Association Between Serum Uric Acid-to-Creatinine Ratio in the Acute Phase of Cerebrovascular Disease and Recurrence of Cerebrovascular Events and Mortality: A Postprint of a Prospective Cohort Study

Authors: Ren Xiaoqiao, Wang Pan, Wu Hao, Ji Yong, Shi Zhihong, Zhihong Shi

Date: 2024-09-09T00:00:00+00:00

Abstract

Background Stroke has high mortality and recurrence rates worldwide. Serum uric acid (SUA) is a product of purine metabolism and has been recognized as a risk factor for cardiovascular and cerebrovascular diseases. The serum uric acid to serum creatinine ratio (SUA/Scr) represents SUA normalized for renal function, and its role in acute cerebrovascular disease remains controversial.

Objective To investigate the relationship between SUA/Scr in the acute phase of cerebrovascular disease and the recurrence of cerebrovascular events and mortality.

Methods This prospective cohort study enrolled consecutive patients with first-ever cerebrovascular events admitted to Tianjin Huanhu Hospital from September 2006 to September 2019, with follow-up until September 2020. Follow-up was conducted through a combination of outpatient visits and telephone calls. The primary endpoint was all-cause mortality, while secondary endpoints included recurrence of cerebrovascular events, recurrence of cardiovascular events, and other vascular events (such as lower extremity arterial or venous thrombosis). Cox proportional hazards regression models were used to explore the relationship between SUA/Scr and cerebrovascular event recurrence and mortality.

Results Based on the quartiles of SUA/Scr in the acute phase of cerebrovascular disease, patients were divided into Q1 group (SUA/Scr $\leq$ 3.16, n=3,520), Q2 group (3.16–4.92, n=3,243). By the end of follow-up, 774 patients (5.8%) had died and 2,064 patients (15.5%) had experienced recurrent cerebrovascular

events. Among patients with SUA/Scr in Q1-Q4 during the acute phase of cerebrovascular disease, the numbers of men with recurrent cerebrovascular disease were 302, 375, 408, and 337, respectively, and the numbers of women were 99, 125, 169, and 249, respectively; the numbers of men with recurrent cerebral infarction were 261, 314, 345, and 283, respectively, and the numbers of women were 90, 101, 142, and 205, respectively; the numbers of men with recurrent large-artery atherosclerotic cerebral infarction were 154, 191, 214, and 183, respectively, and the numbers of women were 58, 52, 45, and 31, respectively; the numbers of men with all-cause mortality were 165, 128, 131, and 88, respectively, and the numbers of women were 57, 63, 62, and 80, respectively; the numbers of men who died from cerebral infarction were 93, 72, 70, and 46, respectively, and the numbers of women were 31, 33, 36, and 44, respectively; the numbers of men who died from large-artery atherosclerotic cerebral infarction were 58, 52, 45, and 31, respectively, and the numbers of women were 29, 37, 42, and 37, respectively. After adjusting for multiple confounding factors, SUA/Scr in Q4 compared with Q1 was an influencing factor for recurrent acute cerebral infarction in men (HR=0.690, 95%CI=0.500-0.953, P=0.026); SUA/Scr in Q4 compared with Q1 was an influencing factor for recurrent large-artery atherosclerotic cerebral infarction in the male cerebral infarction subgroup (HR=0.740, 95%CI=0.578-0.947, P=0.017). SUA/Scr in Q4 compared with Q1 was an influencing factor for all-cause mortality and death from cerebral infarction in men (HR=0.575, 95%CI=0.368-0.901, P=0.003; HR=0.610, 95%CI=0.353-0.814, P=0.011). SUA/Scr in Q3 and Q4 compared with Q1 were influencing factors for post-discharge mortality in men (HR=0.656, 95%CI=0.476-0.904, P=0.010; HR=0.582, 95%CI=0.409-0.829, P=0.001). SUA/Scr in Q4 compared with Q1 was an influencing factor for death from large-artery atherosclerotic cerebral infarction in the male cerebral infarction subgroup (HR=0.580, 95%CI=0.386-0.873, P=0.007).

