose-response relationship with SUA levels and Hazard risk (HR) of all-cause and CVD mortality.

Results: The study showed SUA presented U-shaped relationship with all-cause and cardiovascular mortality. HR of all-cause mortality with hyperuricemia and hypouricemia was 2.11, 95% CI(1.61-3.07), and 2.05, 95% CI(1.35-2.90), respectively. HR of Cardiovascular mortality was 2.42, 95% CI (1.61-3.12), and 1.95, 95% CI(1.29-2.90), respectively.

Conclusion: Abnormal SUA levels maybe significant and independent risk factors for all-cause and cardiovascular mortality. Routine SUA evaluation and intensive management are pressing needed, especially in HAR patients.

Background

The association between hyperuricemia and arterial stiffness as well as endothelial dysfunction has been demonstrated in humans[1] and serum uric acid (SUA) has been suggested to be an important modulator of the inflammatory process[2]. Several studies reported SUA severed as a marker of an underlying pathophysiological process[3,4],and some evidence revealed elevated SUA concentrations were associated with higher risk of hypertension and CVD [6-8]. But the relationship between SUA levels and CVD mortality remained controversial , due to it with established cardiovascular risk factors was complex, and latter could be considered as a confounding factor[9]. Moreover, although previous study simplied hyperuricemia as atherogenesis role in the development of CVD[10-12], there was little research on the hyperuricemia and hypouricemia relationship with all-cause mortality and CVD mortality.

Meanwhile, Framingham Heart Study conferred sufferers with HAR had worse CVD prognosis[21-23]. And that, when abnormal SUA levels combinded with HAR, the synergistic effect on prognosis was still unclear. However, few multi-center cohort study focused on it, especially in China patients. Therefore, the aim of this research wasto expound the relationship with SUA levels and all-cause mortality, cardiovascular mortality in HAR patients.

Methods

Study population

The study (ClinicalTrials.gov Identifier: NCT03616769) was a multi-center prospective Cohort Study. The first cross-sectional survey was conducted in 2011. The eligible participants were followed up from November 2011 to June 2018 (mean follow-up month was 68.71±11.35). During the followup time, 147subjects had missing data and 126 had no compliance. Thus, the study sample actually comprised 3,640 valid participants (1927 male, 1713 female), whose age older than or equal to 35 years (mean age 60.2±10.4 years) were followed up. A total of hospitalized subjects were consecutively enrolled from the cardiology departments of Beijing university affiliated hospitals and Shanghai Tongji university affiliated hospitals. All subjects are under treatment because of cardiovascular diseases. The inclusion criteria were with HAR patients. The exclusion criteria were severe congestive heart failure and severe renal failure subjects. Severe congestive heart failure was defined that above or equal to cardiac functional classify 3 formulated by the New York Heart Association (NYHA). Severe renal failure was defined as an estimated glomerular filtration rate <30 ml/min/1.73m^2 (Figure1). All participants gave written informed consent to this study, which was approved by the ethics committee of Tongji University.

Cardiovascular events definitions

Hospitalized myocardial infarction was classified as definite or probable based on chest pain symptoms, cardiac enzyme levels, and electrocardiographic findings, or angioplasty. Coronary heart disease was determined to be present if there was (1) electrocardiographic (ECG) evidence of a prior myocardial infarction, (2) prior coronary artery bypass surgery or angioplasty, (3) Coronary angiography show coronary heart disease, (4) have symptoms of angina and ECG revealed myocardial ischemia performance or laboratory tests showed cardiac enzymes increased and exclude other types of disease, (5) a self-reported history of a physician-diagnosed heart attack. CAD death was classified as “definite” based on chest pain symptoms, hospital records, and medical history.

Assessment of cardiovascular events and Identification of Death from All-Causes and CVD

Cardiovascular events are composed of cardiac including non-fatal myocardial infarction, unstable angina, and coronary revascularization procedures during follow-up time. Exclusion criteria were stale angina (>6 months), revascularization procedure for CAD (>6 months) and myocardial infarction(>6 months).

In this study, the cardiovascular death was only cardiac event death. Medical records and death certificates of all patients who had an event were obtained and validated by cardiologist. Death was confirmed from hospital records or by contact with participants and their families. All materials were reviewed independently by five senior physicians of the cohort study to confirm the cause of death.

Hyperuricemia and Hyporuricemia definitions

Hyperuricemia refers to undertake normal purpurine diet, twice results of determination in different days, SUA ≥ 420 μmol/L or 7mg/dl (male), ≥ 357 μmol/L or 6mg/dl (female) [15]. Hyporuricemia refers to undertake normal purpurine diet, twice results of determination in different days, SUA ≤ 178μmol/L or ≤ 3 mg/dl（male）, SUA ≤ 149μmol/L or ≤ 2.5 mg/dl (female)[26,27].

Framingham Risk Score and High Atherosclerosis Risk

The Framingham risk score (FRS) was calculated based on coronary risk factors, including age, gender, total cholesterol, LDL-C, hypertension and smoking status according to the National Cholesterol Education Program-Adult Treatment Panel III algorithm[17]. The calculated total scores were used to estimate the 10-year coronary heart disease risk in participants without previous CVD, and when FRS more than 20% or among 10% and 20% was considered HAR[27].

Framingham Risk Factors

Diagnostic criteria of hypertension was receiving antihypertensive medication or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg (1 mm Hg = 133 kPa) as well as both have. The criterion for hypertension refers to patients who have single hypertension disease.

Similarly, the criterion of dyslipidemia also refers to patients who have single dyslipidemia disease. The definition of dyslipidemias is that abnormalities in the serum levels of lipids, including overproduction or deficiency. Abnormal serum lipid profiles include high total cholesterol, high triglycerides, low HDL-C, and elevated LDL-C.

