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Original Paper

U-Shaped Relationship Between Functional Outcome and Serum Uric Acid in Ischemic Stroke

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Abstract
Background/Aims: We sought to assess a consecutive number of patients with first-ever acute ischemic stroke (AIS), the clinical relevance in regard to functional outcome of the serum uric acid (SUA) measured at admission. *Methods:* In 2 prospective centers for observational study, serum concentrations of SUA were measured on admission in the serum of 710 consecutive patients with AIS. SUA concentrations were determined by high-performance liquid chromatography. SUA, NIH stroke scale (NIHSS), and conventional risk factors were evaluated to determine their value to predict functional outcome within 3 months. *Results:* During the follow-up, an unfavorable functional outcome (defined as a mRS score >2) was found in 219 (30.8%) patients. The unfavorable functional outcome distribution across the SUA quartiles ranged between 12.4% (third quartile) and 50.6% (first quartile). After adjusting for all other significant outcome predictors, SUA concentration remained an independent unfavorable outcome predictor with an adjusted OR of 0.996 (95% CI, 0.993-0.998; P<0.001). *Conclusions:* The data show that the U-shaped nature of the exposure-risk relationship was more prominent when the data were assessed in deciles (based on the SUA values). This model predicted the lowest relative risk of unfavorable outcome in the 67th percentile (corresponding to 309 μmol/L). SUA was significantly associated with the risk of poor functional outcomes in Chinese patients with stroke.

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Introduction

Stroke is a more common and frequently occurring disease in middle and old aged people in China. The age-standardized incidence and mortality rates were 1114.8 per 100, 000 people, 246.8 and 114.8 per 100, 000 person-years, respectively [1]. Stroke has been

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divided into two major types, hemorrhagic and ischemic. Ischemic stroke (IS) is the most common type of stroke, accounting for 60% to 80% of all strokes. IS has a poor prognosis and is associated with high mortality rate. Accurate and prompt prediction of functional outcome in stroke patients is essential for clinicians.

Uric acid (UA) is an end-product of the metabolism of purines and a potent antioxidant compound [2]. Previous studies have reported a relationship between the UA concentration and the risk of diabetes mellitus [3], hypertension [4], metabolic syndrome [5], coronary or cerebrovascular ischemic events [6], atrial fibrillation [7], and stroke [8]. The Framingham cohort found a greater risk for developing cardiovascular disease (CVD) in male subjects with gout [9]. UA as a marker of several metabolic disturbances has been used in clinical practice [10]. A study suggested that circulating UA is a major antioxidant and might help protect against free-radical oxidative damage [11]. The allantoin/UA (AL/UA) ratio is considered to be a marker of the oxidative stress burden in patients with various conditions [12, 13].

Oxidative stress has emerged as a key deleterious factor in brain ischemia and reperfusion. Oxidative stress contributes directly to necrosis and apoptosis through a number of pathways in ischemic tissue [14]. However, there were conflicting results about the association between the post-stroke SUA level and the prognosis of stroke in the literature [15-18]. In patients with acute ischemic stroke, Chamorro et al [16]. suggested that there is a 12% increase in the odds of good clinical outcome for each milligram per deciliter increase of SUA. Similarly, a meta-analysis supported that serum uric acid level had a protective effect on neurological outcome after acute ischemic stroke [17]. However, another study found that a low SUA concentration was modestly associated with a very good short-term outcome [18]. We propose a hypothesis that the concentration of SUA, as a marker of antioxidant, could be a protective predictor for stroke functional outcome. The aim of this prospective cohort study was to verify this hypothesis in Chinese patients with IS.

Materials and Methods

Patient Population

This prospective, multicenter cohort study was conducted at 2 Stroke Centers from 2 cities (Changchun and Beijing) in China. The number of AIS patients attended during the study period (From January 2015 through June 2016) determined the sample size.

