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ORIGINAL RESEARCH

Serum Uric Acid to Serum Creatinine Ratio and Risk of Stroke Recurrence in Young Adults with Ischemic Stroke

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Background and Aim: Serum uric acid to serum creatinine ratio (SUA/SCr) is associated with metabolic and cardiovascular diseases. We aimed to investigate the association between SUA/SCr and stroke recurrence among young adults with ischemic stroke.

Methods: A total of 428 young patients with ischemic stroke were included in the present study. SUA/SCr was calculated from the concentration of serum uric acid and creatine (uric acid/creatine). Cox proportional regression models were performed to evaluate the association between SUA/SCr and stroke recurrence. Kaplan–Meier curves were used to compare recurrence rates in different quantiles of SUA/SCr.

Results: During a median follow-up of 3.14 years, 51 (10.7%) patients had stroke recurrence. Multivariable analyses indicated that SUA/SCr was associated with stroke recurrence after being adjusted for potential confounders (quantile four versus quantile one: hazard ratio: 3.420; 95% confidence interval: 1.426–8.200; $P = 0.006$). Kaplan–Meier curves revealed that patients with a high concentration of SUA/SCr had an increased stroke recurrence risk. The time-dependent receiver operating characteristic curve showed that the area under the curve for SUA/SCr was above 0.7 during follow-up. Restricted cubic spline presented an increasing trend for the link between SUA/SCr and stroke recurrence among young adults.

Conclusion: SUA/SCr was positively associated with the risk of stroke recurrence among young adults with ischemic stroke. Further prospective studies are warranted to assess the causality between SUA/SCr and the development of stroke recurrence among young adults.

Keywords: ischemic stroke, recurrence, young adults, uric acid

Introduction

Ischemic stroke is a leading cause of disability and mortality worldwide.[1] The incidence of ischemic stroke has been increasing among young adults in recent years.[2] Previous studies reported that approximately 10% to 15% of the patients with ischemic stroke were young adults.[3] With a long life expectancy, ischemic stroke in young adults usually damages the quality of life and causes poor outcomes.[4] Approximately 11% of the patients will experience recurrence after the index stroke within 1 year,[5] which will cause more devastating consequences and increase the risk of mortality, disability, and retirement.[6] Despite the advancement in secondary strategies for ischemic stroke, young patients with ischemic stroke are still at an increased risk of recurrent events.[7] Due to different risk factors and stroke etiologies from older patients, there were limited data regarding the prognosis and prediction factors.[8]

Uric acid, the end product of purine metabolism, is a modifiable risk factor for cardiovascular and renal diseases.[9] Prior studies indicated that uric acid was associated with poor outcomes in patients with ischemic stroke.[10] However, researchers also reported that uric acid was protective in the process of oxidative stress and neuronal metabolism.[11] Depending on the renal clearance, the concentration of uric acid could be influenced by the renal dysfunction.[12] Previous studies often ignored the impact of renal function regarding the role of uric acid.[13] Renal function-normalized uric acid

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(serum uric acid to serum creatine ratio [SUA/SCr]) has been suggested to be a superior indicator of uric acid. Recent studies found that SUA/SCr was associated with metabolic and cardiovascular diseases.[14] However, few studies have explored the potential role of SUA/SCr among young patients with ischemic stroke.

Hence, we aimed to investigate the association between SUA/SCr and stroke recurrence in young patients with first-ever ischemic stroke.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Consecutive patients with ischemic stroke at People's Hospital of Liyang from January 1, 2013 to June 1, 2015 were retrospectively enrolled. All procedures in this study were performed in accordance with the ethical standards of the 1964 Helsinki declaration and its amendments or comparable ethical standards in People's Hospital of Liyang. Patient's consent was waived due to the retrospective design of the study. Patients' data confidentialities were maintained in People's Hospital of Liyang. This study was approved by the ethics review board of People's Hospital of Liyang.