Measurement of Ankle and Arm Blood Pressures

Qualified ultrasonographers measured ankle and brachial systolic blood pressures. Doppler ultrasound (Nicolet Vascular, Elite 100R, USA) was used to measure systolic blood pressure (SBP) in the bilateral brachial, tibial and dorsal pedal arteries. ABI has been shown to be a powerful independent marker of cardiovascular risk, and predictive ability similar to the Framingham criteria[29, 30].

A questionnaire was designed to collect information about general characteristics, diagnosis, medical history and relation factors, medical treatment and biochemical examination in all participants.

Baseline measurements

Variables were obtained in all subjects, which include daily habits, medical histories, and blood samples. These samples are measured of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Cr), serum uric acid (SUA), glucose and FPG. Blood samples were drawn from an antecubital vein with a 19-gauge needle in a vacutainer system and their serum concentrations were assessed with commercially available kits. Glomerular filtration rate (GFR) was calculated as GFR (ml/min/1.73m^2)= 186×creatinine- 1.154× age- 0.203 and GFR (ml/min/1.73m^2) =142× creatinine- 1.154 ×age-0.203 in males and females, respectively. Glucose was measured on a Hitachi 717 analyzer (Roche) using enzymatic reagents also from Roche. Presence of symptomatic peripheral arterial disease was evaluated by the Rose questionnaire[31]. A previous myocardial infarction or ischemic stroke was documented by hospital records. Physical examination data include Body-Mass index (BMI), blood pressure and ABI. Severe congestive heart failure was defined that above or equal to cardiac functional classify 3 formulated by New York Heart Association (NYHA). Severe renal failure was defined as an estimated glomerular filtration rate <30 ml/ min/1.73m^2.

Follow-up methods

Follow-up participants were contacted by physicians of the cohort study at annual intervals. Outcomes were obtained during annual phone interviews, 6-yearly follow-up examinations, hospital records, and death records. The primary clinical event endpoints of this study were estimated with all-cause mortality and cardiovascularmortality. The secondary endpoints were examined coronary heart disease (CHD) and CHD risk equivale, including peripheral arterial disease (PAD), stroke, DM, cardiovascular disease incident. Follow-up time was the number of years from the baseline first visit to every participant. For subjects who had more than one event, all the clinical events were considered for the analysis.

Statistical Analysis

All analyses were performed using the R statistical package (version 3.6.2) (http://www.r-project.org[32]). Continuous variables are expressed as the mean ± SD, and categorical variables as percentage. Continuous and categorical variables differences comparison was made by Independent samples ANOVA (analysis

of variance) and the Chi-square test, as appropriate. Kruskal-Wallis test for non-normally distributed continuous variables. A p-value < 0.05 was considered statistically significant. Due to skewed distribution, TC, TG, HDL-C, LDL-C, Cr, SUA were logarithm-transformed (log) in analyses. Crude deaths from all-cause and CVD were examined by SUA stratification. Cumulative event rates were estimated with Kaplan-Meier survival curves, and probability values were calculated with the log-rank test. Cox proportional hazard analyses were performed to test the association of the SUA and deaths from all-causes or CVD. Cox regression model was adjusted for potential confounders, including age, gender, duration of hypertension, smoking state, dyslipidemia history, chronic renal insufficiency history, diabetes mellitus (DM) history, percutaneouscoronary angioplasty (PTCA) history, coronary artery bypass grafting (CABG) history, PAD history, myocardial infarction (MI) history, ischemic stroke history, hypertension, ABI, FRS, eGFR, use diuretics, center, year of screening examination. Potential confounding variables with P < 0.10 were adjusted for multivariate analysis. Restricted cubic splines with knots were used to further explore theshape of the dose-response relationship between the SUA levels and the HR of all-cause mortality and CVD mortality. Knots were at the 5th, 95th, and quartile of SUA distribution. Missing values were handled by K-means clustering imputation. All data P values were 2-tailed, and less than 0.05 were considered significant.

Table 1
Comparison of Subjects' Baseline Characteristics of Gender Categories According to Serum Uric Acid Levels.

