High serum uric acid levels are a protective factor against unfavourable neurological functional outcome in patients with ischaemic stroke

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Abstract

Objective: We aimed to evaluate the association between serum uric acid levels at the onset and prognostic outcome in patients with acute ischaemic stroke.

Methods: We retrospectively analysed the outcomes of 1166 patients with ischaemic stroke who were hospitalized in our centre during August 2008 to November 2012. Correlations of serum uric acid levels and prognostic outcomes were analysed.

Results: Men had higher serum uric acid levels and better neurological functional outcomes compared with women. There was a strong negative correlation between serum uric acid levels and unfavourable neurological functional outcomes. Generalized estimated equation analysis showed that a higher serum uric acid level ($>237\ \mu$mol/L) was a protective factor for neurological functional outcome in male, but not female, patients. Among five trial of ORG 10172 in acute stroke treatment classification subtypes, only patients with the large-artery atherosclerosis subtype had a significant protective effect of serum uric acid levels on neurological outcome.

Conclusions: Our study shows that high serum uric acid levels are a significant protective factor in men and in the large-artery atherosclerosis subtype in patients with ischaemic stroke. This is helpful for determining the prognostic value of serum uric acid levels for neurological outcome of acute ischaemic stroke.

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Introduction

Stroke is the second most common cause of death[1] and the third most common cause of disability[2] worldwide. In 2010, the global prevalence of stroke was 33 million, and 16.9 million people had first-ever stroke.[3] In China, the annual stroke mortality rate is 157 per 100,000, and stroke has become the leading cause of adult death.[4] Ischaemic stroke is the most predominant subtype of stroke caused most commonly by occlusion of the intracranial artery,[5] which accounts for more than 60% of stroke cases in the Chinese population.[6] Although major effort has been made for developing therapeutic methods for stroke, it still has a high risk of poor prognosis. A previous study showed that the global number of patients with stroke had stroke-related death and disability-adjusted life-years lost as high as 5.9 million and 102 million, respectively.[3] Identification of potential prognostic factors for ischaemic stroke may enable better prediction of outcome and conducting early interventions may improve the prognosis.[7]

In 1951, Gertler et al.[8] reported a possible relationship between serum uric acid (SUA) levels and coronary heart disease. Since this time, the association between uric acid (UA) and cardio-cerebrovascular diseases has been a focus of attention. UA is a metabolic waste product. Numerous studies have shown that hyperuricaemia is associated with several risk factors for stroke, such as hypertension,[9] diabetes[10] and metabolic syndrome.[11] High SUA levels are a risk factor for coronary heart disease.[12] Nevertheless, UA is not entirely harmful. There is a strong negative correlation between SUA levels and the prognosis of multiple sclerosis,[13] Parkinson disease,[14] Huntington disease,[15] and amyotrophic lateral sclerosis,[16] indicating its neuroprotective function. Similarly, intravenous administration of exogenous UA improves the clinical outcome in patients with acute ischaemic stroke.[17]

Based on the theory that high SUA levels may provide a neuroprotective benefit for preventing neurological injury, several studies that investigated the effect of SUA levels at the onset on the prognostic outcome of ischaemic stroke have been reported since the 2000s. However, these results remain controversial. Some studies showed that patients with high SUA levels had improved survival and good functional outcomes,[18–20] whereas some other studies reported that high SUA levels were associated with a worse outcome.[21–23] Furthermore, Miedema et al.[24] reported that there was no association between SUA levels and prognostic outcome in acute ischaemic stroke. Therefore, the effect of SUA levels on prognostic outcome still requires further investigation. Additionally, the effect of SUA on the outcome of patients with different trial of ORG 10172 in acute stroke treatment (TOAST) subtypes remains unknown. Therefore, in the current study, we aimed to investigate the association between SUA levels in the acute phase (within 2 weeks since the onset of clinical symptoms) of ischaemic stroke and the prognosis.

Methods

Study population

All patients who were hospitalized for ischaemic stroke in the Neurology Department of the First Affiliated Hospital of Sun Yat-sen University during August 2008 to November 2012 were included in this study. The inclusion criteria were as follows: (1) diagnosed with ischaemic stroke according to the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease criteria[25] by means of cranial computed tomography (CT) or brain magnetic resonance imaging (MRI); (2) in the acute stage (within 2 weeks of stroke onset); (3) first episode of ischaemic stroke; and (4) older than 18 years old. The exclusion criteria included the following: (1) a history of cerebral vascular events; (2) events possibly associated with trauma, blood disease, or malignancy; (3) lack of a laboratory test of SUA; and (4) received medication for SUA.