Patients were eligible for inclusion if they were admitted to the emergency department with a first-ever AIS defined according to the World Health Organization ICD-9 criteria and with symptom onset within 24 hours. We excluded patients with missing informed consent, malignant tumor, epileptic seizures, recent surgery or trauma during the preceding 3 months, renal insufficiency (creatinine >1.5mg/dl), systemic infections at study enrollment, autoimmune diseases, recent intake of allopurinol or lithium, as well as those with a history of history of gouty arthritis or nephropathy. The study was approved by the ethics committee of the First Hospital of Jilin University according to the Helsinki Declaration of 1975. The patients or their relatives gave written informed consent prior to entering the study.

Clinical Variables and Neuroimaging

At baseline, the following demographic and clinical data were taken: gender, age, BMI (Body Mass Index) and history of conventional vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, hyperlipoproteinemia and smoking habit) were obtained. Pre-stroke therapy (oral anticoagulants, antiplatelet agents and antihypertensive treatment) and acute treatment (IV thrombolysis and/or mechanical thrombectomy) was recorded. All patients received treatment according to current guidelines. Stroke severity was assessed on admission using the National Institutes of Health Stroke Scale (NIHSS) by a neurologist [19]. Ischemic stroke subtype was classified by a consensus of 2 neurologists, with a third neurologist adjudicating if needed, based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria [20]. The clinical stroke syndrome was determined by applying the criteria of the Oxfordshire Community Stroke Project: total anterior circulation syndrome (TACS); partial anterior circulation syndrome (PACS); lacunar syndrome (LACS); and posterior circulation syndrome (POCS) [21]. Brain imaging (either

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CT or MRI) was performed routinely within 24 hours after admission. If MRI was performed, DWI lesion volumes were determined by one experienced neurologist unaware of the clinical and laboratory results. The infarct volume was calculated by using the formula 0.5×a×b×c (where a is the maximal longitudinal diameter, b is the maximal transverse diameter perpendicular to a and c is the number of 10-mm slices containing infarct) [22].

End Points and follow-up

The primary end-point was functional outcome on month 3. Structured follow-up telephone interview was used, if the patients discharged. The follow-up was conducted base on a standardized interview protocol. The interviewers were centrally trained with the interview protocol. Functional outcome was assessed by the modified Rankin Scale (mRS) [23] blinded to serum biomarkers. A favorable functional outcome was defined as a mRS of 0–2 points, whereas an unfavorable outcome was defined as a mRS of >2 points [24]. Secondary end-points were all-cause mortality within 3 months.

Plasma Samples Test

For all patients, blood was drawn in the emergency room at 6:00 in the first day morning and within 48 hours of symptom onset (within 0–6 [n=175], 6–12 [n=196], 12–24 [n=195], and 24–48 [n=144] hours from symptom onset). After centrifugation for 20 minutes at 3, 000g at room temperature, plasma (from EDTA tube) was aliquoted. SUA concentrations were determined by high-performance liquid chromatography [25]. Diluted samples were filtered through a centrifugal molecular weight cut-off spin filter device (Nanosep, 10kDa MWCO). The deproteinized filtrate was directly injected into an Agilent Series 1100 analytical HPLC system connected to a 250mm Zorbax SB-C8 (5 μmol) analytical column. The mobile phase was 2 mmol/l $NH_4H_2PO_4$ at pH 2.95 (isocratic, 1ml/min flow). Each sample was injected two times and the peak area averaged. The total coefficient of variation was 2.8% at 150μmol/l and 1.2% at 600μmol/l. The reliability coefficient for blind replicate measurements was 0.99. The median levels of SUA in 100 age and sex matched healthy individuals was 272μmol/l and the interquartile ranges (IQRs) was from 190μmol/l to 358 μmol/l. Other biomarkers, such as Fasting blood glucose (FBG), C-reactive protein (CRP), creatinine(Cr), and homocysteine (HCY) were also tested by standard laboratory method. For all measurements, levels that were not detectable were considered to have a value equal to the lower limit of detection of the assay.