	Male					Female				
characteristics	quartile of SUA levels, umol / L					quartile of SUA levels, umol / L				
	0-242.0	242.1-312.0	312.1-386.75	>386.75	P value	0-242.0	242.1-312.0	312.1-386.75	>386.75	P value
Age(years)	67.3±11.3	65.8±11.7	65.7±11.8	68.0±11.5	0.002	65.6±10.8	67.3±10.5	67.7±9.7	70.4±9.9	0.001
Diabetes , N (%)	198(41.8%)	174(35.9%)	154(31.8%)	159(32.9%)	0.006	310(43.7%)	189(42.3%)	134(45.1%)	99(38.2%)	0.372
DM duration(years)	2.8±5.0	3.0±6.0	2.3±4.8	2.5±5.0	0.173	3.6±6.1	3.8±6.4	3.8±7.1	3.6±6.9	0.925
Hypertension, N (%)	309(65.2%)	324(66.8%)	343(70.7%)	380(78.7%)	0.001	479(78.7%)	347(78.7%)	252(84.8%)	216(83.4)	0.001
HT duration(years)	8.5±11.5	8.9±11.2	9.7±12.2	10.8±11.3	0.012	8.3±10.8	10.5±11.6	12.1±11.8	12.6±13.1	0.001
Dyslipidemia, N (%)	134(34.6%)	152(38.0%)	185(46.7%)	171(40.8%)	0.005	271(46.5%)	161(42.5%)	117(50.0%)	98(44.1%)	0.297
DL duration(years)	1.3±0.31	1.8±0.45	1.8±0.41	2.1±0.46	0.069	1.9±0.39	1.9±0.43	2.0±0.42	1.6±0.34	0.532
Smoking, N (%)	310(65.4%)	307(63.3%)	325(67.0%)	320(66.3%)	0.648	57(8.0%)	48(10.7%)	27(9.1%)	29(11.2%)	0.318
Smoking duration(years)	20.7±1.86	20.0±1.81	21.4±1.85	21.3±1.91	0.552	2.7±1.02	3.4±1.08	2.7±0.97	4.3±1.32	0.218
MI History, N (%)	87(18.4%)	83(17.1%)	94(19.4%)	102(21.1%)	0.439	60(8.5%)	51(11.4%)	34(11.4%)	27(10.4%)	0.307
Diuretics, N (%)	105(22.2%)	100(20.7%)	132(27.2%)	195(40.5%)	0.001	140(19.8%)	116(26.0%)	106(35.8%)	111(43.0%)	0.001
PTCA History, N (%)	56(11.8%)	70(14.4%)	69(14.2%)	64(13.3%)	0.631	59(8.3%)	42(9.4%)	24(8.1%)	18(6.9%)	0.721
CABG History, N (%)	18(3.8%)	16(3.3%)	19(3.9%)	20(4.1%)	0.918	9(1.3%)	7(1.6%)	7(2.4%)	5(1.9%)	0.634
IS History, N (%)	182(38.4%)	163(33.6%)	161(33.2%)	167(34.6%)	0.315	212(29.9%)	139(31.1%)	83(27.9%)	83(32.0%)	0.719
CRI History, N (%)	31(6.8%)	29(6.3%)	38(8.1%)	83(17.6%)	0.001	56(8.1%)	29(6.6%)	32(11.0%)	53(21.1%)	0.001
TG, mmol/L	1.4±0.80	1.5±0.90	1.6±1.00	1.8±1.50	0.001	1.6±1.10	1.8±1.3 0	2.0±1.40	2.0±1.20	0.001
HDL-c, mmol/L	1.2±0.40	1.2±0.3 0	1.1±0.40	1.1±0.50	0.106	1.3±0.40	1.2±0.30	1.3±0.40	1.2±0.40	0.001
LDL-c, mmol/L	2.5±0.80	2.7±0.80	2.7±0.90	2.6±0.80	0.001	2.8±0.90	2.9±0.80	3.0±0.90	2.8±1.00	0.052
CRE	93.6±7.39	103.2±8.06	109.2±8.55	138.2±13.17	0.001	79.0±6.73	84.9±6.83	91.2±6.53	143.0±15.9.0	0.001
Blood glucose	6.8±0.30	6.4±0.27	6.0±0.24	6.1±0.26	0.001	6.7±0.32	6.6±0.28	6.6±0.28	6.6±0.32	0.816
BMI, kg/m2	23.2±3.4	24.7±3.3	24.6±3.4	24.9±3.7	0.001	23.8±3.6	24.3±3.8	25.1±3.5	24.9±4.0	0.001
ABI	1.01±0.20	1.02±0.20	0.99±0.20	0.99±0.20	0.066	0.99±0.20	0.97±0.20	0.95±0.20	0.91±0.30	0.001
FRS†	454(24.7%)	459(25.5%)	461(25.3%)	462(25.1%)	0.910	408(21.9%)	446(24.8%)	296(16.7%)	258(13.6%)	0.001
FRS††	357(24.1%)	379(25.5%)	375(25.3%)	373(25.1%)	0.647	488(27.2%)	424(23.1%)	287(15.6%)	247(12.4%)	0.001

systolic blood pressure (SBP), diastolic blood pressure (DBP), Hypertension (HT), BMI (body mass index.), Total cholesterol (TC), Triglycerides (TG), Fasting plasma glucose (FPG), high density lipoprotein (HDL-c), low density lipoprotein (LDL-c), serum creatinine (Cr),serum uric acid (SUA), diabetes mellitus (DM), myocardial infarction (MI), Ischemic Stroke (IS), chronic renal insufficiency (CRI), Dyslipidemia (DL), cardiovascular disease (CVD), Peripheral arterial disease (PAD), ankle-rachial index (ABI), percutaneouscoronary angioplasty (PTCA), Hazard risk (HR), coronary artery bypass grafting (CABG), Framingham Risk Score (FRS), FRS† Analysis participants with Framingham risk score 10%-20%, FRS†† Analysis participants with Framingham risk score > 20% were identified as at high risks for 10-year coronary heart disease.

Table 2
Adjusted Hazards Risks for All-cause Mortality and cardiovascular disease (CVD) Mortality By Cox Regression Models According to Serum Uric Acid Levels.

Variable		SUA			P for difference
Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
SUA level, μmol/L	0-242.0	242.0≤SUA≤312.0	312.0≤SUA≤386.75	386.75≤SUA	
All-causemortality	973	789	672	613	
Number of deaths	238(24.5%)	151(19.1%)	154(22.9%)	220(35.9%)	
Multivariableadjustment					
Model1	2.13(1.45-3.09)	1	1.94(1.23-2.92)	2.20(1.73-3.17)	＜0.001
Model 2	2.10(1.21-3.12)	1	1.90(1.19-2.98)	2.17(1.70-3.09)	＜0.001
Model 3	2.06(1.35-2.90)	1	1.86(1.54-2.89)	2.12(1.63-3.17)	＜0.001
Model 4	2.05(1.35-2.90)	1	1.85(1.54-2.76)	2.11(1.59-3.07)	＜0.001
CV mortality	973	789	672	613	
Number of deaths	119(12.2%)	85(10.8%)	90(13.4%)	112(18.3%)	
Multivariableadjustment					
Model1	2.21(1.32-3.04)	1	1.82(1.36-2.94)	2.57(1.77-3.32)	＜0.001
Model 2	2.18(1.43-2.97)	1	1.81(1.32-2.93)	2.53(1.71-3.30)	＜0.001
Model 3	1.98(1.32-2.94)	1	1.71(1.08-2.85)	2.45(1.67-3.22)	＜0.001
Model 4	1.95(1.29-2.90)	1	1.70(1.05-2.81)	2.42(1.61-3.12)	＜0.001

Model 1 was adjusted for age and gender, eGFR (estimated glomerular filtration rate), use diuretics

Model 2 was adjusted for model 1 covariates and smoking, alcohol drinking, use of diuretics, a history of heart failure,a history of diabetes, a history of renal insufficiency, a history of metabolic syndrome and a history of stroke

