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Elevated serum uric acid is associated with cognitive impairment in acute minor ischemic stroke patients

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ABSTRACT

Background: Acute minor ischemic stroke (AMIS) has been proven to be strongly associated with post-stroke cognitive impairment (PSCI). Few studies have reported that uric acid (UA) levels are linked to PSCI in patients with AMIS, and those results are debatable. We investigated the relationship between serum UA levels and cognitive impairment in patients with AMIS.

Methods: A total of 318 patients who were diagnosed with AMIS were recruited from Suining Central Hospital. Fasting serum samples were collected the day after admission for UA measurement. Cognitive function was evaluated at admission and 3 months after stroke using the Montreal Cognitive Assessment (MoCA). The relationship between UA and PSCI was examined using a multivariate binary logistic regression model. The optimal cut-off point for UA levels to predict PSCI was determined using the receiver operating characteristic (ROC) curve.

Results: A total of 197 (61.9 %) of the 318 participants in this study exhibited cognitive impairment at 3 months. Serum UA was strongly linked with PSCI after adjusting for confounding factors (OR = 1.82, 95 % CI: 1.56 to 2.11, $P < 0.0001$). The ROC curve revealed a cut-off of 363.58 μmol/L serum UA, and the predicted sensitivity and specificity for PSCI were 67.5 % and 83.5 %, respectively. Subgroup analysis showed that confounding factors had no impact on the association between serum UA and PSCI risk.

Conclusions: Higher baseline serum UA levels might be an independent risk factor for cognitive impairment in AMIS patients. Serum UA levels above 363.58 μmol/L may have clinical implications in predicting PSCI.

1. Introduction

Acute minor ischemic stroke (AMIS) with modest, short-lasting clinical symptoms and a favourable prognosis is considered a nondisabling cerebrovascular event. Compared to moderate and severe stroke, which may cause more severe neurological impairment, minor stroke is often taken lightly. In China, AMIS accounts for one in three individuals with acute ischemic stroke [1]. Although stroke is minor, it causes long-lasting impairment that is frequently overlooked. It is well known that post-stroke cognitive impairment (PSCI) is prevalent in patients with stroke, and earlier studies have found that PSCI has a higher prevalence in AMIS [2–4], which includes

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cognitive impairment that does or does not satisfy the criteria for dementia and is associated with a low quality of life [5]. Admittedly, the primary predictors of PSCI are infarct location, lesion volume, and symptom severity, but these factors cannot entirely explain the situation [6].

Uric acid (UA), a byproduct of adenine and guanine metabolism [7], has been demonstrated to actively contribute to neurotoxicity and/or neuroprotection due to its oxidative stress or inflammatory processes in the central nervous system. There is growing data indicating that hyperuricemia may benefit cognitive function through increased antioxidant activity but may also be a possible risk factor due in part to increased inflammatory activity [8–11]. However, the precise relationship between UA levels and cognition is still not well understood. Studies involving AMIS are also scarce. Therefore, the purpose of this prospective study was to investigate the connection between serum UA levels and cognitive impairment following AMIS.

2. Materials and methods

2.1. Participants

In this retrospective cohort study, data from participants with AMIS who were hospitalized at Suining Central Hospital, a hospital in Sichuan Province, China, between January 1, 2015, and December 31, 2018, were reviewed. The inclusion criteria were as follows: 1) patients older than 18 years; 2) patients who were hospitalized within seven days after their stroke; 3) patients suffering from their first acute ischemic stroke identified by magnetic resonance imaging (MRI); and 4) patients who scored less than or equal to 3 on the National Institutes of Health Stroke Scale (NIHSS). The exclusion criteria were as follows: 1) patients with current or past autoimmune illnesses, tumours, thyroid problems, neurological diseases, and mental health issues; 2) patients with dementia or cognitive impairment before current stroke; 3) patients with serious systemic diseases such as liver, kidney and cardiopulmonary disease (Gold pulmonary function class $\geq$3 level; New York Heart Association (NYHA) functional class $\geq$3 level); 4) patients with the recent use of drugs that affect blood UA levels; and 5) patients with significant hearing, vision, and language disorders making the evaluation impossible. According to the Helsinki Declaration, the Ethics Committees at Suining Central Hospital authorized this study.