Patients were included if they 1) were aged between 18 and 49 years,[15] 2) were diagnosed with first-ever ischemic stroke within 14 days, () had brain computed tomography or magnetic resonance imaging examinations before admission or during hospitalization, 4) had follow-up records at least 6 months after the index stroke or deceased before then. Patients were excluded if they 1) had missing serum uric acid and creatine values and 2) had a recurrent stroke within 21 days after the index stroke.[16]

Clinical Data

Demographic, stroke risk factors, laboratory data, and radical images were collected in the study. Stroke etiology was classified according to the trial of ORG 10172 in Acute Stroke Treatment classification criterion.[17] Stroke severity was assessed by the National Institute of Health Stroke Scale score (NIHSS).[18] Smoking status was classified as nonsmokers, former smokers, and current smokers.[19] Social-economic status was collected with face-to-face questionnaires, such as annual family income (1 USD = 6.68 RMB) and educational years. Medication information at discharge was collected. Fasting blood samples were collected in the morning within 24 hours after admission. Estimated glomerular filtration (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. Chronic kidney disease (CKD) was classified according to Kidney Disease Outcomes Quality Initiative guidelines. Serum uric acid and creatine were measured using a Hitachi 7060 automated analyzer (Hitachi Koki Co. Ltd., Hitachinaka City, Japan). SUA/SCr was calculated from the concentration of serum uric acid and creatine (uric acid/creatine).[20]

Assessment of the Endpoint

The endpoint of the study was stroke recurrence during follow-up (3 months, 6 months and then annually) after the index stroke. Stroke recurrence was defined as a new deficit or a deterioration of the previous deficit which met the criterion of ischemic or hemorrhagic stroke using clinical evidence, imaginal examinations or other available data during each follow-up.[21]

Statistical Analysis

Continuous variables presented as mean ± SD or median (interquartile range) were compared with *t*-test or Mann–Whitney *U*-test as appropriate. Categorical variables presented as n (%) were compared with Fisher's exact test or χ^2 test as appropriate. We used the multiple imputation method with chain equations to deal with missing values.

The association between baseline characteristics and stroke recurrence was evaluated with Cox proportional hazard models. The proportional assumption was confirmed with the scaled Schoenfeld residuals. Kaplan–Meier curves were used to compare recurrence rates in different quantiles of SUA/SCr with long-rank tests.[22] Multivariable analyses adjusted for different covariates were used to explore the association between SUA/SCr and stroke recurrence. Model 1 was adjusted for age and sex. Model 2 was further adjusted for blood pressure, hypertension, diabetes mellitus, atrial

fibrillation, dyslipidemia, coronary heart disease, smoking status, drinking, white blood cell, neutrophil counts, lymphocyte counts, C-reactive protein, onset to laboratory data, antiplatelet drugs, anticoagulants, statins, antihypertensive drugs and hypoglycemic agents. Model 3 was adjusted for variables with P value <0.1 in univariate analyses with the backward selection method. Additionally, we explored the association between uric acid and the risk of stroke recurrence after adjustment for eGFR and performed the subgroup analysis according to the stages of CKD.

The discrimination ability of SUA/SCr for stroke recurrence was assessed with the time-dependent receiver operating characteristic curve adjusted for the variables included in model 3.[23] The shape of the association between SUA/SCr and stroke recurrence was examined with restricted cubic spline with four knots (at 5th, 35th, 65th, and 95th percentiles) adjusted for the variables included in model 3.[24] Besides, we used the net reclassification index (NRI) to evaluate the additional performance after adding SUA/SCr into model 3 using continuous, categorical, and inverse probability weighting methods.[25,26]

All statistical tests were conducted with R statistical software version 4.1.0. (R Foundation, Vienna, Austria) and a two-sided P value <0.05 was considered to be statistically significant.

Results

A total of 428 young patients with first-ever ischemic stroke (median age: 44 years; 77.8% male) were included in this study. We excluded 31 patients due to missing values of uric acid and creatine, and 24 patients without follow-up information or who had recurrent stroke within 21 days after the index stroke (Supplementary Figure 1). During a median follow-up of 3.14 years, 51 (10.7%) patients had stroke recurrence. Compared with patients without stroke recurrence, patients with stroke recurrence had a higher proportion of hypertension ($P = 0.043$), diabetes mellitus ($P = 0.001$), large-artery atherosclerosis stroke subtype ($P = 0.016$), and hypoglycemic agents ($P = 0.002$), a lower proportion of antiplatelet drugs usage at discharge ($P = 0.033$), a higher concentration of fasting blood glucose ($P = 0.004$), SUA/SCr ($P = 0.017$), and eGFR ($P = 0.027$), and a lower concentration of serum creatine ($P = 0.044$, Table 1). Patients with a high concentration of SUA/SCr had higher body mass index and eGFR, higher proportions of atrial fibrillation and stains usage at discharge, lower NIHSS scores, and different concentrations of lipid profiles (Supplementary Table 1).