Statistical Analysis

Results are expressed as percentages for categorical variables and as medians (IQRs) for the continuous variables. The distribution of raw biomarker data was skewed. Comparisons for categorical baseline measurements were performed by Fisher exact test and for continuous, not normally distributed baseline data, by the Mann-Whitney U test.

To investigate whether SUA allows predicting of unfavorable functional outcomes, different statistical methods were used. In this study, we included a range of variables as potential confounds in the analyses. These include sex, age, BMI, time from onset to blood collection, prior or acute treatment, stroke subtype, stroke syndrome, vascular risk factors, NIHSS score and serum levels of Hs-CRP, Cr, HCY and FBG. For multivariate analysis, we included SUA and other significant predictors as assessed in univariate analysis. We used crude models and multivariate models adjusted for all significant outcome predictors in univariate analysis and report odds ratios (ORs). For a more detailed exploration of the SUA and outcome relationship, we also used multivariate analysis models to estimate adjusted OR and 95% CIs of outcome for SUA quartiles (with third SUA quartile as reference).

To examine SUA as a continuous variable, we also used second-degree fractional polynomials to explore the relationship between the variables of interest. If the exposure-risk relationship was nonlinear, we planned further analyses to explore the nature of the relationship using more fine-grain deciles and individually assessing the list of variables previously included as covariates for interaction effects with SUA. All statistical analysis was performed with SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA) and STATA 9.2 (Stata Corp, College Station, TX), R version 2.8.1. Statistical significance was defined as P<0.05.

Results

Descriptive Characteristics of Stroke Patients

Of a total of 844 eligible patients, blood samples were collected within day 1 after admission in 752 patients; these samples could not be performed in 92 patients (14 patients

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died before the samples collection, 45 were discharged to another institution, 24 refused to included, and blood sampling was lost in 9 patients). Of the original 752 stroke patients, 710 completed the 3-month follow-up and were available for analysis (30 lost follow-up and 12 withdrawals). However, these included patients were similar in terms of baseline characteristics (age [P=0.55], sex [P=0.71], NIHSS [P=0.28], and BMI [P=0.41]) compared with the overall cohort. Overall median age was 59 years (IQR, 51–69 years), and 52.8% were men. At admission, the median NIHSS score was 7 (IQR, 4–12), and the median SUA concentration was 255 µmol/L (IQR, 175–342 µmol/L). The median SUA in stroke patients was significantly lower than in controls *(*272 [IQR, 190-358] µmol/L; *P*=0.009). The baseline characteristics of the patients presenting with acute ischemic stroke are described in Table 1.

Main Results

Stroke treatment was conservative in 642 (90.4%) patients, and 201 (28.3%) patients underwent thrombolysis. During the 3-month follow-up period, an unfavorable functional outcome (defined as a mRS score >2) was found in 219 patients (30.8%; 95% CI, 27.4%–34.2%). Eighty-four patients died, and the mortality rate was thus 11.8% (95% CI, 9.5%–14.2%). Daily blood samples were obtained for 7 days after admission in a subgroup of 55 patients (26 women; median age [IQR], 58 [50–68] years), 18 of whom subsequently experienced unfavorable functional outcomes. The result illustrates the time course of SUA concentration, showing significant changes with day of sampling (P<0.001), with lowest levels on day 1 (P<0.001, compared with days 0, and 2–7, respectively), increasing to a plateau by days 3 to 7.