Model 3 was adjusted for model 2 covariates ABI (ankle - brachial index), FRS (Framingham risk score)

Model 4 was adjusted for model 3 covariates central effect, year of screening examination

Results

Baseline characteristics

A total of 3813 eligible participants with available baseline data were enrolled in this cohort. Among the participants, 126 individuals had missing follow-up data because of changing the telephone number or family address during follow-up times. 147 Subjects have poor complain (Fig1). Therefore, the study sample actually comprised 3640 valid participants Through careful calculation, the missing participants did not significantly affect the major results. Our research demonstrated that hyperuricemia and hypouricemia prevalence in these patients was 38.4% and 34.2%, respectively. Table1 presents the average SUA for the entire subjects was 322.65 ± 33.12 (standard deviation). Table 1 presents the baseline characteristics of our subjects. According to SUA levels, values were subdivided into 0-242.0, 242.0-312.0, 312.0–386.75 and more than 386.75 subgroups. Among all variables examined, our research revealed abnormal SUA subgroups had hypertension, higher proportion of male subjects, old enough, higher level of Cr, used diuretics and had chronic renal insufficiency. On account of subjects with HAR, there was no significant statistical difference on ischemic stroke, MI history, CABG history, PTCA history, DM, dyslipidemia and smoking state. Of note, femal participants with FRS risk stratification all had statistical differences. But on male participants, FRS risk stratification on subgroups all had not significant statistical difference. Meanwhile, in contrast with the reference group, participants were more likely to be treated with ACEI.

All-Cause and CVD Mortality Rates in the SUAQuartile Groups

As the Figure2 illustrated, amongthe SUA quartile categories, all-cause mortality rates in SUA ≤ 242.0, 242.0 < SUA ≤ 312.0, 312.0 < SUA ≤ 386.75, more than 386.75 four groups were 24.5%, 19.1%, 22.9% and 35.9%, respectively. Meanwhlie, CVD mortality rates were 8.7%, 5.4%, 6.4% and 13.2%, respectively. From the figure, there was a significant increasing tendency in all-cause mortality and cardiovascular mortality with higher and lower levels after 6 years of follow-up. (P < 0.001).

Survival Analysis of the SUA Quartile Groups

Figures 3A and B illustrated the relationship among the SUA quartile categories of all-cause mortality and CVD mortality, respectively. The Kaplan–Meier curves of survival showed that the survival rate decreasing with the two ends of quartile groups, not only all-cause mortality, but also CVD mortality. Fig4 revealed after multivariable adjusted,cubic spline models showed U-shaped association between SUA levels with all-cause mortality (A, B) and CVD mortality (C, D) among male and femal, respectively.

Mortality Risk According to SUA Quartile Groups

Figs5A, B, showed the adjusted proportional hazards risk (HR) of mortality according to SUA quartile groups. Compared with SUA (242.0 - 312.0) subgroup, after adjusting for gender, age, hypertension, stroke, MI history, smoking state, chronic renal disease, PAD history, PTCA history, and CABG history, SUA (0-242.0), SUA (312.0-386.75), SUA > 386.75 subgroups, all-cause mortality and cardiovascular mortality were 2.05, 95% CI (1.35–2.90), 1.85, 95% CI (1.54–2.76) and 2.11, 95% CI (1.59–3.07), respectively and 1.95, 95% CI (1.29–2.90), 1.70, 95% CI (1.05–2.81) and 2.42, 95% CI (1.61–3.12), respectively. Table 2 represented after multivariable adjusted, Cox regression models revealed that compared with SUA (242.0-312.0) subgroup, among SUA (0-242.0), SUA (312.0-386.75), and SUA > 386.75 three subgroups, all-cause mortality and cardiovascular mortality were 2.05, 95% CI (1.35–2.90), 1.85, 95% CI (1.54–2.76) and 2.11, 95% CI (1.59–3.07), respectively. And 1.95, 95% CI (1.29–2.90), 1.70, 95% CI (1.05–2.81) and 2.42, 95% CI (1.61–3.12), respectively. The results showed SUA>386.75 subgroup has mostly all-cause mortality and cardiovascular mortality, followed by SUA (0-242.0) subgroup and (312.0 - 386.75) subgroup. And yet, compared with these groups, SUA (242.0 - 312.0) subgroup has the least mortality.

Other Mortality Risk

From the Figures 6 A and B, Cox regression models also demonstrated that these mortality of risk factors has including gender, age, hypertension, stroke, metabolic syndrome, DM, MI history, PAD history, hyper lipidemia history, smoking state, PTCA history, CABG history, and lower eGFR. Of noted, among these risk factors, age, hypertension, stroke, DM, lower eGFR, abnormal ABI, MI history and CABG history occupied major position..

Discussion

Due to the close relationship between SUA levels and dietary structure, and obvious diet difference among northern and southern China, we selected in-hospital patients from Beijing and Shanghai, to represent the north and south of China. Currently, the association between SUA and all-cause mortality, cardiovascular mortality remains controversial, especially in HAR patients, owing to its complex inter -relationships with other established all-cause and cardiovascular risk factors, such as coronary heart disease, obesity, diabetes, metabolic syndrome, and chronic kidney disease. In this cohort study, according to quartile of SUA levels, after further adjusting potential confounders, the main finding suggest U-shaped, independent relationship with SUA levels and all-cause mortality, CVD mortality both male and female, instead of dose-response relationship.

The data from this research showed prevalence rate of hyperuricemia and hypouricemia was 26% and 17%, respectively. Previous study had indicated gender affected SUA metabolism and normal value range, therefore, gender stratification analysis was taken into account. Considering FRS was potential confounding factor, hence Cox regression model was adjusted for FRS between male and female. Results confirmed the second quartile of SUA level (242.0–312.0 μmol/L) had the least mortality compared with other quartiles. Furthermore, restricted cubic splines and Kaplan–Meier survival estimation implied high and low levels of SUA were undesirable. Due to this research adopted HAR subjects, thus, baseline characteristics indicated no significant statistical difference on stroke, DM, MI history, PTCA history, CABG history, hyperlipidemia and smoking state. Although in this study, we found use of diuretics and lower eGFR were substantially correlated with SUA, after controlling for eGFR and diuretics used, hazard estimates suggested changed only marginally and data represented some collinearity among the eGFR, diuretics and SUA. Consequently, the results revealed the association between SUA and all-cause mortality, CVD mortality was independent.

