Increased serum uric acid level is associated with better outcome after endovascular treatment for acute ischemic stroke—a prospective cohort study

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Background: The role of serum uric acid (SUA) in affecting outcomes after endovascular treatment (EVT) in patients with ischemic stroke remains unclear. This study investigated the association of SUA with outcomes of patients with acute large vessel occlusion (LVO) who had received EVT.

Methods: Patients with acute LVO stroke who underwent EVT within 24 hours were enrolled from a prospective, nationwide registry study. Baseline characteristics and SUA level within 24 hours of EVT were collected. The primary outcome was an excellent 90-day functional outcome [modified Rankin Scale (mRS) score 0–1]. Secondary outcomes included a favorable 90-day outcome (mRS score 0–2), symptomatic intracranial hemorrhage (sICH), and 90-day mortality. The SUA level was analyzed in quartiles and as a continuous variable. We investigated the independent association of SUA with the primary outcome using multivariable logistic regression.

Results: Among 780 patients (mean age 64 years; 66.28% males), 230 (29.49%) had an excellent 90-day outcome. A higher SUA level was significantly associated with an excellent outcome in univariate logistic regression (P=0.045) and after adjusting for confounders in multivariate analysis [adjusted odds ratio (aOR), 0.998; 95% confidence interval (CI), 0.996–1.000; P=0.018]. Multivariate logistic regression analysis showed patients with SUA level in the fourth quartile had an excellent 90-day outcome (aOR, 0.367; 95% CI, 0.154–0.876; P=0.024). There was no significant association for SUA level with favorable 90-day outcome, sICH, or 90-day mortality (P>0.05).

Conclusions: Among patients with acute LVO type of stroke who received EVT, baseline high SUA level may predict a better 90-day functional outcome.

Keywords: Serum uric acid (SUA); ischemic stroke; endovascular treatment (EVT); outcome

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Submitted Aug 19, 2022. Accepted for publication Oct 10, 2022.
doi: 10.21037/atm-22-4494
View this article at: https://dx.doi.org/10.21037/atm-22-4494

Introduction

Endovascular treatment (EVT) is effective for patients with an acute ischemic stroke (AIS) from a large vessel occlusion (LVO) (1-3). Although successful recanalization leads to the restoration of cerebral circulation, these patients may still have a poor functional outcome (4,5), which might be related with advanced age, higher baseline National Institutes of Health Stroke Scale (NIHSS) (6) score, delayed puncture to reperfusion, and the use of general anesthesia (7). Cerebral ischemia-reperfusion injury may be partly responsible for this undesirable result. Reperfusion injury after revascularization may be related to the inflammatory process with the release of free radicals once the occluded artery is re-opened (8).

Serum uric acid (SUA) is an end-product of the metabolism of purines and is an important endogenous free radical scavenger (9). While in the process of SUA production, reactive oxygen species are generated, increasing oxidative stress (10) and exerting proinflammatory effects such as the stimulation of some cytokines (11). The benefit of SUA against the risk of stroke and other cardiovascular events is unclear from epidemiological studies (12-14). Two meta-analyses indicated that hyperuricemia could modestly increase the risk of both stroke and mortality (15,16). Two prospective studies with conflicting results have been published since then (17,18). As higher SUA levels often coexist with other metabolic syndrome risk factors, almost all of the studies point out that elevated SUA level is an independent predictor of stroke in stroke-free people. However, 2 studies have revealed a protective effect of SUA in brain ischemia at the preclinical level (19,20). For instance, SUA reduced the exacerbated oxidative stress in hyperperfused rats after an ischemic stroke (21). However, there is no consensus about the relationship between SUA levels and stroke outcomes in AIS patients (22,23), especially after EVT (24,25). Furthermore, whether there is a dose-response relationship between SUA level and risk of stroke is unknown.

Our study aimed to explore the effect of SUA on functional outcomes at 90 days in LVO-related AIS patients with EVT and identify whether a dose-response correlation exists. We hypothesized that higher baseline SUA level could have a positive effect on functional outcomes at 90 days in these patients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4494/rc).