2.2. Data collection

At the time of admission, all patients' baseline clinical features and demographic information were documented, including age, sex, body mass index, education, smoking status, alcohol consumption, hypertension, diabetes, atrial fibrillation, and other past medical history. All patients underwent CT examination of the head to exclude intracranial hemorrhage and underwent a physical examination, neurological physical examination, brain MRI, and head and neck CT angiography. Fasting venous blood was drawn on the second day of hospitalization to measure the levels of serum UA, blood lipids, glycosylated haemoglobin (HbA1c), and fasting blood glucose. Within 24 h of admission, the NIHSS was used to determine the severity of the stroke, and a score of 3 or less was considered a minor ischemic stroke. Three months after stroke, the Modified Rankin Scale (mRS) was used to assess functional outcomes, and cognitive function was assessed by MoCA. Neurologists with clinical expertise served as the evaluators and they were blinded to the trials and data. The mRS is a simplified overall assessment of function, with a score of 0 indicating no symptoms and a score of 5 indicating severe disability [12]. A score of 0–2 was defined as a good outcome, and a score of 3–5 was defined as a poor outcome [13]. A score of less than 26 was regarded as cognitive impairment, and there were a total of 30 potential MoCA points. A score of less than 25 was considered cognitive impairment if the years of schooling were less than or equal to 12 [14].

2.3. Statistical analysis

For continuous variables, the mean (standard deviation) and median (minimum and maximum) are stated, whereas categorical variables are expressed as frequencies and percentages. First, we tested for differences between various UA levels (tertiles) using the $\chi 2$ test (for categorical variables), one-way ANOVA (for normal distribution), or Kruskal-Wallis H test (for skewed distribution). Second, univariate logistic regression analysis was used to evaluate the impact of each variable on PSCI risk. Third, we tested the relationship between UA and PSCI using three different multivariate binary logistic regression models. Model 1 had no adjusted factors and was an non-adjusted model. Only sociodemographic factors were altered in Model 2, which was a slightly adjusted model. With the corrected variables shown in Table 3, Model 3 was a completely adjusted model. Then, we conducted a sensitivity analysis to evaluate the robustness of our findings. To confirm the outcomes of UA as the continuous variable and to examine the possibility of nonlinearity, we changed the UA level into a categorical variable according to the tertile and computed the *P* for trend. Next, we performed a subgroup analysis and used the likelihood ratio test to examine subgroup interactions. Finally, the best cut-off value for serum UA levels to predict PSCI was investigated using the receiver operating characteristic (ROC) curve. R (http://www.r-project.org, The R Foundation) and EmpowerStats (http://www. empowerstats.com, X&Y Solutions, Inc., Boston, MA) are statistical software programs that were used for modelling. Statistical significance was defined as a two-sided *P* value less than 0.05.

3. Results

3.1. Participants' initial characteristics according to UA tertiles

A total of 318 patients aged 23–96 years (mean age 67.43 $\pm$ 11.88 years) were included in this study, including 204 (64.15 %)

males. Among them, 197 patients (61.9 %) developed cognitive impairment following AMIS. Using classical cut-off points for hyperuricemia (UA above 420 μmol/L for males and 360 μmol/L for females), 42 of 204 males (20.59 %) had hyperuricemia and 26 of 114 females (22.81 %) had hyperuricemia. Table 1 displays the sociodemographic and clinical features. Tertiles 1–3 (T1-3) had UA ranges of 54–279, 280–361, and 362–1047 mmol/L. The groups with differing UA levels showed significant variations in the following variables: creatinine (Cr) levels, sex, smoking status, alcohol consumption, blood urea nitrogen (BUN) levels, MOCA scores, and cognitive impairment (Table 1).