Clinical data collection

Serum samples were collected from all of the patients for laboratory tests, such as SUA and cholesterol levels, within 48 h after admission. All of the patients received detailed neurological physical examinations and evaluation using the modified Rankin Scale by well-trained neurological physicians. A favourable neurological functional outcome was defined as patients with a modified Rankin Scale score of 0 or 1, and an unfavorable outcome was defined as those with a modified Rankin Scale score of 2 or more.[20,26] Head CT/brain MRI and 12-lead electrocardiogram examinations were performed for all of the patients. At least one of the following examinations was performed to assist the TOAST classification: digital subtraction angiography, magnetic resonance angiography, CT angiography, transcranial Doppler, and ultrasound images of large vessels in the neck. TOAST subtypes included large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery atherosclerosis (SAA), stroke of other determined aetiology (SOE), and stroke of undetermined aetiology (SUE) subtypes.[27] At the 1st, 3rd, 6th, and 12th months after stroke, patients were followed up by telephone to evaluate the endpoint events and neurological functional outcomes. Demographic and clinical data were collected from all of the patients. This study was approved by the institutional review board of our hospital. Informed consent was waived by the institutional review board because this was a retrospective study.

Statistical analysis

Continuous variables with a normal distribution are expressed as the mean $\pm$ standard deviation (SD), while continuous variables without a normal distribution are described as median and quartile intervals (median [P25, P75]). Categorical variables are expressed as case number and percentage. Mean differences between two groups were compared using the t-test. Median differences were compared using the Wilcoxon rank-sum test. The chi-square test was used to compare the differences in rates between groups. For SUA levels without a normal distribution, the chi-square test was used to compare the differences in neurological outcome and the endpoint events among the groups. For the 1st, 3rd, 6th, and 12th months of follow-up outcome measures, the collected longitudinal data were analysed by the binary generalized estimated equation (GEE). The binary GEE model was used to assess the association of explanatory variables with the probability of unfavourable neurological functional outcome, and the

estimated parameter was the odds ratio (OR). The references of all explanatory variables are the first variables shown among the categories. An autoregressive structure (AR^1 structure) was used for the correlation matrix for repeated measure outcomes. The significance level was set at $P < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic and clinical characteristics

A total of 1166 patients were included in the current study. The demographic and clinical characteristics of all included patients are shown in Table 1. Generally, male patients had a significantly higher rate of smoking and drinking, and higher SUA and creatinine levels than did female patients (all $P < 0.001$). However, female patients had a significantly higher mean age and high-density lipoprotein cholesterol levels, and a higher incidence of rheumatic heart disease compared with male patients (all $P < 0.001$). With regard to endpoint events, there were no differences in the rate of death and cardio-cerebral events between male and female patients (both $P > 0.05$). However, unfavourable neurological functional outcomes at 1, 3, 6, and 12 months post-stroke were significantly worse in female patients than in male patients (all $P < 0.001$). This finding indicated that SUA level may have an effect on neurological functional outcomes.

Correlation between SUA levels and neurological functional outcomes

We then investigated if SUA levels affect prognostic outcomes. The patients were divided into quartiles according to their SUA levels (QUA) as follows: QUA1, ≤ 237 μmol/L; QUA2, 237.1–295 μmol/L;

QUA3, 295.1–370 μmol/L; and QUA4, > 370 μmol/L. Among the four QUA groups, there were no significant differences in the incidence of death and cardiocerebral events (Table 2, both $P > 0.05$). However, unfavourable neurological functional outcomes were significantly different among groups at 1, 3, 6 and 12 months post-stroke (all $P \leq 0.001$). A clear trend was observed that neurological functional outcomes gradually improved in proportion to an increase in SUA levels. Generally, the QUA4 group (SUA levels > 370 μmol/L) had the best neurological functional outcome, while the QUA1 group (SUA levels ≤ 237 μmol/L) had the worst outcome (Table 2). Furthermore, Point–Biserial correlation analysis further showed a strong negative correlation between SUA levels and an unfavourable neurological functional outcome at all of the time points (Table 3).