Methods

Study design and population

The RESCUE-RE (Registration Study for Critical Care of Acute Ischemic Stroke after Recanalization) registry is an ongoing, prospective, observational cohort study involving 18 comprehensive stroke centers across China (Registration number: ChiCTR1900022154). Patients with acute LVO-related AIS who underwent EVT within 24 hours were enrolled and followed up for 90 days (26). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the medical ethics committee of the Beijing Tiantan Hospital, Capital Medical University (No. KY2018-057-01). All participating hospitals/institutions were informed and agreed the study. All patients or their legally authorized representatives provided written informed consent before taking part in the study.

Patients of the current study were screened from the RESCUE-RE registry. Enrollment criteria were: (I) >18 years of age; (II) acute ischemic stroke with LVO; (III) EVT within 24 hours of stroke onset; and (IV) with SUA data recorded within 24 hours of EVT. The following patients were excluded: a premorbid modified Rankin Scale (mRS) (27) score ≥3, diagnosed with malignant tumor, or loss of follow-up at 90 days. Data related to this study are available from the corresponding author upon reasonable request.

Treatment procedures

Intravenous recombinant human tissue-type plasminogen activator (r-tPA) was administered within 4.5 hours of the onset of symptoms when indicated. Mechanical thrombectomy (MT) was conducted with stent retrievers and/or thrombus aspiration, intra-arterial thrombolysis (with r-tPA or urokinase), balloon angioplasty, stent

implantation, or various combinations of these approaches, upon the decision of the treating neurologists/neurointerventionalists.

Clinical data and parameters

Baseline data, including demographic characteristics, history of symptomatic cardiovascular diseases and vascular risk factors, prior medications (especially those that may affect SUA level), characteristics of the index stroke and LVO, treatment procedures and laboratory results, were collected. Neurological deficits were assessed by stroke neurologists using the NIHSS. The location of LVO was identified on computed tomography or magnetic resonance angiography (CTA/MRA) or digital subtraction angiography (DSA). Stroke subtype was classified according to the Trial of ORG 10172 in Acute Stroke Treatment classification (TOAST). Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b/3 (28). Postprocedural blood pressure parameters were measured and recorded every 2 hours for 24 hours after EVT. SUA and serum creatinine levels were measured within 24 hours of EVT using standard laboratory procedures. Estimated glomerular filtration (eGFR) was calculated using the formula adapted from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation on the basis of data from an Asian population (29). For any other relevant laboratory test of interest, the worst result within 48 hours of EVT, if there were multiple measures, was recorded.

Clinical outcomes

Primary outcome was defined as an excellent 90-day outcome by an mRS score of 0 to 1. Secondary outcomes included a favorable 90-day outcome defined by an mRS score of 0 to 2, symptomatic intracranial hemorrhage (sICH) within 24 hours of EVT according to the European Cooperative Acute Stroke Study II (ECASS II) classification (30), and 90-day mortality.

Statistical analysis

Baseline characteristics were described with means and standard deviation (SD) or medians and interquartile range (IQR) for quantitative variables and with numbers and percentage for qualitative variables. χ^2 test or Fisher's exact test was used for univariate analyses of categorical variables. Student *t*-test or Wilcoxon signed-rank test was used for continuous variables.

Significant variables associated with SUA or 90-day mRS according to univariate logistic regression (P value <0.05) were then entered into multivariable logistic regression analysis, respectively, and significant variables from the multivariable logistic regression were included in the adjusted model. In the analysis of factors affecting SUA level, SUA was used as a dependent variable for multiclassification multivariate logistic regression analysis. Multivariable logistic regression was performed to assess whether SUA level was associated with the primary outcome (mRS 0–1 at 90 days), adjusting for potential confounders, including: age, male sex, atrial fibrillation, diabetes mellitus, baseline NIHSS, prior stroke, smoking, drinking, onset to recanalization time, location of LVO, and stroke subtype (factors that have had an impact on 90-day functional outcomes in previous studies); diuretics before stroke onset, triglyceride level, blood urea nitrogen, and eGFR (factors affecting SUA level in the present study); and intravenous r-tPA, white blood cell (WBC), and mTICI 2b/3 (factors affecting 90-day functional outcomes in the current study). Sensitivity analysis was further performed to confirm that SUA level was an important predictor of 90-day functional outcome. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and two-sided P value <0.05 was considered statistically significant.