Table 1 Baseline Characteristics of Patients with or without Recurrence

Characteristics	Without Recurrence (N = 377)	Recurrence (N = 51)	*P* value
Age, years	44 [40, 47]	44 [40, 47]	0.856
Male, n (%)	295 (78.2)	38 (74.5)	0.672
BMI (kg/m^2)	25.0 [23.1, 27.1]	25.4 [23.3, 27.5]	0.425
SBP (mmHg)	142 [130, 159]	145 [138, 160]	0.072
DBP (mmHg)	83 [76, 91]	87 [80, 91]	0.185
Hypertension, n (%)	221 (58.6)	38 (74.5)	0.043
Diabetes mellitus, n (%)	58 (15.4)	18 (35.3)	0.001
Atrial fibrillation, n (%)	9 (2.4)	2 (3.9)	0.858
Dyslipidemia, n (%)	264 (70.0)	40 (78.4)	0.281
Coronary heart disease, n (%)	7 (1.9)	2 (3.9)	0.657
Smoking, n (%)			0.076
Nonsmokers	149 (39.5)	13 (25.5)	
Former smokers	17 (4.5)	1 (2.0)	
Current smokers	211 (56.0)	37 (72.5)	
Drinking, n (%)	113 (30.0)	19 (37.3)	0.371
NIHSS, score	2 [0, 6]	3 [1, 8]	0.101
Onset to laboratory data, days	4.0 [2.0, 8.0]	4.0 [2.5, 8.0]	0.988
Laboratory data			
White blood cell (10^9/L)	7.6 [6.1, 9.2]	7.8 [6.2, 9.7]	0.660
Neutrophil counts (10^9/L)	4.8 [3.6, 6.5]	5.1 [3.6, 8.0]	0.536

(*Continued*)

Table 1 (Continued).

Characteristics	Without Recurrence (N = 377)	Recurrence (N = 51)	*P* value
Lymphocyte counts (10^9/L)	1.8 [1.4, 2.2]	1.7 [1.2, 2.2]	0.169
C-reactive protein (mg/L)	2.0 [0.5, 4.7]	1.7 [0.5, 4.7]	0.599
Total cholesterol (mmol/L)	3.8 [3.3, 4.5]	3.9 [3.2, 4.5]	0.997
Triglyceride (mmol/L)	1.4 [1.0, 1.9]	1.4 [1.0, 1.8]	0.930
High density lipoprotein (mmol/L)	1.0 [0.8, 1.2]	1.0 [0.8, 1.2]	0.555
Low density lipoprotein (mmol/L)	2.2 [1.7, 2.9]	2.4 [1.7, 3.0]	0.695
Fasting blood glucose (mmol/L)	4.8 [4.5, 5.4]	5.1 [4.7, 6.6]	0.004
Uric acid (μmol/L)	306 [247, 371]	308 [256.5, 362]	0.716
Creatine (μmol/L)	64 [55, 75]	59 [50.5, 72]	0.044
eGFR (mL/min/1.73 m^2)	112.1 [104.7, 118.8]	117.1 [106.1, 123.1]	0.027
SUA/SCr	4.7 [3.8, 5.6]	5.2 [4.3, 6.5]	0.017
TOAST, n (%)			0.016
Large-artery atherosclerosis	101 (26.8)	25 (49.0)	
Cardio-embolism	16 (4.2)	3 (5.9)	
Small-vessel disease	74 (19.6)	7 (13.7)	
Stroke of other determined source	40 (10.6)	2 (3.9)	
Stroke of undetermined source	146 (38.7)	14 (27.5)	
Education years, n (%)			0.108
0–6	28 (7.4)	6 (11.8)	
6–9	236 (62.6)	26 (51.0)	
9–12	54 (14.3)	13 (25.5)	
>12	59 (15.6)	6 (11.8)	
Family income, $, n (%)			0.730
1–1497	5 (1.3)	2 (3.9)	
1497–4492	47 (12.5)	7 (13.7)	
4492–7486	134 (35.5)	18 (35.3)	
7486–14,973	121 (32.1)	15 (29.4)	
>14,973	70 (18.6)	9 (17.6)	
Medication at discharge, n (%)			
Antiplatelet drugs	333 (88.3)	39 (76.5)	0.033
Anticoagulants	41 (10.9)	6 (11.8)	1.000
Stains	364 (96.6)	50 (98.0)	0.888
Antihypertensive drugs	284 (75.3)	40 (78.4)	0.756
Hypoglycemic agents	57 (15.1)	17 (33.3)	0.002