Table 1
Participants' initial characteristics.

UA tertiles, μmol/L	Low(54.00–279.00)	Middle(280.00–361.00)	High(362.00–1047.00)	*P*-value
No. of subjects	105	106	107	
Age, mean (SD), year	68.48 (11.61)	66.25 (11.95)	67.57 (12.06)	0.394
BMI, mean (SD), kg/m^2	22.58 (2.78)	23.06 (2.72)	23.36 (2.88)	0.124
HDL, mean (SD), mmol/L	1.42 (0.37)	1.46 (0.42)	1.43 (0.45)	0.703
LDL, mean (SD), mmol/L	2.56 (0.95)	2.58 (1.16)	2.53 (0.80)	0.935
TG, median (min-max), mmol/L	1.74 (0.05–6.63)	1.52 (0.03–7.61)	1.76 (0.04–6.22)	0.920
TC, mean (SD), umol/L	4.39 (1.35)	4.36 (1.51)	4.48 (1.37)	0.825
FPG, mean (SD), mmol/L	6.72 (3.11)	6.42 (2.86)	5.87 (2.23)	0.078
HbA1c, mean (SD), %	6.57 (1.93)	6.36 (1.70)	6.15 (1.47)	0.208
HCY, mean (SD), μmol/L	13.94 (9.69)	14.28 (6.68)	15.00 (5.54)	0.575
Cr, mean (SD), μmol/L	65.80 (16.14)	77.33 (23.13)	91.87 (39.53)	**<0.001**
BUN, mean (SD), mmol/L	5.64 (2.03)	6.30 (2.28)	7.09 (2.82)	**<0.001**
UA, mean (SD), μmol/L	222.10 (47.73)	319.75 (22.80)	447.14 (93.08)	**<0.001**
hs-CRP, median (min-max), mg/L	3.05 (0.15–84.24)	2.36 (0.31–72.01)	4.69 (0.04–704.00)	0.086
MoCA, mean (SD)	25.79 (1.69)	24.45 (1.93)	22.82 (2.07)	**<0.001**
Gender, n (%)				**<0.001**
Male	53 (50.48 %)	70 (66.04 %)	81 (75.70 %)	
Female	52 (49.52 %)	36 (33.96 %)	26 (24.30 %)	
Education, n (%)				0.364
Junior high school or above	31 (29.52 %)	39(36.79 %)	28 (26.17 %)	
Primary school	42 (40.00 %)	41 (38.68 %)	52 (48.60 %)	
Illiteracy	32 (30.48 %)	26 (24.53 %)	27 (25.23 %)	
Smoking status, n (%)				**0.033**
Never smoking	84 (80.00 %)	72 (67.92 %)	66 (61.68 %)	
Used to smoke, but I quit now	13 (12.38 %)	14 (13.21 %)	20 (18.69 %)	
Currently smoking	8 (7.62 %)	20 (18.87 %)	21 (19.63 %)	
Alcohol consumption, n (%)				**0.004**
Yes	15 (14.29 %)	26 (24.53 %)	36 (33.64 %)	
No	90 (85.71 %)	80 (75.47 %)	71 (66.36 %)	
Hypertension, n (%)				0.105
Yes	56 (53.33 %)	61 (57.55 %)	72 (67.29 %)	
No	49 (46.67 %)	45 (42.45 %)	35 (32.71 %)	
Diabetes mellitus, n (%)				0.966
Yes	20 (19.05 %)	20 (18.87 %)	19 (17.76 %)	
No	85 (80.95 %)	86 (81.13 %)	88 (82.24 %)	
Hyperlipidemia, n (%)				0.221
Yes	2 (1.90 %)	7 (6.60 %)	4 (3.74 %)	
No	103 (98.10 %)	99 (93.40 %)	103 (96.26 %)	
Atrial fibrillation, n (%)				0.271
Yes	4 (3.81 %)	2 (1.89 %)	1 (0.93 %)	
No	101 (96.19 %)	104 (98.11 %)	106 (99.07 %)	
mRS, n (%)				0.300
1	9 (8.57 %)	19 (17.92 %)	12 (11.21 %)	
2	79 (75.24 %)	74 (69.81 %)	82 (76.64 %)	
3	13 (12.38 %)	12 (11.32 %)	11 (10.28 %)	
4	0 (0.00 %)	0 (0.00 %)	1 (0.93 %)	
5	4 (3.81 %)	1 (0.94 %)	1 (0.93 %)	
NIHSS, n (%)				0.956
0	14 (13.33 %)	13 (12.26 %)	15 (14.02 %)	
1	29 (27.62 %)	30 (28.30 %)	29 (27.10 %)	
2	38 (36.19 %)	35 (33.02 %)	32 (29.91 %)	
3	24 (22.86 %)	28 (26.42 %)	31 (28.97 %)	
Cognitive impairment, n (%)				**<0.001**
No	77 (73.33 %)	37 (34.91 %)	7 (6.54 %)	
Yes	28 (26.67 %)	69 (65.09 %)	100 (93.46 %)	