SUA concentration was higher in men (median, 298 µmol/L compared with 219 µmol/L in women), and among those with ischemic heart disease and hypertension (P<0.05). The differences in SUA in those with diabetes were not significant (P=0.322). A significant relationship was observed between serum Cr and SUA (r=0.246, P<0.001). SUA was also inversely correlated with FBG (r=-0.242; P<0.001) and the infarct volume (N=448; r=-0.183; P=0.003). At admission, in patients with a minor stroke (NIHSS score <5), the median SUA concentration was higher than that observed in patients with moderate-to-high clinical severity (287 µmol/L [IQR, 201–392 µmol/L] vs 222 µmol/L (IQR, 159–303 µmol/L); P<0.001). Nonparametric Spearman rank correlation revealed a statistically significant negative correlation

Table 1. Baseline Characteristics of Stroke Patients. IQR, interquartile range; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; Hs-CRP, High-sensitivity-C-reactive protein; TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; LACS, lacunar syndrome; POCS, posterior circulation syndrome; SUA, serum uric acid; FBG, Fasting Blood Glucose. [†]The results presented as n (%) or median(IQRs)

Baseline Characteristics[†]	ALL (N=710)
Age, median (IQR), y	59(51-69)
Male gender, n (%)	375(52.8)
BMI, median (IQR), kg/m2	26.0(24.5-28.6)
Vascular risk factors, n (%)	
Hypertension	445(62.7)
Diabetes mellitus	178(25.1)
Coronary artery disease	155(21.8)
Congestive heart failure	142(20.0)
Hypercholesterolemia	159(22.4)
Atrial fibrillation	113(15.9)
Current smoking	165(13.2)
History of cerebrovascular event	133(18.7)
NIHSS score at admission, median (IQR)	7(4-12)
DWI lesion size(N=448), median (IQR), ml	28(11-47)
Time to blood collection from onset, median (IQR), h	12.0(5.5-21.5)
Stroke syndrome, n (%)	
TACS	159(22.4)
PACS	243(34.2)
LACS	165(23.2)
POCS	143(20.1)
TOAST subtype, n (%)	
Large-vessel disease	178(25.1)
Small-artery disease	149(21.0)
Cardioembolic	155(21.8)
Multiple causes	105(14.8)
Undetermined	123(17.3)
Laboratory findings, median (IQR)	
FBG, mmol/l	6.37 (5.62–6.93)
Creatinine, mmol/l	88.4 (71.5–103.2)
Hs-CRP, mg/l	0.44 (0.21–1.15)
SUA, µmol/l	255(175–342)
Therapies before admission, n (%)	
Anti-platelet agents	233(32.8)
Anti-coagulation	176(24.8)
Acute treatment, n (%)	
IV thrombolysis	201(28.3)
Mechanical thrombectomy	82(11.5)
IV thrombolysis and/or mechanical thrombectomy	248(34.9)

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Fig. 1. The incidence for unfavorable functional outcome (95%CI) according to the baseline concentration of SUA quartiles. The unfavorable outcome distribution across the SUA quartiles ranged between 12.4 % (third quartile) to 50.6% (first quartile), P for trend<0.001. The red symbol represents incidence for unfavorable functional outcome; The blue and green symbols represent 95% CI of incidence: low and high. SUA=Serum uric acid.
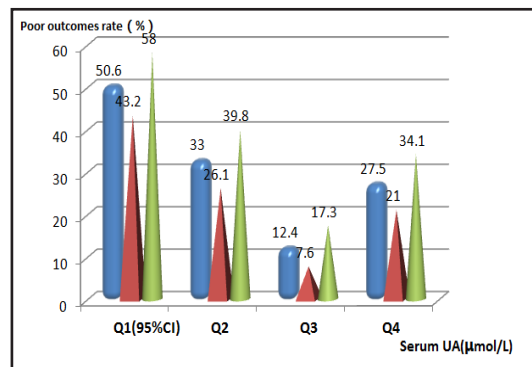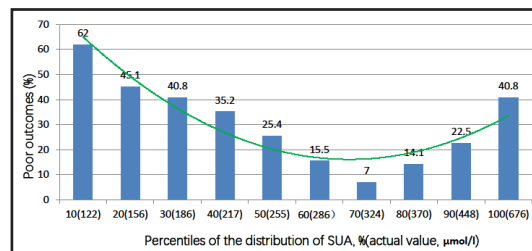