Identification of factors for unfavourable neurological functional outcomes by the GEE model

Because an association between SUA levels and neurological functional outcomes was observed, the GEE model was used to further identify risk factors associated with unfavourable neurological functional outcomes. The analysed variables, including sex, time, age, SUA levels, and TOAST classification, were modelled with the TOAST classification adjusted or fully adjusted (drinking, smoking, and history of disease). Table 4 shows that a steady decreasing trend in risk was observed in each visit over time (all $P < 0.001$). Female sex (OR $= 1.38$, 95% confidence interval [CI]: 1.04–1.84) and older patients (OR $= 1.02$, 95% CI: 1.01–1.03) were risk factors for unfavourable neurological functional outcomes compared with male and younger patients. We consistently observed that SUA levels higher than 237 μmol/L were a protective factor for neurological functional

Table 1. Demographic and clinical characteristics

	Whole population (n = 1166)	Men (n = 731)	Women (n = 435)	P value
Age, years	64.48 ± 13.35	62.65 ± 13.10	67.54 ± 13.22	<0.001
Smoking, n (%)				<0.001
Never	734 (63.0)	315 (43.1)	419 (96.3)	
Current	366 (31.4)	351 (48.0)	15 (3.4)	
Former	66 (5.7)	65 (8.9)	1 (0.2)	
Drinking, n (%)				<0.001
Never	962 (82.5)	532 (72.8)	430 (98.9)	
Current	175 (15.5)	171 (23.4)	4 (0.9)	
Former	29 (2.5)	28 (3.8)	1 (0.2)	
Past medical history				
Hypertension, n (%)	685 (58.7)	409 (56.0)	276 (63.4)	0.012
Diabetes mellitus, n (%)	238 (20.4)	133 (18.2)	105 (24.1)	0.015
Hyperlipidaemia, n (%)	65 (5.6)	44 (6.0)	21 (4.8)	0.391
Coronary heart disease, n (%)	108 (9.3)	58 (7.9)	50 (11.5)	0.043
Rheumatic heart disease, n (%)	21 (1.8)	4 (0.5)	17 (3.9)	<0.001
Atrial fibrillation, n (%)	57 (4.9)	25 (3.4)	32 (7.4)	0.003
Biomarkers				
Uric acid (μmol/L)	305.02 ± 103.05 (range: 0.76–2219)	320.21 ± 101.63 (range: 0.76–2219)	279.51 ± 100.48 (range: 2.60–631)	<0.001
Creatinine(μmol/L)	86.71 ± 47.83	96.21 ± 53.83	70.68 ± 29.20	<0.001
HbA1c (%)	6.77 ± 1.88	6.73 ± 1.84	6.83 ± 1.96	0.499
Fasting glucose (mmol/L)	6.04 ± 2.53	5.9 ± 2.43	6.28 ± 2.68	0.016
Cholesterol (mmol/L)	5.04 ± 1.30	4.96 ± 1.33	5.19 ± 1.25	0.005
Triacylglycerol (mmol/L)	1.58 ± 1.10	1.61 ± 1.17	1.53 ± 0.96	0.253
HDL-C (mmol/L)	1.11 ± 0.30	1.07 ± 0.28	1.19 ± 0.33	<0.001
LDL-C (mmol/L)	3.31 ± 1.05	3.25 ± 1.05	3.4 ± 1.04	0.028
TOAST classification				
LAA	328 (28.1)	224 (30.6)	104 (23.9)	0.013
CE	146 (12.5)	67 (9.2)	79 (18.2)	<0.001
SAA	355 (30.4)	227 (31.1)	128 (29.4)	0.559
SOE	39 (3.3)	22 (3.0)	17 (3.9)	0.409
SUE	298 (25.6)	191 (26.1)	107 (24.6)	0.562
Endpoint events and neurological functional outcomes				
Deaths	35 (3.0)	22 (3.0)	13 (3.0)	0.984
Cardio-cerebral events	59 (5.1)	31 (4.2)	28 (6.4)	0.100
Unfavourable neurological functional outcomes, n (%)				
1st month	409 (45.7)	235 (40.7)	174 (54.9)	<0.001
3rd month	361 (40.4)	206 (35.7)	155 (48.9)	<0.001
6th month	319 (35.7)	180 (31.2)	139 (43.8)	<0.001
12th month	294 (32.9)	166 (28.8)	128 (40.4)	<0.001

HbA1c, glycated haemoglobin; TOAST, trial of ORG 10172 in acute stroke treatment; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. LAA, large-artery atherosclerosis; CE, cardioembolism; SAA, small-artery atherosclerosis, SOE, stroke of other determined aetiology; SUE, stroke of undetermined aetiology.