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HCY homocysteine; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; hs-CRP, high sensitive C-reaction; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

3.2. Univariate analysis for PSCI at 3 months

A univariate regression analysis revealed a connection between UA and cognitive impairment (OR 1.02, 95 % CI 1.02–1.02, $p < 0.0001$). Additionally, creatinine (OR 1.02, 95 % CI 1.01–1.03, $p = 0.0005$) and BUN levels (OR 1.13, 95 % CI 1.02–1.25, $p = 0.0200$) may potentially be related to PSCI (Table 2). The distribution of UA between the non-PSCI and PSCI groups is shown in Fig. 1.

3.3. The relationship between UA and PSCI in different models

To assess the relationship between UA and PSCI, we employed a univariate linear regression model. Table 3 displays the non-adjusted and adjusted models. In Model 1, there was a significant positive correlation between UA and PSCI (OR = 1.67, 95 % confidence interval (CI): 1.49 to 1.87, $P < 0.0001$). In Model 2 (adjusted for age and sex), the results did not show obvious changes (OR = 1.76, 95 % CI: 1.54 to 1.99, $P < 0.0001$). In Model 3, we also found a similar result to Model 2 (OR = 1.82, 95 % CI: 1.56 to 2.11, $P < 0.0001$). We also used UA as a categorical variable (tertiles) for the sensitivity analysis and discovered the same trend (p for trend was <0.0001).

3.4. The relationship between UA and PSCI in various subgroups

We further investigated the potential risks between UA and PSCI by subgroup analysis to assess additional factors that may influence the results. The results showed that the relationship between UA and PSCI was not affected by other confounding factors (Table 4).

Table 2
Effects of risk factors on cognitive impairment following acute ischemic minor stroke by univariate analysis.