Results

Baseline characteristics of the population

Overall, 780 patients enrolled in RESCUE-RE between July 2018 and October 2020 were analyzed in the current study (*Figure 1*). The mean age was 64.40±12.14 years, and 66.28% were male (Table S1).

The mean SUA level within 24 hours of EVT was 310.02±96.22 μmol/L (Table S1). Compared with patients in the first quartile, those with SUA level in the fourth quartile were more likely to be male (78.46% *vs.* 51.28%; P<0.001), smokers (41.54% *vs.* 25.64%; P=0.002), drinkers (50.26% *vs.* 33.85%; P=0.007), and on diuretics (6.67% *vs.* 1.54%; P=0.003), and they were more likely to have a history of hypertension (66.67% *vs.* 52.82%; P=0.034), a higher level of triglycerides (1.56±0.96 *vs.* 1.33±1.17 mmol/L; P<0.001), a lower level of high density lipoprotein cholesterol (HDL-C) (1.07±0.29 *vs.* 1.21±0.36 mmol/L; P<0.001), a higher level of blood urea nitrogen (6.85±3.03 *vs.* 4.85±1.65 mmol/L;

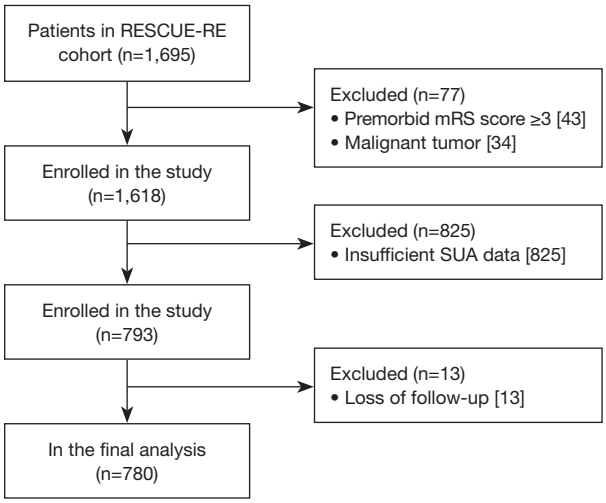

Figure 1 Flowchart of the current study. RESCUE-RE, A Registration Study for Critical Care of Acute Ischemic Stroke after Recanalization; mRS, modified Rankin Scale; SUA, serum uric acid.

P<0.001), and a lower level of eGFR (80.78±27.18 *vs.* 101.39±17.09 mL/min/1.73 m^2; P<0.001) (*Table 1*). *Table 2* lists the factors that affected SUA level, including being male, a smoker, on diuretics before stroke onset, triglyceride level, blood urea nitrogen level, and eGFR.

Association between SUA level in quartiles and the primary outcome

Among the 780 patients, 230 (29.49%) had an excellent 90-day outcome, the primary outcome of our study (Table S1). Patients with an excellent outcome were younger (61.89±12.70 *vs.* 65.45±11.75 years; P<0.001), less likely to have a history of diabetes mellitus (13.91% *vs.* 26.36%; P<0.001), hypertension (52.61% *vs.* 61.45%; P=0.022), or prior stroke (13.91% *vs.* 22.36%; P=0.007), and had a lower baseline NIHSS {12 [8–17] *vs.* 16 [12–22]; P<0.001}. Patients with an excellent outcome more likely had intravenous r-tPA (27.83% *vs.* 17.82%; P=0.002), a higher rate of successful reperfusion (82.17% *vs.* 74.00%; P=0.014), lower maximum systolic blood pressure (SBP) within 24 hours of EVT (144.16±21.09 *vs.* 150.53±26.30 mmHg; P<0.001), lower WBC [(9.80±5.13 *vs.* 11.14±3.73)×10^9/L; P<0.001], lower fasting blood glucose (6.69±2.44 *vs.* 8.07±3.13 mmol/L; P<0.001), and a higher level of SUA (320.72±97.59 *vs.* 305.54±95.37 μmol/L; P=0.049) (Table S1).