Table 2. Comparison of prognosis between quartiles in the whole population

Quartiles (μmol/L)	QUA1 ≤237	QUA2 237.1–295	QUA3 295.1–370	QUA4 >370	P value
Unfavourable neurological functional outcomes, n (%)					
1st month	125 (57.3)	99 (43.8)	93 (41.9)	92 (40.4)	0.001
3rd month	117 (53.7)	86 (38.1)	83 (37.4)	75 (32.9)	<0.001
6th month	106 (48.6)	77 (34.1)	71 (32.0)	65 (28.5)	<0.001
12th month	101 (46.3)	67 (29.6)	66 (29.7)	60 (26.3)	<0.001
Cardio-cerebral events, n (%)	11 (4.8)	13 (5.5)	21 (8.8)	14 (5.8)	0.289
Deaths, n (%)	9 (3.1)	8 (2.8)	9 (3.1)	9 (3.2)	0.992

QUA, quartile according to SUA levels.

Table 3. Correlations between SUA levels and unfavourable neurological functional outcomes

Time	ra[a]	P
1st month	−0.111	0.001
3rd month	−0.131	<0.001
6th month	−0.134	<0.001
12th month	−0.146	<0.001

[a]Point–biserial correlation coefficient.

outcome because the ORs gradually decreased as SUA levels increased. With regard to the TOAST subtypes, the SAA subtype was a significant protective factor (OR = 0.29, 95% CI: 0.20–0.41, P < 0.001). In the fully adjusted model, female sex became a marginally significant risk factor (P = 0.075), while all the other analysed variables remained significant.

Effect of sex on neurological functional outcomes

Because the significance of sex was reduced in the fully adjusted GEE model, we decided to determine if there were any differential risk factors between male and female patients. The GEE model was used to separately analyse the risk factors in male and female patients. The significance and trends in time, age, and TOAST classification were the same as those in the whole population (Table 5). However, SUA levels remained a significant protective factor in male, but not in female, patients.

Effect of TOAST classification on neurological functional outcomes

We found that patients with different TOAST subtypes may have different neurological functional outcomes (Table 4). We then investigated if patients with different TOAST subtypes had differential risk factors for unfavourable neurological functional outcomes. Among five subtypes, female sex was a risk factor only in the SAA subtype (OR = 2.52, 95% CI: 1.27–3.87, P = 0.005), and a marginal significant risk factor in the CE subtype (OR = 2.52, 95% CI: 0.99–6.37, P = 0.051) (Table 6). The significance and trends in time were consistently the same in each TOAST subtype as those in the whole population. Older age was still a significant risk factor only in SOE and SUE (both P < 0.05). Notably, a protective effect of SUA levels was observed only in the LAA subgroup.

Discussion

In this study, we investigated the effect of SUA levels at the onset of acute ischaemic stroke on the outcome of these patients

Table 4. Factors for unfavourable neurological functional outcomes by the generalized estimated equation model

	TOAST adjusted		Fully adjusted*	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Sex				
Male	ref		ref	
Female	1.38 (1.04–1.84)	0.027	1.38 (0.97–1.97)	0.075
Time				
1st month	ref		ref	
3rd month	0.78 (0.73–0.84)	<0.001	0.78 (0.72–0.84)	<0.001
6th month	0.63 (0.57–0.69)	<0.001	0.61 (0.55–0.68)	<0.001
12th month	0.54 (0.48–0.61)	<0.001	0.53 (0.47–0.60)	<0.001
Age (continuous)	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	0.002
Uric acid levels[a]				
QUA1	ref		ref	
QUA2	0.62 (0.43–0.90)	0.012	0.66 (0.45–0.97)	0.033
QUA3	0.58 (0.40–0.85)	0.005	0.57 (0.39–0.84)	0.005
QUA4	0.54 (0.37–0.78)	0.001	0.52 (0.35–0.77)	0.001
TOAST classification				
LAA	ref		ref	
CE	1.55 (0.96–2.50)	0.074	1.94 (1.09–3.44)	0.024
SAA	0.29 (0.20–0.41)	<0.001	0.27 (0.19–0.38)	<0.001
SOE	1.15 (0.57–2.31)	0.697	1.31 (0.64–2.66)	0.460
SUE	0.78 (0.56–1.11)	0.166	0.80 (0.56–1.14)	0.223