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimate glomerular filtration rate; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; SUA/SCr, serum uric acid/serum creatine.

Univariate analyses revealed that hypertension (hazard ratio [HR]: 2.050; 95% confidence interval [CI]: 1.091–3.852; $P = 0.026$), diabetes mellitus (HR: 2.860; 95% CI: 1.609–5.085; $P < 0.001$), SUA/SCr (HR: 1.348; 95% CI: 1.130–1.609; $P = 0.001$), smoking status (Current smokers versus nonsmokers: HR: 1.904; 95% CI: 1.012–3.583; $P = 0.046$), stroke etiology (small-vessel occlusion versus large-artery atherosclerosis: HR: 0.403; 95% CI: 0.174–0.932; $P = 0.034$), hypoglycemic agents (HR: 2.691; 95% CI: 1.502–4.821; $P = 0.001$), and antiplatelet drugs at discharge (HR: 0.509; 95% CI: 0.266–0.974; $P = 0.041$) were associated with stroke recurrence among young patients (Supplementary Table 2). Multivariable analyses indicated that SUA/SCr was associated with stroke recurrence after adjusted for covariates included in model 1 (quantile four versus quantile one: HR: 3.576; 95% CI: 1.501–8.519; $P = 0.004$), model 2 (quantile four versus quantile one: HR: 3.323; 95% CI: 1.258–8.780; $P = 0.007$), and model 3 (quantile four versus quantile one: HR: 3.420; 95% CI: 1.426–8.200; $P = 0.006$; Table 2 and Supplementary Table 3). Patients with higher quantiles of SUA/SCr had higher risks of stroke recurrence in Kaplan–Meier curves (Figure 1). The time-dependent receiver

Table 2 Risk of Recurrence in Young Patients with Ischemic Stroke

SUA/SCr	No. of Events (%)	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value
Quantile 1	7 (13.7)	Reference		Reference		Reference	
Quantile 2	15 (29.4)	2.479 (1.009–6.092)	0.048	3.262 (1.240–8.578)	0.017	2.686 (1.086–6.642)	0.032
Quantile 3	9 (17.6)	1.340 (0.498–3.607)	0.562	1.815 (0.616–5.349)	0.280	1.489 (0.550–4.031)	0.433
Quantile 4	20 (39.2)	3.576 (1.501–8.519)	0.004	3.323 (1.258–8.780)	0.007	3.420 (1.426–8.200)	0.006
Per 1 SD increase	51 (100)	1.562 (1.202–2.030)	0.001	1.435 (1.086–1.896)	0.015	1.520 (1.181–1.955)	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; SUA/SCr, serum uric acid/serum creatine.

operating characteristic curve revealed that the area under the curve for SUA/SCr was greater than 0.7 during the long-term follow-up (Figure 2). The net reclassification index indicated that adding SUA/SCr into model 3 could slightly improve the predictive ability without reaching statistical significance (Supplementary Table 4). Uric acid alone was not significantly associated with stroke recurrence after adjustment for eGFR according to the stages of CKD (Supplementary Table 5). The restricted cubic spline showed an increasing trend for the association between SUA/SCr and stroke recurrence among young adults (*P* for non-linearity = 0.663, Figure 3).