	Statistics	Odds ratio (95 % CI)	*P*-value
Age, mean (SD), year	67.43 ± 11.88	1.00 (0.98, 1.02)	0.7415
Gender, n (%)			
Male	204 (64.15 %)	Ref	
Female	114 (35.85 %)	0.96 (0.60, 1.55)	0.8808
BMI, mean (SD), kg/m^2	23.00 ± 2.81	1.03 (0.95, 1.12)	0.4972
Education, n (%)			
Junior high school or above	98 (30.82 %)	Ref	
Primary school	135 (42.45 %)	1.46 (0.86, 2.50)	0.1615
Illiteracy	85 (26.73 %)	1.36 (0.75, 2.47)	0.3091
Smoking status, n (%)			
Never smoking	222 (69.81 %)	Ref	
Used to smoke, but I quit now	47 (14.78 %)	1.04 (0.54, 1.98)	0.9094
Currently smoking	49 (15.41 %)	1.33 (0.69, 2.56)	0.3946
Alcohol consumption, n (%)			
Yes	77 (24.21 %)	Ref	
No	241 (75.79 %)	0.84 (0.49, 1.44)	0.5356
Hypertension, n (%)			
Yes	189 (59.43 %)	Ref	
No	129 (40.57 %)	0.65 (0.41, 1.02)	0.0633
Diabetes mellitus, n (%)			
Yes	59 (18.55 %)	Ref	
No	259 (81.45 %)	1.25 (0.70, 2.22)	0.4491
Hyperlipidemia, n (%)			
Yes	13 (4.09 %)	Ref	
No	305 (95.91 %)	0.48 (0.13, 1.76)	0.2662
Atrial fibrillation, n (%)			
Yes	7 (2.20 %)	Ref	
No	311 (97.80 %)	4.20 (0.80, 22.01)	0.0892
HDL, mean (SD), mmol/L	1.44 ± 0.41	1.23 (0.70, 2.16)	0.4639
LDL, mean (SD), mmol/L	2.56 ± 0.98	1.01 (0.80, 1.27)	0.9378
TG, median (min-max), mmol/L	2.06 ± 1.53	1.09 (0.94, 1.27)	0.2453
TC, mean (SD), μmol/L	4.41 ± 1.41	1.03 (0.88, 1.21)	0.7184
FPG, mean (SD), mmol/L	6.33 ± 2.77	0.95 (0.87, 1.03)	0.1759
HbA1c, mean (SD), %	6.36 ± 1.71	0.89 (0.78, 1.01)	0.0780
HCY, mean (SD), μmol/L	14.41 ± 7.48	1.00 (0.97, 1.03)	0.9081
Cr, mean (SD), μmol/L	78.25 ± 29.81	1.02 (1.01, 1.03)	**0.0005**
BUN, mean (SD), mmol/L	6.35 ± 2.47	1.13 (1.02, 1.25)	**0.0200**
UA, mean (SD), μmol/L	330.37 ± 111.09	1.02 (1.02, 1.02)	**<0.0001**
hs-CRP, median (min-max), mg/L	12.58 ± 42.55	1.00 (0.99, 1.01)	0.5433

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HCY homocysteine; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; hs-CRP, high sensitive C-reaction.

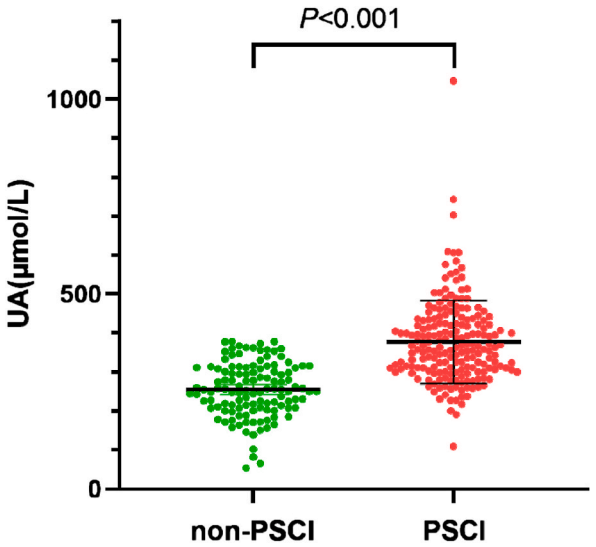

Fig. 1. The scatter plots showing the variances in UA levels distribution between non-PSCI and PSCI groups.

Table 3
Relationship between UA and PSCI in different models.