Similarly, several studies including longitudinal Taiwanese cohort study[33], USA adults cohort study[34] and Korea study[35] also showed U-shaped associations between SUA levels and all-cause mortality as well as cardiovascular mortality. However, these studys were limited in the specific subjects or absence of important covariates such as BMI, diuretics used, a history of renal insufficiency and excluded severe renal dysfunction (eGFR < 60 mL/min per1.73 m^2), therefore conclusion could not be extrapolated to other population. Although early studies including Framingham Heart Study[14,] Atherosclerosis Risk In Communities study[36] and Vorarlberg Health Monitoring and Promotion Program[37]manifested SUA relationship with coronary heart disease and death, when multivariate adjustment was performed, data displayed this correlation affected by confounding factors .

Previous studies revealed hyperuricemia may determine the endothelium and functions of platelets[38], induce oxidative stress, active local renin-angiotensin system in cultured vascular smooth muscle cells[39]and lead to attenuate nitric oxide bioavailability, promote proliferation of vascular smooth muscle[38, 40, 41]. Further studies had reported reduced SUA levels maybe contribute to treating hyperuricemia associated diseases[28, 42].

It was note worthy, according to our results, hypouricemia was also found associated with all-cause mortality and cardiovascular mortality. Lately, several studies involve USA Adults Study reported similar results[34]. At present, there was no recognized standard for the diagnosis of hypouricemia. According to the definition of hypouricemia in most previous researchs[26, 27, 43, 44,] the reference limit of hypouricemia was defined as the level of SUA below 149 μmol/L or 2.5 mg/dl. A possible etiology of hypouricemia increasing all-cause mortality maybe caused by malignancy[45, 46], DM and concomitant medication[47, 48]. But, these studies were limited by the absence of important covariates such as smoking status and BMI. Recently, growing evidence implied SUA played an

important role in immune regulation and tumor inhibition[48]. Therefore, hypouricemia increasing mortality was partly due to cancer incidence [49]. It was similar to our result, the research indicated cancer mortality account for 38% of all-cause mortality. Meanwhile, malignant tumor, as a kind of consumptive disease, later period appeared hypouricemia repeatedly[50]. These explicated hypouricemia populations tended to higher all-cause mortality, especially among aging patients. However, about how hypouricemia was associated with CVD remains to be clarified. The possible explanation was SUA acts as an antioxidant to protect endothelium within normal limits.

Besides hyperuricemia and hypouricemia, this study also demonstrated age, smoking state, hypertension, ischemic stroke, myocardial infarction, PAD, BMI and lower eGFR were independent mortality risk factors.

In conclusion, this finding revealed SUA levels showed U-shaped relationship with all-cause mortality and cardiovascular mortality in HAR patients whether male or female. The results implied hyperuricemia and hypouricemiaall increased mortality and SUA served as an ideal tool to predict mortality. Therefore, in clinical practice, more intensive management SUA are pressing needed, especially in HAR patients.

Study Limitations And Strengths

Firstly, with high atherosclerotic risk (HAR) patients had worse prognosis and in order to have a study population as homogenous as possible, this research adopted subjects with HAR. For this reason, results cannot be extended to the entire population. Secondly, as follow-up participant were contacted by annual phone interview, results maybe have information bias. In addition, some patients had inferior compliance,thus withdrawal bias maybe lied in this research. Finally, in comparison with western countries prospective cohort study, the follow-up times were not long. Hence, date from this research was not comprehensive, additional studies are also needed.

The strengths of our study included its prospective design and reliable assessment of mortality and cardiovascular events. Secondly, this research was multi-central prospective cohort registration study and had fine homogenous. In addition, compared with other China researches, this cohort study had the longer follow-up time and larger sample size.

Conclusion

After adjusting for gender and other covariates, the study revealed that the quartile of SUA levels showed U-shaped relationship with all-cause mortality and cardiovascular mortality. Abnormal SUA value was strongly, independently, and inversely correlated with all-cause and cardiovascular mortality. The HR of hyperuricemia and hypouricemia all-cause mortality was 2.11, 95% CI(1.59–3.07), and 2.05, 95% CI (1.35–2.90), respectively. HR of Cardiovascular mortality was 2.42, 95% CI (1.61–3.12) and 1.95, 95% CI (1.29–2.90), respectively. Abnormal SUA levels maybe ansignificant, independent risk factor for all-cause mortality and cardiovascular mortality with HAR patients.

Abbreviations

CVD: cardiovascular disease; SUA: serum uric acid; ABI: ankle–brachial index; HAR: high atherosclerotic risk; RCS: restricted cubic splines; BMI: body mass index; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C:LDL-cholesterol; DM: diabetes mellitus; HR:hazard ratios; FRS: Framingham risk score; PAD: Peripheral arterial disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; IS: Ischemic Stroke; CRI: chronic renal insufficiency; DL: Dyslipidemia; GFR: Glomerular filtration rate; CHD: coronary heart disease ; PCI: percutaneous coronary stent implantation; CABG: coronary artery bypass grafting; MI: myocardial infarction; Cr: serum creatinine

Declarations

Ethics approval and consent to participate

Approved by the ethics committee of Tongji University (NCT03616769).

Conflict of interest

The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Consent to Publish

The Author confirms:that the work described has not been published before; that it is not under consideration for publication elsewhere; that its publication has been approved by all co-authors.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

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Contributors

Yan Cang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yan Cang. Acquisition of data: Yan Cang, ShaojieXu. Analysis and interpretation of data: Yan Cang. Drafting of the manuscript: Yan Cang. Critical revision of the manuscript for important intellectual content: Yan Cang. Statistical analysis: Yan Cang.Study supervision: Yan Cang, YaweiXu.