Patients with an SUA level in the fourth quartile were less likely to achieve poor 90-day functional outcome compared with those in the first quartile in univariate logistic regression [66.67% *vs.* 76.92%; odds ratio (OR), 0.600; 95% confidence interval (CI), 0.384–0.938; P=0.025]. However, the rates of poor outcome were similar in patients with an SUA level in the first (76.92%), second (68.21%), and third (70.26%) quartiles (*Table 3*). In multivariate logistic regression, SUA level in the fourth quartile was independently associated with a lower risk of achieving poor outcome after adjusting for potential confounders in 3 models [adjusted odds ratio (aOR) in Model 3, 0.367; 95% CI, 0.154–0.876; P=0.024] (*Table 3*). This result was verified by sensitivity analysis (aOR, 0.354; 95% CI, 0.137–0.912; P=0.032) (Table S2).

Association between SUA level as a continuous variable and the primary outcome

The SUA level, when analyzed as a continuous variable, was also associated with the primary outcome in univariate logistic regression (Tables S1,S3). In multivariate logistic regression, SUA level as a continuous variable (aOR, 0.998; 95% CI, 0.996–1.000; P=0.018), history of diabetes mellitus (aOR, 2.009; 95% CI, 1.257–3.209; P=0.004), baseline NIHSS (aOR, 1.090; 95% CI, 1.059–1.121; P<0.001), use of intravenous r-tPA (aOR, 0.631; 95% CI, 0.422–0.945; P=0.026), successful reperfusion (mTICI 2b/3; aOR, 0.565; 95% CI, 0.366–0.871; P=0.010), and WBC level (aOR, 1.071; 95% CI, 1.016–1.129; P=0.011) were independently associated with the primary outcome (Table S3).

Association between SUA level and secondary outcomes

For the secondary outcomes, 328 (42.05%), 47 (6.03%), and 144 (18.46%) patients had a favorable 90-day outcome, sICH, and 90-day death, respectively. There was no significant association for SUA level as a continuous variable with a favorable 90-day outcome, sICH, or 90-day mortality (P>0.05) (Table S4). The same results were obtained when further analyzed in quartiles (P>0.05) (*Table 4* and Table S5).

Discussion

In this prospective, nationwide registry, a higher SUA level within 24 hours of EVT was associated with a higher chance of achieving an excellent 90-day functional outcome in patients with AIS from an LVO, independent of other confounders, and was not significantly associated with favorable 90-day outcome, risk of sICH, and 90-day mortality.

Table 1 Baseline demographic and clinical characteristics according to serum uric acid

Characteristics	Serum uric acid (μmol/L)				P
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Age (years),	63.95±11.30	64.65±11.61	63.52±13.15	65.49±12.41	0.386
Male	100 (51.28)	122 (62.56)	142 (72.82)	153 (78.46)	<0.001*
BMI (kg/m^2)	23.89±3.68	23.89±4.29	24.30±4.63	24.53±5.57	0.518
Risk factors					
Diabetes mellitus	52 (26.67)	39 (20.00)	39 (20.00)	47 (24.10)	0.310
Hypertension	103 (52.82)	109 (55.90)	117 (60.00)	130 (66.67)	0.034*
Coronary heart disease	32 (16.41)	39 (20.00)	31 (15.90)	38 (19.49)	0.628
Lipid metabolism disorders	17 (8.72)	17 (8.72)	24 (12.31)	12 (6.15)	0.205
Smoker	50 (25.64)	76 (38.97)	82 (42.05)	81 (41.54)	0.002*
Using alcohol	66 (33.85)	81 (41.54)	91 (46.67)	98 (50.26)	0.007*
Prior medications					
Aspirin before stroke onset	39 (20.00)	45 (23.08)	39 (20.00)	39 (20.00)	0.840
Diuretics before stroke onset	3 (1.54)	3 (1.54)	3 (1.54)	13 (6.67)	0.003*
Prior statin treatment	10 (5.13)	10 (5.13)	11 (5.64)	7 (3.59)	0.802
Baseline parameters					
Baseline NIHSS	15 [11–20]	15 [12–20]	15 [11–18]	15 [9–21]	0.476
Location of occlusion					0.534
ICA	66 (33.85)	71 (36.41)	57 (29.23)	63 (32.31)	
MCA (M1/M2)	82 (42.05)	83 (42.56)	93 (47.69)	89 (45.64)	
ACA	0 (0)	2 (1.03)	3 (1.54)	2 (1.03)	
VA	30 (15.38)	17 (8.72)	19 (9.74)	20 (10.26)	
BA	17 (8.72)	22 (11.28)	23 (11.79)	21 (10.77)	
Stroke subtype					0.064
Large-artery atherosclerosis	118 (60.51)	124 (63.59)	122 (62.56)	113 (57.95)	
Cardioembolic	61 (31.28)	62 (31.79)	57 (29.23)	77 (39.49)	
Others	16 (8.21)	9 (4.62)	16 (8.21)	5 (2.56)	
Procedure process					
Onset to recanalization (min)	432 [230–705]	450 [225–649]	410 [255–600]	430 [305–590]	0.694
Laboratory data					
Fasting blood glucose (mmol/L)	7.98±2.99	7.24±2.74	8.00±3.38	7.61±2.92	0.062
Triglycerides (mmol/L)	1.33±1.17	1.30±0.89	1.19±0.70	1.56±0.96	<0.001*
Total cholesterol (mmol/L)	4.16±1.15	4.23±0.96	4.13±1.05	4.27±1.17	0.727
HDL-C (mmol/L)	1.21±0.36	1.18±0.31	1.13±0.27	1.07±0.29	<0.001*
LDL-C (mmol/L)	2.50±0.96	2.59±0.82	2.55±0.89	2.73±0.98	0.124