*Fully adjusted includes sex, age, TOAST subtype, history of drinking, smoking, hypertension, diabetes mellitus, hyper-lipidaemia, coronary artery disease, rheumatic heart disease, and atrial fibrillation.
[a]Uric acid levels were defined as QUA1 ($\leq$ 237 μmol/L), QUA2 (237.1-295 μmol/L), QUA3 (295.1–370 μmol/L), and QUA4 (>370 μmol/L).
TOAST, trial of ORG 10172 in acute stroke treatment; CI, confidence interval; ref, reference; QUA, quartile according to SUA levels; LAA, large-artery atherosclerosis; CE, cardioembolism; SAA, small-artery atherosclerosis; SOE, stroke of other determined aetiology; SUE, stroke of undetermined aetiology.

with a sample size of 1166 cases. We found that male patients had higher SUA levels, as well as better neurological functional outcomes at 1, 3, 6, and 12 months post-stroke compared with female patients. Additionally, there was a strong negative correlation between SUA levels and unfavourable neurological functional outcomes at all of the time points. GEE multivariate analysis further confirmed that SUA levels higher than 237 μmol/L were a protective factor for neurological functional outcome in male, but not female, patients. Furthermore, among all TOAST classification subtypes, only patients with the LAA subtype showed a significant protective effect of SUA levels. Our findings provide evidence supporting the protective effect of SUA on functional outcome of ischaemic patients.

At present, there is still disagreement about the effect of SUA levels on prognostic outcomes of ischaemic stroke. Some studies reported that high SUA levels were a protective factor for functional outcomes,[18–20] while some studies reported that SUA levels were a risk factor.[21–23] Recently, Wang *et al.*[28] conducted a meta-analysis that included 10 studies with a total of 8131 patients with acute ischaemic stroke

Table 5. Sex subgroup analysis

	Male (n = 729)		Female (n = 433)	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Time				
1st month	ref		ref	
3rd month	0.79 (0.72–0.87)	<0.001	0.76 (0.67–0.86)	<0.001
6th month	0.63 (0.56–0.72)	<0.001	0.60 (0.51–0.72)	<0.001
12th month	0.56 (0.48–0.65)	<0.001	0.51 (0.41–0.62)	<0.001
Age (continuous)	1.02 (1.00–1.03)	0.008	1.02 (1.00–1.04)	0.018
Uric acid levels[a]				
QUA1	ref		ref	
QUA2	0.57 (0.34–0.94)	0.029	0.70 (0.40–1.21)	0.199
QUA3	0.53 (0.32–0.88)	0.014	0.67 (0.37–1.20)	0.177
QUA4	0.48 (0.30–0.78)	0.003	0.66 (0.33–1.31)	0.236
TOAST classification				
LAA	ref		ref	
CE	1.30 (0.67–2.54)	0.437	1.89 (0.92–3.88)	0.083
SAA	0.24 (0.15–0.37)	<0.001	0.37 (0.21–0.65)	<0.001
SOE	1.00 (0.41–2.43)	0.998	1.50 (0.47–4.78)	0.493
SUE	0.94 (0.62–1.43)	0.780	0.54 (0.29–0.99)	0.045

[a]Uric acid levels were defined as QUA1 ($\leq$ 237 μmol/L), QUA2 (237.1–295 μmol/L), QUA3 (295.1–370 μmol/L), and QUA4 (> 370 μmol/L).
TOAST, trial of ORG 10172 in acute stroke treatment; CI, confidence interval; ref, reference; QUA, quartile according to SUA levels; LAA, large-artery atherosclerosis; CE, cardioembolism; SAA, small-artery atherosclerosis; SOE, stroke of other determined aetiology; SUE, stroke of undetermined aetiology.