Exposure	Model 1 OR (95%CI) *P* value	Model 2 OR (95%CI) *P* value	Model 3 OR (95%CI) *P* value
UA/30 μmol/L	1.67(1.49, 1.87)<0.0001	1.76(1.54, 1.99)<0.0001	1.82(1.56, 2.11)<0.0001
UA tertiles			
Low	Ref	Ref	Ref
Middle	5.13 (2.85, 9.24) <0.0001	6.11 (3.26, 11.44) <0.0001	6.30 (3.12, 12.72) <0.0001
High	39.29 (16.30, 94.71) <0.0001	51.27 (20.32, 129.34) <0.0001	61.39 (20.66, 182.38) <0.0001
P for trend	5.95 (4.00, 8.85) <0.0001	6.90 (4.49, 10.61) <0.0001	7.43 (4.48, 12.32) <0.0001

Model 1: Non-adjusted model.
Model 2: Adjusted for Age and Gender.
Model 3: Adjusted for Age, Gender, BMI, Education level, Smoking Status, Drinking Status, Hypertension, Diabetes mellitus, Atrial fibrillation, HDL, LDL, TG, TC, FPG, HbA1c, Hyperlipidemia, HCY, Cr, BUN, hs-CRP, mRS and NIHSS.

3.5. The ROC curve for UA in identifying cognitive impairment in AMIS patients

As shown in the ROC curve, the area under the curve (AUC) for PSCI was 0.85 at a cut-off point of 363.58 μmol/L UA, and the specificity and sensitivity were 67.5 % and 83.5 %, respectively (95 % CI: 0.809 to 0.891, Fig. 2).

4. Discussion

To our knowledge, this study is the first to investigate the relationship between serum UA and cognitive decline after AMIS. The key findings in our study were that patients who suffered from AMIS experienced more severe cognitive impairment when their UA levels were higher, and the association persisted after adjusting for confounding factors. Further ROC curve analysis verified a cut-off of 363.58 μmol/L serum UA, with high sensitivity and specificity to predict the occurrence of PSCI, indicating that serum UA may be a reliable predictor of cognitive impairment in patients with post minor ischemic stroke.

According to a recent meta-analysis, PSCI was detected in 48.8 % of patients with acute ischemic stroke [15]. The prevalence of cognitive impairment in acute mild ischemic stroke was 63 % and 59.76 %, respectively, in two small-scale studies [4,16]. Consistent with previous conclusions, our study revealed that 61.9 % of patients with acute ischemic minor stroke had cognitive impairment. Although earlier studies have shown a connection between UA and PSCI, these results are controversial. Ran et al. found that higher serum UA levels were related to better cognitive performance in 197 patients with ischemic stroke [17]. Another study also reported that low serum UA levels were linked to cognitive impairment in vascular dementia [10]. However, some studies indicated that serum UA levels were an independent risk factor for PSCI; compared to those in the non-PSCI group, the serum UA levels in the PSCI group were significantly higher [18]. In addition, hyperuricemia has also been connected to an increased risk of cerebrovascular disease and vascular dementia, according to an earlier study [4,19]. Moreover, in patients with cerebral small vascular disease, UA levels were higher in the vascular mild cognitive impairment (VMCI) group than in the non-VMCI group [20]. The disparities between these studies may be due to the study population, sample size, cognitive assessment tool, assessment duration, etc. Our results show that a UA cut-off point of 363.58 μmol/L may predict the occurrence of PSCI, which is consistent with the Italian URRAH study (an UA cut-off

Table 4
Relationships between UA and PSCI in various subgroups.