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Serum uric acid (μmol/L)				P
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Serum albumin (g/L)	37.86±5.67	38.41±5.20	38.80±5.84	38.08±6.27	0.283
Blood urea nitrogen (mmol/L)	4.85±1.65	5.11±1.56	5.53±2.17	6.85±3.03	<0.001*
eGFR (mL/min/1.73 m^2)	101.39±17.09	97.92 ±18.54	94.78±21.29	80.78±27.18	<0.001*

The data are expressed as mean ± SD or n (%) or median [IQR]. Quartile 1: <245.85; Quartile 2: 245.85–297.45; Quartile 3: 297.45–364.95; Quartile 4: ≥364.95. *, P<0.05. SD, standard deviation; BMI, body mass index; NIHSS, National Institute of Health stroke scale; IQR, interquartile range; ICA, internal carotid artery; MCA (M1/M2), middle cerebral artery (the first/second segment of MCA); ACA, anterior cerebral artery; VA, vertebral artery; BA, basilar artery; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 2 Multivariate analysis of the factors that affect SUA level

Variable	SUA (μmol/L)							
	Quartile 1	Quartile 2		Quartile 3		Quartile 4	
		aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
Male	Reference	0.671 (0.378–1.191)	0.173	0.333 (0.185–0.600)	<0.001*	0.151 (0.076–0.297)	<0.001*
Hypertension	Reference	1.023 (0.669–1.564)	0.916	1.102 (0.710–1.709)	0.665	0.933 (0.571–1.523)	0.780
Smoker	Reference	2.012 (1.158–3.494)	0.013*	1.831 (1.062–3.160)	0.030*	1.999 (1.117–3.579)	0.020
Using alcohol	Reference	0.901 (0.511–1.588)	0.718	0.921 (0.527–1.610)	0.774	1.031 (0.570–1.865)	0.919
Diuretics before stroke onset	Reference	0.749 (0.121–4.651)	0.756	1.159 (0.217–6.203)	0.863	4.780 (1.084–21.084)	0.039*
Triglyceride	Reference	0.912 (0.730–1.140)	0.418	0.709 (0.539–0.932)	0.014*	1.126 (0.906–1.399)	0.286
HDL-C	Reference	0.872 (0.455–1.669)	0.679	0.561 (0.278–1.128)	0.105	0.466 (0.207–1.046)	0.064
Blood urea nitrogen	Reference	1.020 (0.887–1.172)	0.783	1.098 (0.957–1.258)	0.182	1.262 (1.095–1.455)	0.001*
eGFR	Reference	0.982 (0.969–0.996)	0.010*	0.975 (0.962–0.988)	<0.001*	0.950 (0.937–0.964)	<0.001*

Quartile 1: <245.85; Quartile 2: 245.85–297.45; Quartile 3: 297.45–364.95; Quartile 4: ≥364.95. *, based on multivariate regression analysis. SUA, serum uric acid; aOR, adjusted odds ratio; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 3 Multivariate analysis between SUA and 90-day functional outcome