Discussion

In the present study, we found that stroke recurrence occurred in 10.7% of the young adults with ischemic stroke in China, and renal function-normalized uric acid (SUA/SCr) was associated with an increased risk of stroke recurrence. To the best of our knowledge, this was the first study to investigate the relation between SUA/SCr and stroke recurrence in young adults.

The role of uric acid in ischemic stroke remains controversial. Weir et al found that uric acid was associated with poor outcomes and future vascular events in patients with ischemic stroke.[10] Retrospective research suggested that uric acid was related to stroke recurrence in older adults with interaction to inflammatory factors.[27] Packer et al proved that uric acid could increase the production of reactive oxygen species and enhance oxidative stress.[28] However, uric

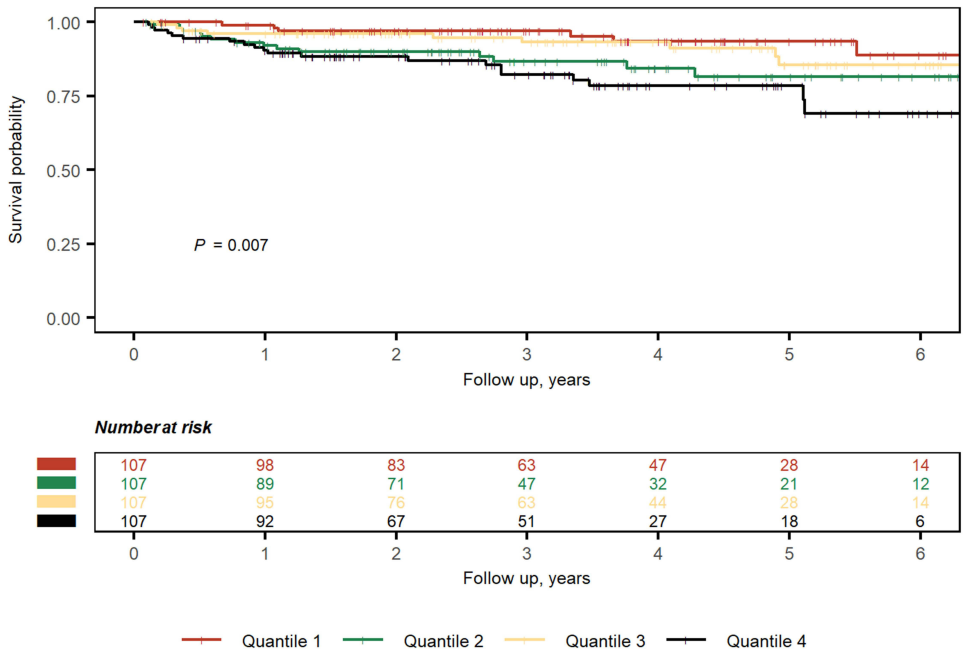

Figure 1 Recurrence probability after ischemic stroke stratified by SUA/SCr.
Abbreviation: SUA/SCr, serum uric acid/serum creatine.