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Figures

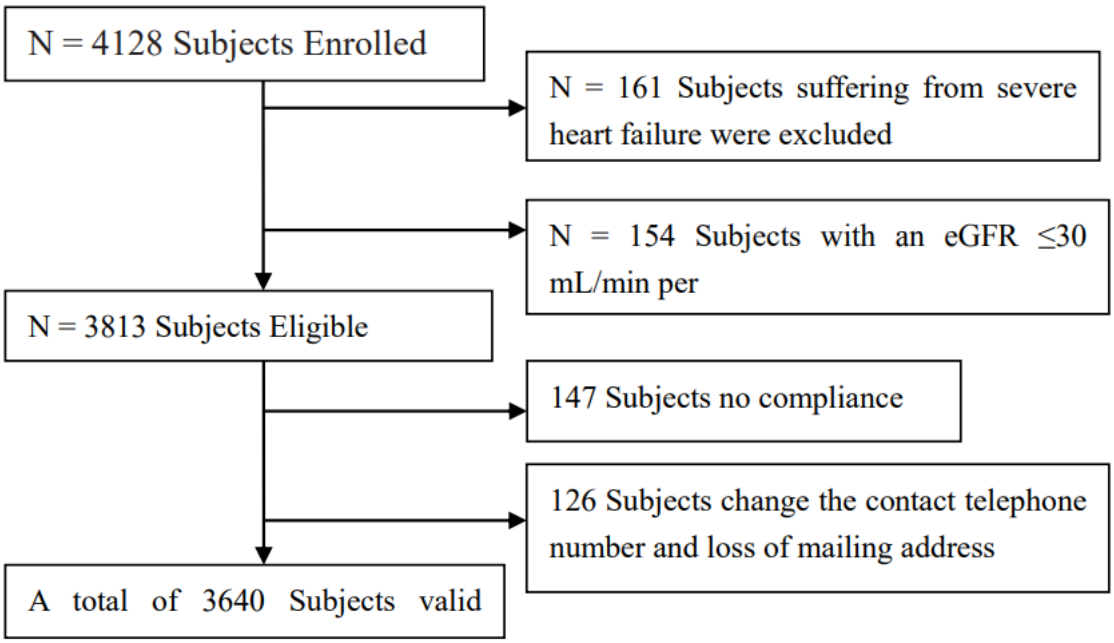

Figure 1

Study flow chart.

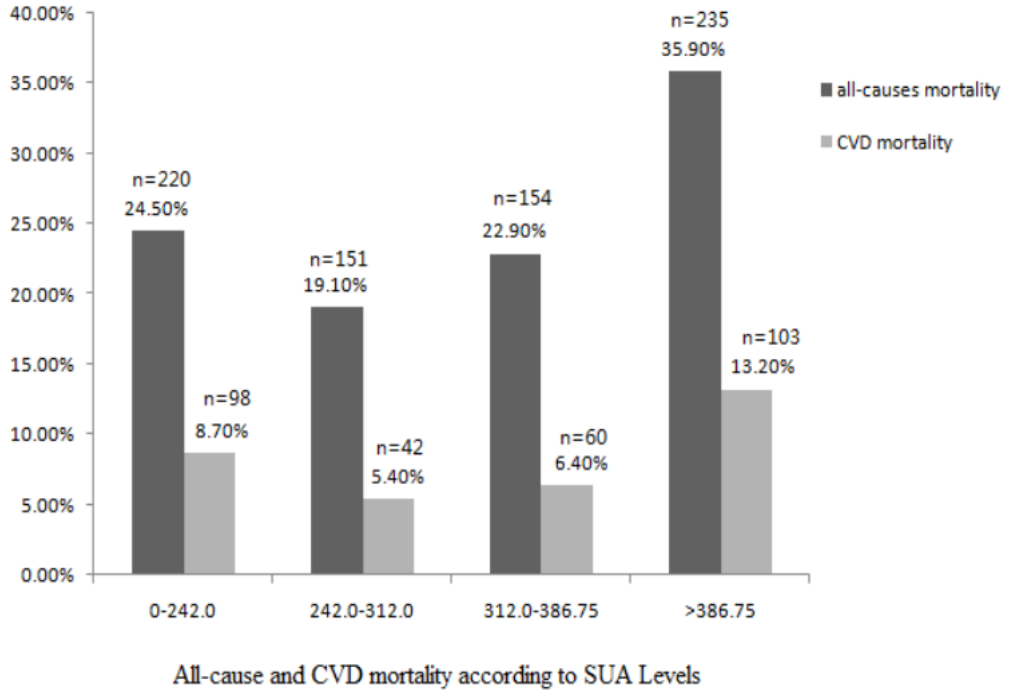

Figure 2

All-cause and cardiovascular disease (CVD) mortality according to Serum Uric Acid (SUA) Levels in the Cohort Study during 6-years follow-up (n=3,640).