Conclusion Within a certain range, elevated SUA/Scr in the acute phase of cerebrovascular disease has a protective effect against cerebrovascular event recurrence and mortality in male patients, and low SUA/Scr is associated with increased risk of death and recurrence from large-artery atherosclerotic cerebral infarction, but is not related to the recurrence and mortality of small-artery occlusive cerebral infarction and cardioembolic stroke. No relationship between SUA/Scr and cerebrovascular event recurrence or mortality was observed in female patients.

Full Text

Correlation of Serum Uric Acid to Serum Creatinine Ratio with the Recurrence and Mortality of Cerebrovascular Events in Patients with Acute Cerebrovascular Disease: A Prospective Cohort Study

Ren Xiaoqiao[1], Wang Pan[2], Wu Hao[2], Ji Yong[2], Shi Zhihong[2]*

[1]Clinical College of Neurology, Neurosurgery and Neurorehabilitation, Tianjin Medical University, Tianjin 300070, China
[2]Tianjin Huanhu Hospital, Tianjin University, Tianjin 300350, China

Corresponding author: Shi Zhihong, Associate chief physician; E-mail: shzhh1204@126.com

Abstract

Background: Stroke is characterized by high mortality and recurrence rates worldwide. Serum uric acid (SUA), a product of purine metabolism, has been identified as a risk factor for cardiovascular and cerebrovascular disease. The serum uric acid to serum creatinine ratio (SUA/Scr) represents a renal function-normalized measure of SUA, though its role in acute cerebrovascular disease remains controversial.

Objective: To investigate the association between SUA/Scr during the acute phase of cerebrovascular disease and the recurrence of cerebrovascular events and mortality.

Methods: This prospective cohort study enrolled consecutive patients with first-ever cerebrovascular events admitted to Tianjin Huanhu Hospital from September 2006 to September 2019. Patients were followed up through a combination of outpatient visits and telephone contacts until September 2020. The primary endpoint was all-cause mortality, while secondary endpoints included recurrent cerebrovascular events, recurrent cardiovascular events, and other vascular events (e.g., lower extremity arteriovenous thrombosis). Cox proportional hazard models were used to explore the relationship between SUA/Scr and cerebrovascular event recurrence and mortality.

Results: Based on quartiles of SUA/Scr during the acute phase of cerebrovascular disease, patients were divided into Q1 (SUA/Scr $\leq$ 3.16, n=3,520), Q2 (3.16<SUA/Scr $\leq$ 3.94, n=3,280), Q3 (3.94<SUA/Scr $\leq$ 4.92, n=3,270), and Q4 (SUA/Scr>4.92, n=3,243). By the end of follow-up, 774 patients (5.8%) had died and 2,064 (15.5%) experienced recurrent cerebrovascular events. Among patients in Q1-Q4, the numbers of men with recurrent cerebrovascular disease were 302, 375, 408, and 337, respectively, while the corresponding numbers for women were 99, 125, 169, and 249. For recurrent cerebral infarction, the numbers were 261, 314, 345, and 283 among men, and 90, 101, 142, and 205 among women. For recurrent large-artery atherosclerotic cerebral infarction, the numbers were 154, 191, 214, and 183 among men, and 58, 52, 45, and 31 among women. All-cause mortality among men was 165, 128, 131, and 88 cases in Q1-Q4, respectively, compared to 57, 63, 62, and 80 among women. Mortality due to cerebral infarction among men was 93, 72, 70, and 46 cases in Q1-Q4, respectively, compared to 31, 33, 36, and 44 among women. Mortality due to large-artery atherosclerotic cerebral infarction among men was 58, 52, 45, and 31 cases in Q1-Q4, respectively, compared to 29, 37, 42, and 37 among women.