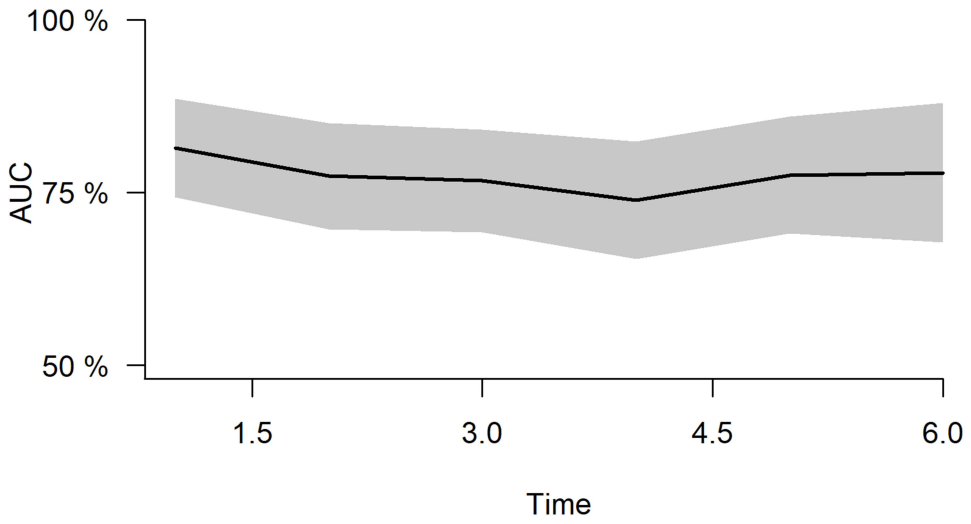

Figure 2 Time-dependent ROC curve for SUA/SCr.
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; SUA/SCr, serum uric acid/serum creatine.

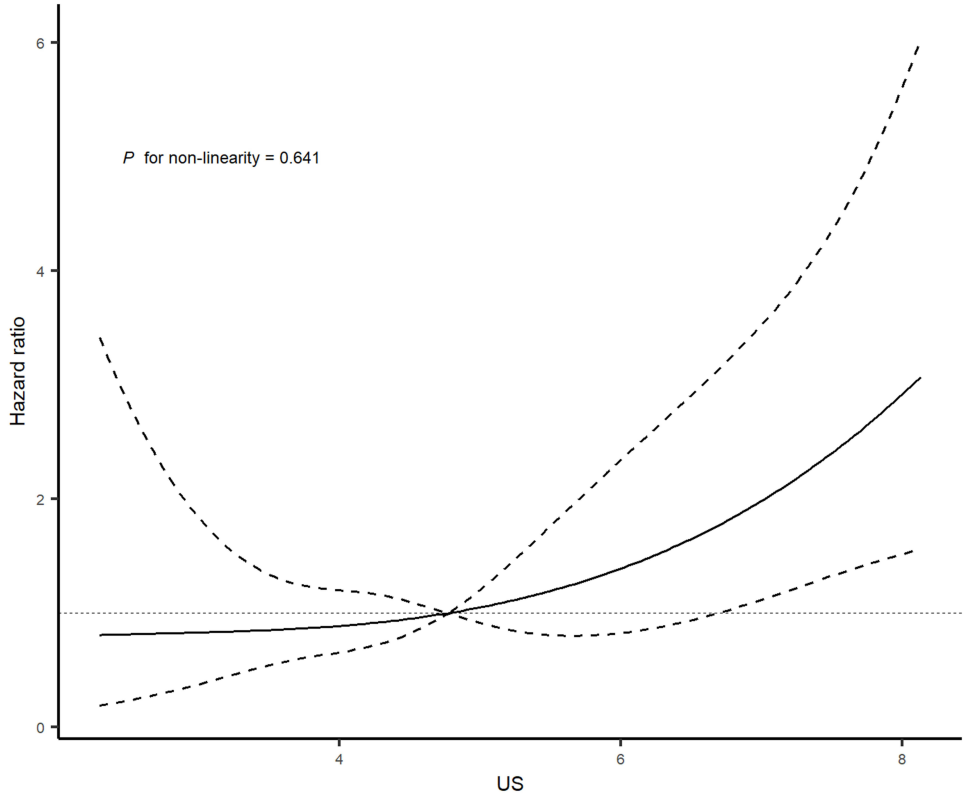

Figure 3 Association between SUA/SCr and risk of stroke recurrence.
Note: Hazard ratio was compared with a median SUA/SCr of 4.77 in model 2.
Abbreviation: SUA/SCr, serum uric acid/serum creatine.

acid was a neuroprotective biomarker. Sun et al found that uric acid had antioxidant activities that could scavenge reactive oxygen species and improve the prognosis of ischemic stroke. Wang et al performed a retrospective study and found that a higher concentration of uric acid was associated with better neurological functions in male patients and large-artery atherosclerosis stroke.[29] Chamorro conducted the URICO-ICTUS trial to assess the combined effect of uric acid and alteplase for patients with acute ischemic stroke. They reported that uric acid therapy could prevent early

ischemic stroke progression,[30] and the additional use of uric acid did not increase the proportion of patients with excellent outcomes.[31] Besides, uric acid could be affected by kidney function in individuals with normal kidney function. Gianni et al found that uric acid was associated with kidney function in healthy normotensive individuals.[32] Nishida et al found that uric acid excretion was significantly related to creatinine in both healthy individuals and patients with gout.[33] In the present study, we found that SUA/SCr SUA/SCr was associated with stroke recurrence instead of uric acid alone, which might be explained by the controversial role of uric acid and its physiological metabolism.