to address this issue. They showed that high SUA levels were significantly associated with a better outcome after acute ischaemic stroke (hazard ratio = 0.77, 95% CI 0.68–0.88, P = 0.0001). This finding suggests that high SUA levels have a protective effect on neurological outcome after acute ischaemic stroke. In agreement with their results, our data showed that neurological functional outcomes at the 1st, 3rd, 6th, and 12th months after stroke were significantly different among patients in four quartiles. There was also a strong negative correlation between SUA levels and unfavourable neurological functional outcomes at all of the time points. Furthermore, GEE multivariate analysis further confirmed that SUA levels higher than 237 μmol/L were a protective factor. In the fully adjusted GEE model, the effects of all of the baseline characteristics and time points were under-controlled, which greatly improved the reliability of evidence supporting the protective effect of SUA.

The protective effect of SUA may be attributed to its antioxidant property. At the onset of stroke, neurons in the ischaemic core undergo irreversible death in minutes because of complete ischaemia. However, neurons in ischaemic penumbra still have the opportunity to recover because of reperfusion and collateral circulation. Reperfusion is not entirely harmless, and it causes generation of reactive oxygen species (ROS) and subsequent brain injury.[29] Ischaemic stroke reperfusion brain injury is a consequence of the ischaemic cascade, including ATP depletion, mitochondrial dysfunction, intracellular calcium overload, elevated ROS levels,

Table 6. TOAST subgroup analysis

	LAA (n = 328)		CE (n = 146)		SAA (n = 355)		SOE (n = 39)		SUE (n = 289)	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Sex										
Male	ref		ref		ref		ref		ref	
Female	1.31 (0.78–2.18)	0.311	2.52 (0.99–6.37)	0.051	2.22 (1.27–3.87)	0.005	1.72 (0.34–8.71)	0.515	0.71 (0.40–1.25)	0.238
Time										
1st month	ref		ref		ref		ref		ref	
3rd month	0.79 (0.70–0.89)	<0.001	0.77 (0.61–0.98)	0.030	0.81 (0.70–0.93)	0.004	0.63 (0.36–1.09)	0.098	0.76 (0.65–0.89)	<0.001
6th month	0.70 (0.60–0.82)	<0.001	0.44 (0.30–0.65)	<0.001	0.68 (0.56–0.82)	<0.001	0.53 (0.29–0.99)	0.048	0.56 (0.45–0.69)	<0.001
12th month	0.61 (0.51–0.73)	<0.001	0.35 (0.23–0.55)	<0.001	0.58 (0.45–0.75)	<0.001	0.51 (0.27–0.96)	0.036	0.48 (0.37–0.63)	<0.001
Age (continuous)	1.02 (1.00–1.03)	0.110	1.00 (0.96–1.03)	0.936	1.02 (0.99–1.04)	0.173	1.06 (1.01–1.11)	0.020	1.03 (1.01–1.05)	0.006
Uric acid levels[a]										
QUA1	ref		ref		ref		ref		ref	
QUA2	0.67 (0.35–1.28)	0.225	0.90 (0.26–3.13)	0.871	0.87 (0.42–1.80)	0.701	0.64 (0.09–4.72)	0.666	0.37 (0.17–0.79)	0.010
QUA3	0.50 (0.25–0.98)	0.043	1.08 (0.32–3.62)	0.903	0.99 (0.48–2.04)	0.970	0.23 (0.02–3.21)	0.273	0.38 (0.19–0.79)	0.009
QUA4	0.47 (0.24–0.91)	0.026	0.96 (0.26–3.50)	0.955	0.62 (0.28–1.39)	0.250	0.45 (0.07–2.93)	0.403	0.54 (0.26–1.13)	0.100

[a]Uric acid levels were defined as QUA1 (≤237 μmol/L), QUA2 (237.1–295 μmol/L), QUA3 (295.1–370 μmol/L), and QUA4 (>370 μmol/L).
TOAST, trial of ORG 10172 in acute stroke treatment; CI, confidence interval; ref, reference; QUA, quartile according to SUA levels; LAA, large-artery atherosclerosis;
CE, cardioembolism; SAA, small-artery atherosclerosis; SOE, stroke of other determined aetiology; SUE, stroke of undetermined aetiology.