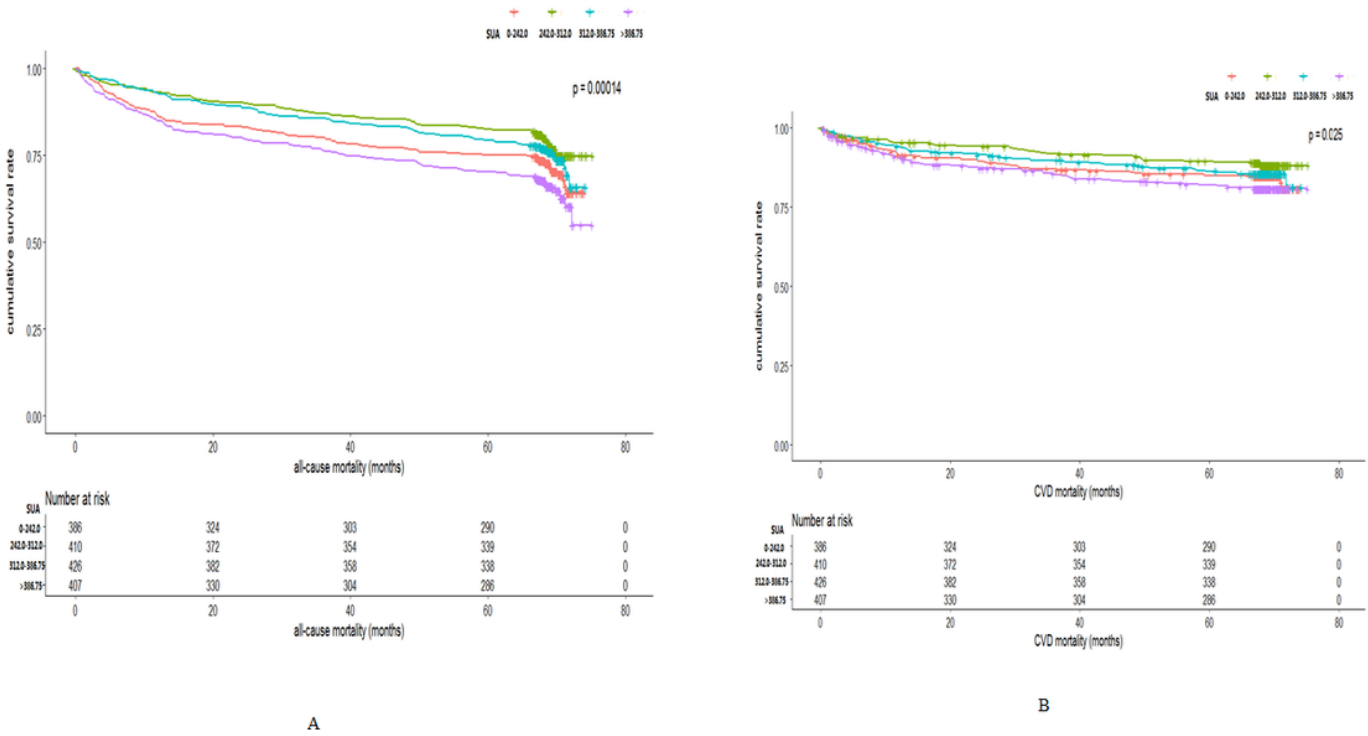

Figure 3

Time course to death from all causes (A) and cardiovascular disease (CVD) (B) according to serum uric acid levels in the cohort study during 6-years follow-up.

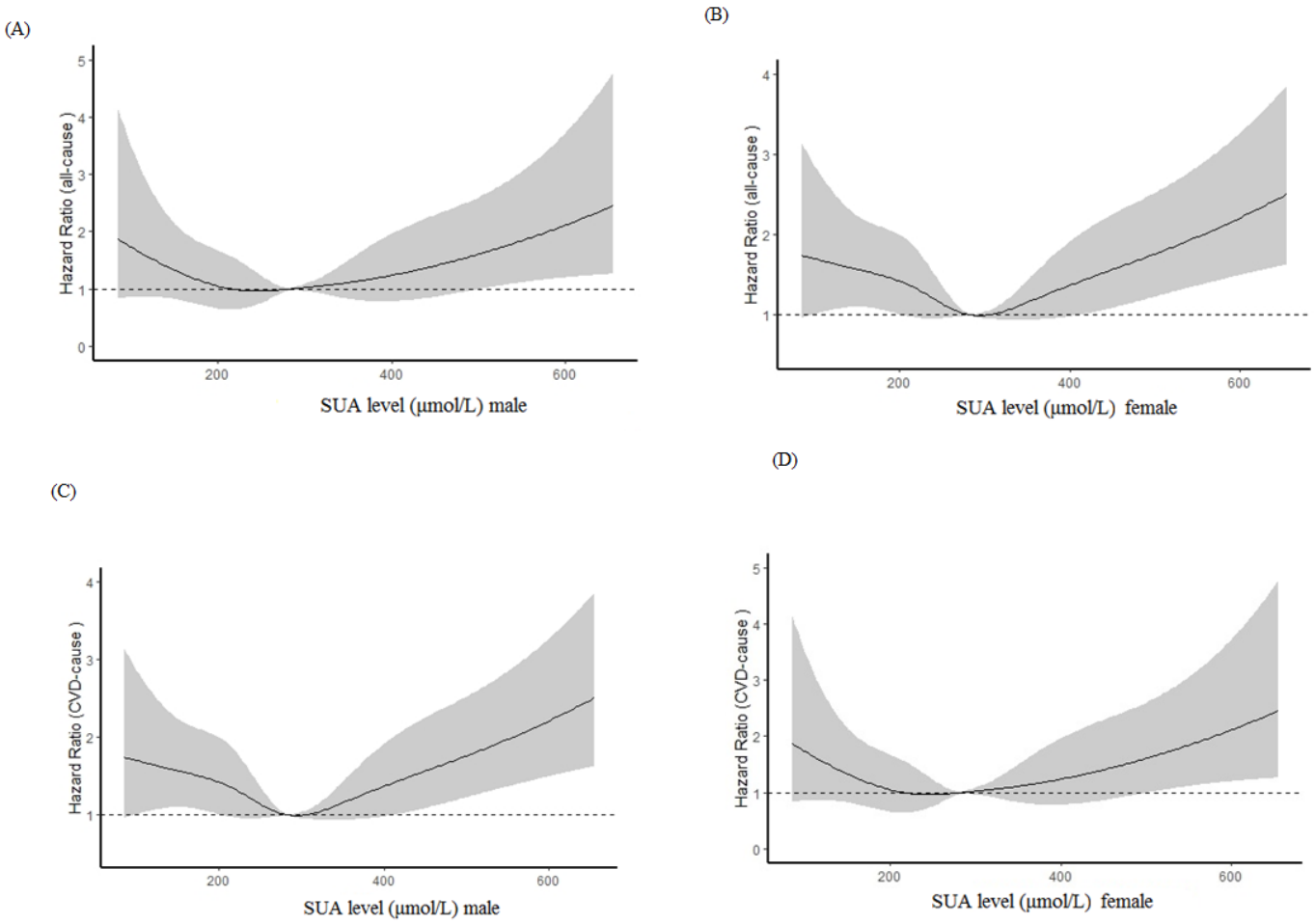

Figure 4

Multivariable adjusted cubic spline models for the association between serum uric acid (SUA) levels with hazard ratios (HR) for all-cause among male (A) and femal (B), and cardiovascular disease (CVD) mortality between male (C) and femal (D).