Uric acid, the end product of purine, is excreted through the kidney. The kidney reabsorbs most uric acid in the proximal tubular cells and balances the synthesized and excreted uric acid in human bodies.[34] The relationship between uric acid and renal function indicated that researchers might combine them to explore their roles in diseases. The renal function-normalized uric acid (SUA/SCr) might reflect the net production of uric acid and is a new biomarker for metabolic and cardiovascular diseases.[35] In the Staged Diabetes Targeting Management Study, researchers found that SUA/SCr was positively correlated to β-cell function and insulin resistance in patients with type 2 diabetes.[20] Kawamoto et al found that SUA/SCr was related to the annual estimated glomerular filtration rate decline rate in diabetic patients.[36] Wang et al performed a nationwide study and reported that SUA/SCr was positively associated with cardiovascular disease and partially mediated by metabolic factors.[14] However, studies regarding SUA/SCr and stroke recurrence among young adults were limited.

In our study, the incidence of stroke recurrence among young adults was similar to previous reports. Putaala et al reported that the recurrence rate was 9.4% for young adults with ischemic stroke.[7] Uric acid is also controversial among young adults. Regarding risk factors for ischemic stroke, Krishnan et al performed a 15-year follow-up study to reveal that hyperuricemia was an independent marker of insulin resistance, prediabetes, and diabetes in young adults.[37] Oikonen et al found that uric acid was associated with markers of subclinical atherosclerosis in young adults.[38] Alternatively, Zhang et al found that elevated uric acid was an independent predictor for good outcomes in young Chinese patients with acute ischemic stroke and supported that uric acid may be neuroprotective in the acute phase of young patients.[39] Our study suggested that renal function-normalized uric acid might be more predictive than uric acid among young adults with stroke recurrence in the long term. SUA/SCr might help identify high-risk patients who might benefit from interventions for metabolic diseases like weight control and healthy diets.[40] Physicians should also pay attention to patients with high SUA/SCr values, while uric acid is normal and employs protective strategies such as serum urate-lowering and renal protection therapies.[41]

Additionally, we found that diabetes mellitus, hypertension, antiplatelet drug usage at discharge, and smoking status were associated with stroke recurrence in young adults. Sarecka-Hujar et al conducted a literature review and found that hypertension and diabetes mellitus were more prevalent in young patients with recurrent stroke.[42] Zhao et al performed a retrospective study among young stroke patients with Moyamoya disease and reported that diabetes was an independent risk factor for recurrent stroke.[43] The Italian Project on Stroke in Young Adults suggested that young patients should take secondary preventative medications at discharge routinely, especially antiplatelet drugs.[44] Cigarette consumption could promote atherosclerosis, arterial vasoconstriction and blood pressure elevation and increases the risk of stroke recurrence.[45]

To the best of our knowledge, few studies have investigated the relationship between SUA/SCr and stroke recurrence among young adults. This innovation was a strength of our research. However, several limitations should be addressed in this study. First, this was a single-center database with limited sample size. Second, due to the retrospective nature, we could not provide time-varying changes in SUA/SCr. Repeated measurements of SUA/SCr might be more informative than baseline SUA/SCr. Third, discontinuation of secondary medications might provide additional information on stroke recurrence. Fourth, we could not interpret the metabolic relationship between uric acid and creatine and whether uric acid reduction therapy could reduce stroke recurrence risk due to the retrospective nature of this study.

In conclusion, the results of this study found that SUA/SCr was positively associated with the risk of stroke recurrence among young adults with ischemic stroke. Further prospective studies are warranted to assess the causality between SUA/SCr and the development of stroke recurrence among young adults.

Disclosure

The authors have declared no conflicts of interest with respect to the authorship or publication of this article.

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