and release of inflammatory cytokines. This eventually leads to neuronal death in ischaemic penumbra via apoptosis and necrosis.[30] Because of protection of the blood–brain barrier, the brain has less anti-oxidant resources available compared with other organs. Consequently, the brain is highly susceptible to oxidative stress damage. Neurological injury in ischaemic penumbra can be partly or completely recovered within a critical time period.[31] Use of neuroprotectants is one of the strategies for rescuing neurons in the ischaemic penumbra from irreversible cell death.[32] UA possesses excellent antioxidant properties.[33] Additionally, serum UA levels are significantly higher than other antioxidants,[34] which means that it is an excellent antioxidant for the brain. Therefore, a higher SUA level at the onset of ROS-induced injury could protect neurons, eventually promoting neurological functional outcome.

The TOAST classification system is an aetiological stroke classification system with good interobserver agreement.[27] Aetiologically, the LAA subtype has significant stenosis or occlusion of a major brain artery or branch cortical artery because of atherosclerosis. The CE subtype has arterial occlusions, presumably due to an embolus arising in the heart. The SAA subtype has hypertension or diabetes-induced small artery occlusions. Our analyses in the whole population, as well as both sex subgroups consistently showed that the SAA subtype had the best neurological functional outcome, whereas the CE subtype was a risk factor in the fully adjusted GEE model. Our findings are in line with previous reports that the CE subtype has the highest mortality and worst prognosis, while the SAA subtype possesses the lowest mortality and best prognosis among all TOAST subtypes.[35,36] The prognostic difference among all of the subtypes may be attributed

to their different pathophysiological mechanisms.

Notably, our TOAST subgroup analysis showed that the significant protective effect of SUA levels was only observed in patients with the LAA subtype. To the best of our knowledge, this is the first study to report the effect of SUA levels on neurological functional outcomes among different TOAST subtypes. Future studies need to determine if patients with the different TOAST subtypes have different oxidative stress, which might account for the differential protective effect of SUA levels. Interestingly, a previous study showed that patients with the LAA subtype had higher oxidative stress, but lower antioxidant defence, compared with those with the SAA subtype after acute ischaemic stroke.[37] Further studies should be conducted to determine the underlying mechanism of the protective effect of SUA levels.

We observed that male patients had significantly higher mean SUA levels than did female patients, which is consistent with previous reports.[20,38] Further sex subgroup analyses showed that SUA levels higher than 237 μmol/L were a significant protective factor for neurological functional outcome in male patients. Although there was a trend that ORs gradually decreased as SUA levels increased in female patients, none of the differences were significant. A sex difference in the role of UA levels on functional outcome has also been reported in a previous study.[38] However, the difference in SUA levels between sexes may be attributed to hormonal and body composition differences between sexes. Therefore, our results require cautious interpretation and further investigation.

There are some limitations in this study. Although we included 1166 patients, the sample size was unequal among the five TOAST subtypes. Especially the SOE subtype had a small sample size of 39 cases, which would have affected the statistical

results. A well-designed study with a large sample size is required in the future to further verify the findings of this study. Additionally, we did not collect other variables, including medication, nutritional state, lifestyle, physical activity, comorbidity, and complications for adjustment of confounding factors in the GEE model. Furthermore, we did not assess alterations in SUA levels during the whole acute phase. Recently, Wu *et al*.[39] suggested that the relationship between SUA levels and stroke outcome most likely depends on the pattern of the dynamic change in SUA levels post-stroke, but not on SUA values at a specific time point after stroke. This possibility might contribute to the contradictory results on the relationship between SUA levels and stroke outcome in the literature. Therefore, the pattern of the dynamic change in SUA levels post-stroke should be evaluated. All of these limitations should be addressed in a following study.

In summary, our study shows that SUA levels are associated with unfavourable neurological functional outcomes of patients with acute ischaemic stroke. High SUA levels are a significant protective factor in male patients and in those with the LAA subtype in ischaemic stroke. Our findings may provide new insight on the prognostic value of SUA for neurological outcome of patients with acute ischaemic stroke.

Declaration of conflicting interest

The author(s) declare that there is no conflict of interest.

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