Fig. 2. The incidence for unfavorable functional outcome according to the baseline concentration of SUA deciles. This model predicted the lowest risk of unfavorable outcome in the 60~70percentile (corresponding to 286~324 µmol/l of SUA) with 7.0% of unfavorable outcome. SUA=Serum uric acid.

between SUA concentration and NIHSS score ($r=-0.216$; $P<0.001$). We also examined the relationship between SUA concentration and stroke subtypes. The median SUA concentration was significantly lower for atherosclerosis than that for the other stroke subtype groups (223 [IQR, 162320 µmol/L] vs. 276 µmol/L [IQR, 195-367 µmol/L], respectively; $P=0.002$).

SUA and functional outcome after 3 months

SUA concentration in patients with an unfavorable outcomes were significantly lower than those patients with favorable outcomes (192 µmol/L [IQR, 138-235 µmol/L] vs. 275 µmol/L [IQR, 195-344 µmol/L]; P<0.001). The unfavorable functional outcome distribution across the SUA quartiles ranged between 12.4% (third quartile) and 50.6% (first quartile), P for trend<0.001 (Fig. 1). Interestingly, Fig. 2 shows that the nature of the SUA functional outcome relationship was more prominent when the data were assessed in deciles (based on the SUA values). This model predicted the lowest relative risk of unfavorable outcome in the 60th to 70th percentile (corresponding to 286–324 µmol/L of SUA) with 7.0% of unfavorable outcome.

In univariate logistic regression analysis, we calculated the ORs of SUA concentration as compared with the NIHSS score and other risk factors as presented in Table 2. With an unadjusted OR of 0.992 (95% CI, 0.988-0.995; P<0.001), SUA concentration had a strong association with unfavorable functional outcome. After adjusting for all other significant outcome predictors in univariate logistic regression analysis, SUA concentration remained an independent unfavorable outcome predictor with an adjusted OR of 0.996 (95% CI, 0.993-0.998; P<0.001). In addition, age, BMI, the NIHSS score, FBG, and Hs-CRP remained as significant outcome predictors, unlike all others assessed. For a more detailed exploration of the SUA concentration–functional outcome relationship, we also used multivariate analysis models to estimate adjusted OR and 95% CIs of unfavorable functional outcome for SUA quartiles (with third quartile of SUA as reference). In multivariate models comparing the first, second, and fourth quartiles against the third quartile of the SUA (Table 3), levels of SUA were associated with unfavorable functional outcome. The independent association of SUA with unfavorable functional outcome was confirmed using the likelihood ratio test (P=0.005).

Again, Fig. 3 shows that the U-shaped nature of the exposure-risk relationship was more prominent when the data were assessed in deciles (based on the SUA values). Patients in the 60th to 70th percentile of the distribution were chosen as the reference

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category for the categorical analyses. In multivariate logistic regression analysis adjusting for sex, age, BMI, time from onset to blood collection, prior or acute treatment, stroke subtype, stroke syndrome, vascular risk factors, NIHSS score, and serum levels of Hs-CRP, Cr, HCY, and FBG, SUA concentration remained an independent unfavorable outcome predictor (Fig 3). The line shows the best-fit analysis for the continuous data (a second-degree fractional polynomial with orders 3 and 3). This polynomial had a significantly better fit compared with both a straight line (P=0.021) and the null model (P=0.003). This model predicted the lowest relative risk of unfavorable outcome in the 67th percentile (corresponding to 309 μmol/L of SUA).