SUA (μmol/L)	mRS 2–6, n (%)	Unadjusted model		Model 1		Model 2		Model 3	
		OR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Quartile 1	150 (76.92)	Reference		Reference		Reference		Reference	
Quartile 2	133 (68.21)	0.644 (0.411–1.009)	0.055	0.621 (0.382–1.008)	0.054	0.675 (0.311–1.462)	0.319	0.624 (0.285–1.365)	0.238
Quartile 3	137 (70.26)	0.709 (0.451–1.115)	0.136	0.754 (0.461–1.233)	0.260	1.000 (0.449–2.231)	0.999	0.905 (0.405–2.021)	0.807
Quartile 4	130 (66.67)	0.600 (0.384–0.938)	0.025	0.567 (0.345–0.933)	0.026	0.364 (0.154–0.858)	0.021	0.367 (0.154–0.876)	0.024

Quartile 1: <245.85; Quartile 2: 245.85–297.45; Quartile 3: 297.45–364.95; Quartile 4: ≥364.95. Model 1, adjusted for age, male, atrial fibrillation, diabetes mellitus, baseline NIHSS, prior stroke, smoker, using alcohol, onset to recanalization, location of occlusion, and stroke subtype. Model 2, Model 1 + diuretics before stroke onset, triglyceride level, blood urea nitrogen, and eGFR (significant variables from Table 2). Model 3, Model 2 + intravenous r-tPA, mTICI 2b/3, and WBC (significant variables from Table S3). SUA, serum uric acid; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; NIHSS, National Institute of Health stroke scale; eGFR, estimated glomerular filtration rate; r-tPA, recombinant human tissue-type plasminogen activator; mTICI, modified thrombolysis in cerebral infarction score; WBC, white blood cell.

Table 4 Association between different serum uric acid levels and outcomes

Characteristics	Serum uric acid (μmol/L)				P value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Primary outcome, n (%)					
90-day mRS 0–1	45 (23.08)	62 (31.79)	58 (29.74)	65 (33.33)	0.125
Secondary outcomes, n (%)					
90-day mRS 0–2	75 (38.46)	88 (45.13)	81 (41.54)	84 (43.08)	0.595
sICH	14 (7.18)	9 (4.62)	15 (7.69)	9 (4.62)	0.426
90-day mortality	29 (14.87)	34 (17.44)	40 (20.51)	41 (21.03)	0.362

Quartile 1: <245.85; Quartile 2: 245.85–297.45; Quartile 3: 297.45–364.95; Quartile 4: ≥364.95. mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage.

The central nervous system is highly vulnerable to oxidative damage because of its high oxygen consumption, high concentrations of peroxidizable lipids, low levels of protective antioxidants, and high levels of iron acting as pro-oxidants under pathological conditions (31). Oxidative stress begins early after stroke onset and increases sharply and rapidly after recanalization (32). Reactive oxygen/nitrogen species (ROS/RNS) generated by pericytes are highly expressed after ischemia and reperfusion, leading to structural and functional alterations in the microvasculature. This process may partially offset or outweigh the benefit of recanalization/reperfusion (33), which may be a major mechanism in futile reperfusion (34). Uric acid could ameliorate secondary hypoperfusion after reperfusion by blocking the generation of free radicals in the vessel wall in the brain and inducing passive lumen expansion (10). In the current study, LVO-related AIS patients with higher SUA level within 24 hours of EVT were less likely to have a poor 90-day outcome (OR, 0.600; 95% CI, 0.384–0.938; P=0.025). This relationship was independent of confounding factors associated with 90-day mRS and SUA (aOR in Model 3, 0.367; 95% CI, 0.154–0.876; P=0.024) (*Table 3*).