Subgroup	No. of subjects	Odds ratio (95 % CI)	*P*-value	*P* for interaction
Age, year				0.6580
23 - 63	105	1.03 (1.02, 1.04)	<0.0001	
64 - 73	102	1.02 (1.01, 1.03)	<0.0001	
74 - 96	111	1.02 (1.02, 1.03)	<0.0001	
Gender				0.2282
Male	204	1.02 (1.01, 1.03)	<0.0001	
Female	114	1.03 (1.02, 1.04)	<0.0001	
BMI, kg/m2				0.6970
15.63–21.61	105	1.02 (1.01, 1.03)	<0.0001	
21.64–23.88	106	1.02 (1.01, 1.03)	<0.0001	
24.03–33.33	107	1.04 (1.02, 1.05)	<0.0001	
Education				0.0658
Undergraduate, college or above	11	1.03 (0.97, 1.10)	0.2975	
High school (including technical secondary school)	20	1.03 (1.00, 1.07)	0.0342	
Junior high school	67	1.01 (1.01, 1.02)	0.0015	
Primary school	135	1.02 (1.01, 1.03)	<0.0001	
Illiteracy	85	1.04 (1.02, 1.06)	<0.0001	
Smoking status,				0.8837
Never-smoker	222	1.02 (1.02, 1.03)	<0.0001	
Past smoker who has quit	47	1.02 (1.01, 1.04)	0.0024	
Current smoker	49	1.02 (1.01, 1.03)	0.0022	
Alcohol consumption				0.4088
Yes	77	1.03 (1.01, 1.04)	<0.0001	
No	241	1.02 (1.02, 1.03)	<0.0001	
Hypertension				0.1528
Yes	189	1.02 (1.01, 1.03)	<0.0001	
No	129	1.03 (1.02, 1.04)	<0.0001	
Diabetes mellitus				0.2544
Yes	59	1.02 (1.01, 1.03)	0.0007	
No	259	1.02 (1.02, 1.03)	<0.0001	
Hyperlipidemia				0.6660
Yes	13	1.03 (0.99, 1.07)	0.1165	
No	305	1.02 (1.02, 1.03)	<0.0001	
mRS score				0.3755
0-2	275	1.02 (1.02, 1.03)	<0.0001	
3-4	43	1.02 (1.01, 1.03)	0.0053	
NIHSS score				0.4524
0	42	1.02 (1.01, 1.04)	0.0035	
1	88	1.02 (1.01, 1.03)	<0.0001	
2	105	1.02 (1.01, 1.03)	<0.0001	
3	83	1.03 (1.02, 1.05)	<0.0001	

Abbreviations: BMI, body mass index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. Notes: Above model adjusted for Age, Gender, BMI, Education level, Smoking Status, Drinking Status, Hypertension, Diabetes mellitus, Atrial fibrillation, HDL, LDL, TG, TC, FPG, HbA1c, Hyperlipidemia, HCY, Cr, BUN, hs-CRP, mRS, and NIHSS. In each case, the model is not adjusted for the stratification variable.

point of 342 can predict fatal myocardial infarction) [21]. The threshold we found is lower than the classical diagnostic threshold for hyperuricemia, and the reason may be related to mechanisms other than urate deposition.

UA is the byproduct of purine nucleotide metabolism and is frequently considered detrimental to health, but it has also demonstrated a critical antioxidant role [7]. Oxidative stress has been recognized as one of the initiating factors of neurodegenerative diseases (Alzheimer's disease and Parkinson's disease) and is involved in regulating the expression levels of the peptides amyloid beta (Aβ) and α-synuclein [22]. Therefore, UA is considered to possess certain neurological and cognitive protective effects [23,24]. Nevertheless, UA accelerates the process of cognitive impairment through multiple mechanisms, which has also been proven in some studies [25,26]. According to a recent review, hyperuricemia has antioxidants that may be beneficial for cognitive function but may also be a risk factor for cognitive impairment [27]. Our study showed that a higher level of UA was associated with cognitive impairment in patients with AMIS, which was consistent with the results of previous studies. The effect of serum UA on cognitive function may be related to the concentration and duration of exposure, but the exact mechanisms remain incompletely elucidated. The main hypothesis suggests that UA is involved in oxidative stress and inflammatory processes. Significantly hyperuricemia cannot play an antioxidant role, but it can trigger the oxidative stress response, enhance the expression of c-reactive protein, interleukin-6 and other inflammatory factors, damage vascular endothelial function and lead to microvascular dysfunction [28,29]. Animal studies revealed that the rats in the hyperuricemia groups exhibited worse cognitive performance, more extensive pathological damage, a stronger inflammatory response, and higher levels of oxidative stress and β-amyloid peptide than those in the normal control groups [30]. UA produces pro-oxidative stress effects by boosting the generation of free radicals, inducing inflammation, and changing the production of NO, protein, lipid, and DNA oxidation and nitration in the central nervous system (CNS), thereby causing necrosis and apoptosis of neurons [31] and ultimately causing CNS oxidative damage. The proinflammatory effect of UA is thought to occur by inducing interleukin