The relationship between levels of SUA and functional outcome was also assessed between sexes. In
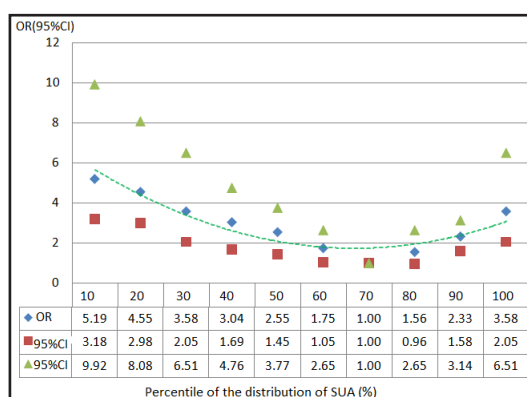
Table 2. Univariate and multivariate logistic regression analysis for unfavorable functional outcome. [†] Note that the odds ratio corresponds to a unit increase in the explanatory variable. [#] In the subgroup of patients (N=448) in whom MRI evaluations were performed. OR, odds ratio; CI, confidence interval; Hs-CRP, High-sensitivity-C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; TACS, total anterior circulation syndrome; SUA, serum uric acid; FBG, Fasting Blood Glucose

Parameter	Univariate Analysis			Multivariate Analysis		
	OR [†]	95% CI [†]	P	OR [†]	95% CI [†]	P
Age (increase per unit)	1.12	1.04-1.22	<0.001	1.08	1.02-1.17	0.003
NIHSS score (increase per unit)	1.28	1.15-1.39	<0.001	1.20	1.12-1.29	<0.001
Lesion volumes [#] (increase per unit)	1.22	1.09-1.38	0.006	1.10	1.03-1.24	0.012
Atrial fibrillation (Yes vs. no)	1.75	1.22-3.02	0.025	1.50	0.95-3.12	0.232
Smoking history (Yes vs. no)	1.33	1.06-2.01	0.042	1.24	0.92-2.12	0.283
Hypertension (Yes vs. no)	1.60	1.03-2.45	0.048	1.48	0.90-2.69	0.424
Stroke syndrome (TACS VS. other)	3.12	1.76-4.87	0.009	1.50	0.76-3.66	0.511
Stroke etiology (Small-vessel occlusive vs. other)	0.69	0.54-0.86	0.033	0.76	0.60-1.08	0.079
Hs-CRP (increase per unit)	1.21	1.09-1.42	0.004	1.09	1.03-1.35	0.006
FBG (increase per unit)	1.15	1.07-1.30	0.022	1.06	1.02-1.25	0.039
HCY (increase per unit)	1.10	1.04-1.19	0.009	1.08	1.01-1.20	0.012
SUA (increase per unit)	0.992	0.988-0.995	<0.001	0.996	0.993-0.998	<0.001

Table 3. Multivariate logistic regression analysis models to estimate adjusted OR and 95% CIs of stroke unfavorable functional outcome for SUA quartiles [††] adjust for sex, age, BMI, time from onset to blood collection, prior or acute treatment, stroke subtype, stroke syndrome, vascular risk factors, NIHSS score and serum levels of Hs-CRP, Cr, HCY and FBG. [#] SUA levels in Quartile 1 (<175μmol/l), Quartile 2 (175–255μmol/l), Quartile 3 (256–342μmol/l), and Quartile 4 (>342μmol/l); Q3 as reference with OR=1. OR, odds ratio; CI, confidence interval; Hs-CRP: high-sensitivity C-reactive protein; FBG: fasting blood glucose; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; SUA, serum uric acid

SUA quartiles [#]	Unfavorable Outcome	
	OR(95%CI) [‡]	P
Q1	3.26(2.14-4.97)	0.006
Q2	2.15(1.47-3.38)	0.015
Q3	reference	—
Q4	1.89(1.25-3.01)	0.027

Fig. 3. Odds ratio (OR) of unfavorable functional outcome according to the concentration of SUA, measured by the percentile of the distribution of SUA among the stroke patients. The upper and down points indicate 95% confidence intervals (CI). Patients in the 60th to 70th percentile of the distribution were chosen as the reference category for the categorical analyses. In multivariate logistic regression analysis, the adjusted factors including sex, age, BMI, time from onset to blood collection, prior or acute treatment, stroke subtype, stroke syndrome, vascular risk factors, NIHSS score and serum levels of Hs-CRP, Cr, HCY and FBG. OR=odds ratio; CI=confidence interval; Hs-CRP=High-sensitivity-C-reactive protein; NIHSS=National Institutes of Health Stroke Scale; SUA=serum uric acid; FBG= Fasting Blood Glucose.