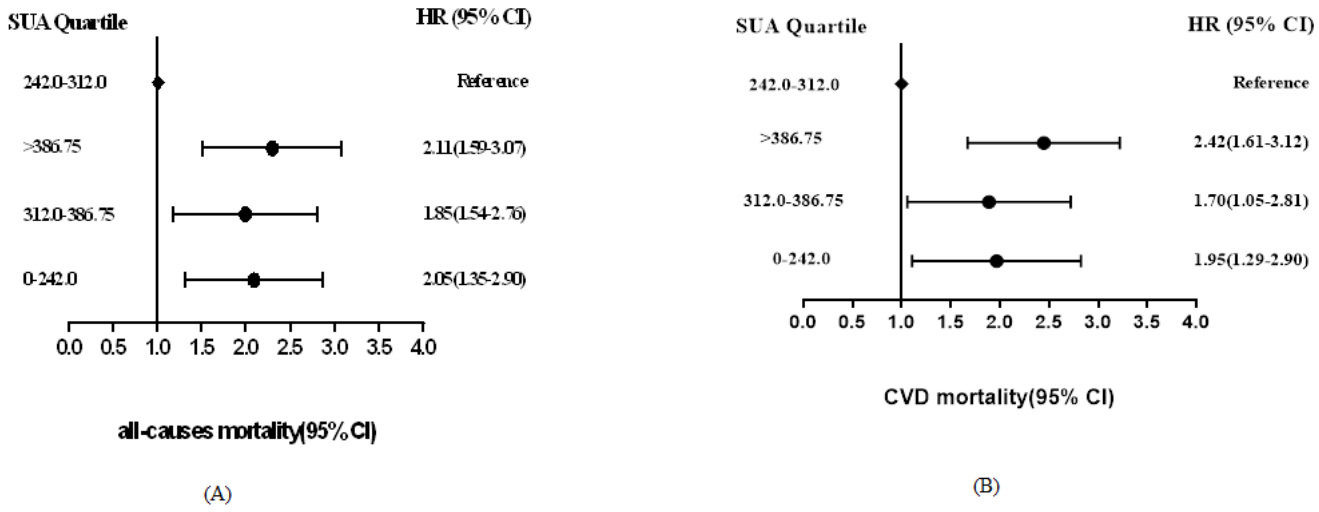

Figure 5

Adjusted hazard ratios (HR) for (A) all-cause mortality and (B) CVD mortality according to baseline SUA quartile groups in the Cohort Study during 6-years follow-up. CI (confidence interval).

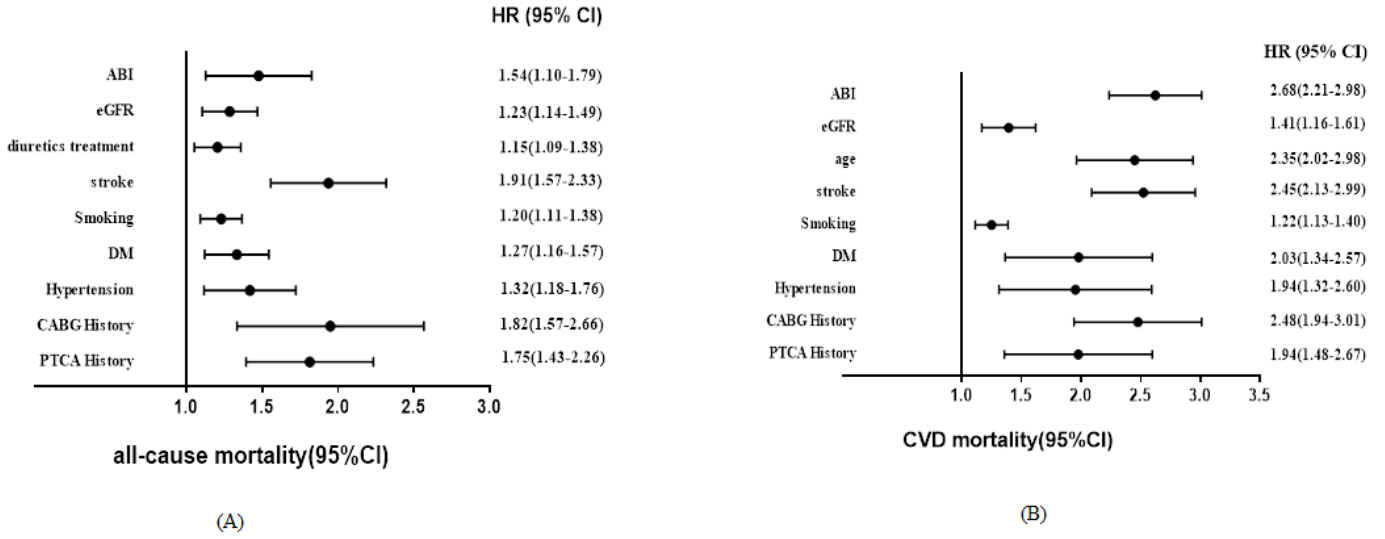

Figure 6

Adjusted other hazards risks for (A) all-cause mortality and (B) CVD mortality in the Cohort Study during 6-years follow-up. CVD, (cardiovascular disease); HR (hazards risk); CI (confidence interval); eGFR (estimated glomerular filtration rate); ABI (ankle - brachial index).