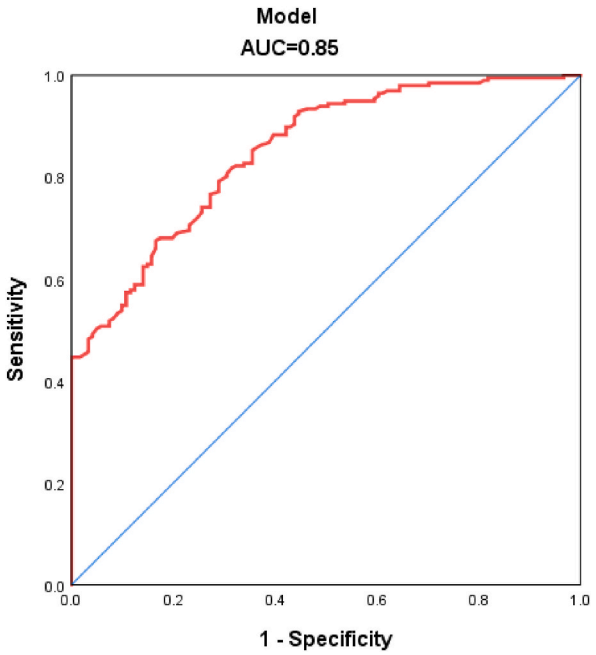

Fig. 2. Analysis of receiver operating characteristic curves of the PSCI at discharge for the UA cut-off point. Area under the curve (c-statistic) = 0.85 (UA).

(IL)-1-mediated inflammation and stimulating the expression of CRP [32,33]. In addition, a previous study confirmed that serum UA was able to cross the blood–brain barrier, and in patients with blood–brain barrier impairment, higher UA levels were more easily observed in cerebrospinal fluid [34]. Hyperuricemia facilitates the development of cognitive impairment in individuals with AMIS, probably as a result of these complex biological interactions and mechanisms.

The present study has several limitations. First, this is a small sample study, and the included population from Suining Central Hospital, Sichuan Province, China, generalizing the conclusion to all AMIS patients may be limited and insufficient. Second, patients with severe cardiopulmonary disease were excluded, perhaps reducing the prevalence of cognitive impairment. Third, approximately 35 % of patients are over 74 years old; the population is probably affected by neurodegenerative conditions that affect cognition, which may bias the incidence of cognitive impairment. Fourth, we did not collect data on some variables that may affect UA levels, such as antihypertensive drugs and hypoglycemic drugs. Finally. UA probably increases in the acute phase of cerebrovascular and cardiovascular diseases [35,36], while serum UA levels were measured only once alone, and cognitive function was also assessed only once after 3 months, which may have some influence on the results. Therefore, the association between the two may be further confirmed by dynamic monitoring of serum UA levels and cognitive function following stroke.

5. Conclusion

Our study initially demonstrated that higher serum UA levels are linked to more severe cognitive impairment in patients with AMIS. The higher level of serum UA at a cut-off point of 363.58 μmol/L, revealed good sensitivity to predict the occurrence of cognitive impairment after AMIS.

Author contribution statement

Lei Xu, Ming Yu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Qing-rong Ouyang: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Qin Xiong: Performed the experiments; Analyzed and interpreted the data. Lu-wen Huang: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

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Ethics approval and consent to participate

The need for informed consent was waived by the ethics committee of Suining Central Hospital, because of the retrospective nature of the study. All protocols were approved by the Suining Central Hospital ethics committee and were conducted in accordance with their regulations and guidelines.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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