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univariate logistic regression analysis, for each increase per unit of SUA, the adjusted risks of unfavorable outcome were determined as 0.997 (95% CI, 0.994–0.999; P=0.003) and 0.995 (95% CI, 0.992–0.998; P<0.001) for men and women, respectively—thus, indicating that SUA is an independent unfavorable outcome predictor. The AUROCs for SUA to diagnose unfavorable outcome in men and women were 0.703 (95% CI, 0.644–0.775; P<0.001) and 0.724 (95% CI, 0.668–0.786; P<0.001), respectively.

Discussion

The relationship between UA and stroke prognosis is ambiguous. Contrasting observations have been made between SUA and ischemic stroke outcomes in studies involving Caucasian populations [15-18]. In this study, we found that SUA was significantly associated with the risk of unfavorable functional outcome, and the nature of this relationship was nonlinear (U-shaped). Depending on its concentration, SUA may exhibit protective and deleterious effects on 3 months of stroke outcomes in Chinese population, in agreement with a previous report [25], which found that more patients with low (<280 μM) and high (>410 μM) UA levels had poor functional outcomes (36% and 27%, respectively) compared with those with UA levels between 340 and 410 μM (14%). In this study, we confirmed that stroke patients with the SUA concentration in 286 to 324 μmol/L had the best functional outcome (7%). In addition, The URICO-ICTUS trial showed that uric acid therapy improved clinical outcome in women than in men [26]. In this study, we also found that the predictive value of SUA was better in women than in men.

Previous studies suggested that SUA had protective or deleterious effects on stroke outcomes. Hyperuricemia was an independent risk factor of ischemic stroke [27] and early death in acute stroke [28]. Chiquete et al [18]. confirmed that a low SUA concentration is modestly associated with a very good short-term outcome. However, a meta-analysis supported that serum uric acid level had a protective effect on neurological outcome after acute ischemic stroke [17]. Wu et al [29]. have shown that lower serum uric acid levels independently predicted poor functional outcomes at 1 year after ischemic stroke onset (OR, 0.335; P = 0.003), whereas another study reported that low SUA level (<221 μmol/L) independently and strongly predicts the short-term poor functional outcome in acute stroke with normoglycemia other than diabetes or prediabetes [30].

It had also been proven in another study that low SUA was associated with larger infarction area and worse neurological deficit in the stroke patients [31]. In this study, we also found that SUA was also inversely correlated with infarct volume (P=0.003) and neurological deficit (P<0.001). Consistent with those data, a study suggested that decreases in UA during the first week after onset of stroke correlates with more severe stroke, unfavorable stroke evolution, and poor long-term stroke outcome [32]. This study also found that UA concentrations decreased significantly during the first 7 days after stroke onset before returning to baseline (P < 0.001). Interestingly, we found that the SUA concentration was with lowest levels on day 1 (P<0.001), increasing to a plateau by days 3 to 7. Similarly, in untreated patients, SUA declined at 6 to 12 hours (P=0.298), 48 hours (P=0.010), and 90 days (P=0.030) after stroke onset [26]. When recorded on admission, different variables were associated with poor outcome in stroke patients, for example, HS-CRP [33], HCY [33], glucose [34], and NIHSS score [35]. In this study, we also found that the NIHSS score, FBG, and Hs-CRP remained significant outcome predictors.