Two previous studies on the relationship between SUA and functional prognosis after reperfusion therapy in stroke had smaller sample sizes. Moreover, these 2 studies only enrolled patients with LVO-related AIS in the anterior circulation (24), or those who received intravenous thrombolysis (25). The time of onset to recanalization or mTICI were not adjusted in multivariate analyses (25). Discrepancies between the findings of previous studies and the current study may have been due to differences in patients' age, sex, race, time when SUA was measured, heterogeneity of stroke subtypes, means of intervention, and outcome measures. Although SUA level is easily affected by diet (9), medications (35), renal function and metabolic syndrome (36), and dynamic after stroke (37), the current study indicated that SUA level in the acute stage predicted the 90-day outcome, which was confirmed by sensitivity analysis. This was likely due to the neuronal protection from reducing the exacerbated oxidative stress after recanalization in LVO-related AIS patients with EVT. The current study minimized possible interference through rigorous screening of SUA, a relatively large sample size, and correction of factors affecting SUA level.

In the phase 2b/3 URICO-ICTUS trial, the safety of adding uric acid to alteplase treatment was confirmed (38). In post-hoc analysis of the URICO-ICTUS data, uric acid was associated with reduced infarct growth in patients with early recanalization (39) and a reduced rate of early ischemic progression in patients with good pretreatment collaterals (40) but not in those with delayed or no recanalization (38). These observations suggested that the benefit of uric acid as a neuroprotective agent might be relatively more prominent in circumstances of higher oxidative stress, such as in those with early reperfusion (41). A previous study has considered hyperuricemia as a risk factor for stroke through several potential pathophysiological mechanisms, such as enhancing lipid peroxidation and causing vascular inflammation (42). The balance between the antioxidant and pro-oxidant effects of SUA may shift in favor of tissue protection in conditions of extraordinary oxidative stress (43). A recent study indicated that the hyperactive microglia in ischemic penumbra might play a key role in post-stroke inflammation, while uric acid could alleviate the ischemia-reperfusion injury by suppressing the excessive activation of microglia (44).

All patients enrolled in this study were treated with EVT, which could supply oxygen to the ischemic area rapidly when blood flow was re-established through early and rapid recanalization, accelerating the oxidative damage. In our study, the potential protective effect for the 90-day functional outcome was only found for SUA in the highest quartile (*Table 3*), indicating that only a certain level of SUA could offset the damage caused by oxidative stress. The same result was derived by sensitivity analysis (Table S2), providing evidence for treatment with exogenous uric acid as an antioxidant agent after EVT and thereby, a potentially beneficial neuroprotective strategy.

The current study had a number of limitations. First, although most factors affecting level of SUA were analyzed, information about the history of gout and dietary structure was absent. Second, the proportion of favorable 90-day outcome was modestly higher in the fourth quartile than in the first, but there was no statistical significance. This may have been related to the relatively weak effect of SUA and relatively small sample size. Third, as there was only one measure of SUA, we failed to observe the effect of changes in SUA level on 90-day functional outcomes.

Conclusions

In summary, higher SUA level within 24 hours of EVT in AIS was associated with a higher chance of an excellent 90-day functional outcome. The possible beneficial effect of SUA in such patients warrants further investigation in prospective studies or therapeutic trials.

Acknowledgments

We thank all the participants and investigators who took part in the RESCUE-RE study (Registration Study for Critical Care of Acute Ischemic Stroke After Recanalization).

Funding: This research was supported by the National Key R&D Program of China (grant Nos. 2016YFC1307301, 2018YFC1312402), the National Natural Science Foundation of China (grant No. 81820108012), Medical Science Research Project of Hebei Province (grant No. 20211242) and partially supported by Boehringer-Ingelheim China.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4494/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4494/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4494/coif). All authors report that this research was supported by the National Key R&D Program of China (grant Nos. 2016YFC1307301, 2018YFC1312402), the National Natural Science Foundation of China (grant No. 81820108012), Medical Science Research Project of Hebei Province (grant No. 20211242) and partially supported by Boehringer-Ingelheim China. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the Beijing Tiantan Hospital, Capital Medical University (No. KY2018-057-01). All participating hospitals/institutions were informed and agreed the study. Informed consent was obtained from all subjects involved in the study.

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Cite this article as: Bai H, Nie X, Leng X, Wang D, Pan Y, Yan H, Yang Z, Wen M, Pu Y, Zhang Z, Duan W, Ma N, Miao Z, Liu X, Lu Q, Wei Y, Liu L, Liu J. Increased serum uric acid level is associated with better outcome after endovascular treatment for acute ischemic stroke—a prospective cohort study. Ann Transl Med 2022;10(20):1111. doi: 10.21037/atm-22-4494