This observational study cannot determine the causal relationship between SUA and functional outcomes. We cannot confirm the role of UA treatments on the stroke outcomes. URICO-ICTUS trial suggested that UA therapy may prevent early ischemic worsening (EIW) after acute stroke in thrombolysed patients [36]. In women with acute ischemic stroke treated with alteplase, the administration of UA reduced infarct growth in selected patients and was better than placebo to reach excellent outcome [26]. Another study confirmed that UA improves glucose-driven oxidative stress in human ischemic stroke, and UA therapy

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was associated with reduced infarct growth and improved outcome in patients with hyperglycemia during acute stroke [37]. However, Chamorro et al [38]. suggested that the addition of uric acid to thrombolytic therapy did not increase the proportion of patients who achieved excellent outcome after stroke compared with placebo, but it did not lead to any safety concerns. Further study on the role of UA treatments on the stroke outcomes in China population should be carried out.

The U shape suggests that SUA may exhibit protective and deleterious effects on stroke outcomes. Previous studies suggested that hyperuricemia was a risk factor for the poor outcomes [30] and through the following pathway: (1) insulin resistance [39]; (2) increasing the risk of hypertension and further aggravated atherosclerosis [40]; (3) impair the self-regulation of the arteriole [41]; (4) UA induces cardiomyocyte apoptosis through activation of calpain-1 and endoplasmic reticulum stress [42]. Furthermore, high UA exposure activated the ROS-AMPK pathway, impaired CD68 expression [43], and induced oxidative damage and inhibited the viability of cardiomyocytes by activating ERK/p38 signaling [44]. The neuroprotective function of SUA can be explained from the following aspects. First, UA is the main endogenous antioxidant in human plasma, its multiple effects include scavenging hydroxyl radicals, hydrogen peroxide, and peroxynitrite and prevent lipid peroxidation [45], and these effects mainly take place within the walls of the brain vessels [46]. Second, it has been argued that SUA could be a compensatory mechanism to counteract oxidative damage related to atherosclerosis and aging in humans [47]. Third, the administration of UA allowed a more efficient clearance of peroxynitrite-derived free radicals that limited glucose toxicity and secondary cell death [37, 48]. Lastly, SUA was one of the most important serum antioxidant factors and an anti-inflammatory factor [49]; it could decrease the degradation of the extracellular superoxide dismutase-3(SOD3) [50]. In addition, in the chronic disease, UA was a reaction of the negative feedback mechanism to counterbalance the increased level of reactive oxygen species (ROS) [51].

The following limitations of our study must be taken into account. The overwhelming majority of our sample was Chinese, limiting the generalizability to other ethnicities. In addition, median age of 59 (IQR: 51-69) years seems too low. This may cause selective bias. Second, it is not yet established whether UA treatment improve the prognosis of stroke, and any causal role of these parameters in stroke pathophysiology is unproven. Third, several medical conditions, including cancer, dementia, or other chronic diseases, are associated with UA levels, and could also be associated with stroke. In addition, it is possible that insufficient nutrient intake in more severe strokes may be the reason for worse outcome in the lowest quartile of SUA. However, in this study, we did not obtain the information about nutrient intake. Interestingly, a previous study suggested that higher levels of meat and seafood consumption are associated with an increased risk of gout [52]. Therefore, we could not eliminate all of those factors. Fourth, there is evidence that UA may favorably influence stroke outcomes through multiple pathways, including hypertension, insulin resistance and secretion, 2 diabetes, and chronic inflammation. The inclusion of those factors in the models could possibly lead to over-adjustment, which tends to attenuate the associations. In addition, there were several drugs having impacts on SUA levels, for example, aspirin and diuretics. However, we did not collect this information and consider those factors as confounding factors. Lastly, this study measured biomarkers in plasma, not in cerebral spinal fluid (CSF). It is still uncertain whether peripheral UA levels reflect similar changes in the central nervous system (CNS). Further study is needed to confirm the correction between UA levels in serum and in CSF.

Conclusion

SUA was significantly associated with the risk of poor functional outcomes in Chinese patients with stroke, independent of established conventional risk factors. The nature of those relationships was nonlinear (U-shaped). Whether stroke with abnormal UA concentrations

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should be supplemented or eliminated to maintain their optimal UA concentrations to prevent poor outcomes requiring further long-term controlled clinical trials.

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Disclosure Statement

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