After adjusting for multiple confounding factors, SUA/Scr in Q4 compared with Q1 was an influencing factor for recurrence of acute cerebral infarction in men (HR=0.690, 95%CI=0.500-0.953, P=0.026). SUA/Scr in Q4 compared with Q1 was also an influencing factor for recurrence of large-artery atherosclerotic cerebral infarction in the male cerebral infarction subgroup (HR=0.740, 95%CI=0.578-0.947, P=0.017). SUA/Scr in Q4 compared with Q1 was an influencing factor for all-cause mortality and death from cerebral infarction in men (HR=0.575, 95%CI=0.368-0.901, P=0.003; HR=0.610, 95%CI=0.353-0.814, P=0.011). SUA/Scr in Q3 and Q4 compared with Q1 were influencing factors for death after discharge in men (HR=0.656, 95%CI=0.476-0.904, P=0.010; HR=0.582, 95%CI=0.409-0.829, P=0.001). SUA/Scr in Q4 compared with Q1 was an influencing factor for death due to large-artery atherosclerotic cerebral infarction in the male cerebral infarction subgroup (HR=0.580, 95%CI=0.386-0.873, P=0.007).

Conclusion: Within a certain range, elevated SUA/Scr during the acute phase of cerebrovascular disease appears to have a protective effect against recurrence and mortality of cerebrovascular events in male patients. Low SUA/Scr is associated with increased risk of death and recurrence in male patients with large-artery atherosclerotic cerebral infarction, but not with recurrence and mortality of small-artery occlusion cerebral infarction or cardiogenic stroke. No association between SUA/Scr and cerebrovascular event recurrence or mortality was observed in female patients.

Keywords: Cerebrovascular disorders; Stroke; Serum uric acid to serum creatinine ratio; Atherosclerosis; Male; Recurrence; Death; Cohort studies; Prospective studies; Cox proportional-hazards model

Introduction

Stroke carries substantial mortality and recurrence rates worldwide. However, traditional risk factors cannot fully explain the recurrence and death associated with acute stroke, and identifying prognostic markers could more effectively prevent cerebrovascular disease and reduce mortality. Serum uric acid (SUA), a product of purine metabolism, has been recognized as a risk factor for cardiovascular and cerebrovascular disease. SUA appears to be closely associated with hypertension, dyslipidemia, and glucose metabolism disorders—all of which play roles in the pathogenesis of acute cerebrovascular disease—suggesting SUA may serve as an indicator of acute cerebrovascular disease risk. However, SUA levels are primarily influenced by renal clearance function, and patients with lower estimated glomerular filtration rates (eGFR) may have elevated SUA levels. In studies linking SUA with stroke, renal function represents an important confounding factor. Therefore, a more accurate predictor of mortality and recurrence in acute cerebrovascular disease is renal function-normalized SUA, which reflects net SUA production. The serum uric acid to serum creatinine ratio

(SUA/Scr) represents such a renal function-normalized measure. Some studies have shown that SUA/Scr is significantly associated with various metabolic diseases and their mortality, though evidence regarding its role in acute cerebrovascular disease remains limited, and the potential pathways linking SUA/Scr with acute cerebrovascular disease have not been fully elucidated. Moreover, previous studies have measured SUA at inconsistent time points, yet measurement timing is critical as SUA concentrations change with lifestyle and dietary modifications. Many patients alter their habits after stroke onset, so measuring SUA during the acute phase of stroke may more accurately predict mortality and recurrence risk. This prospective study of a large stroke population investigates the relationship between SUA/Scr during the acute phase of cerebrovascular disease and the recurrence of cerebrovascular events and associated mortality.

Methods

1.1 Study Population Consecutive patients with first-ever cerebrovascular events admitted to Tianjin Huanhu Hospital from September 2006 to September 2019 were enrolled and followed up. The cohort included 13,313 patients with cerebral infarction (n=11,817), intracerebral hemorrhage (n=805), and transient ischemic attack (n=691). Cranial CT or MRI was performed within 24 hours of admission. According to the TOAST classification, cerebral infarction subtypes included large-artery atherosclerosis (n=7,526), cardioembolism (n=355), small-artery occlusion (n=2,774), other determined causes (n=93), and undetermined causes (n=1,069).

Inclusion criteria: (1) First cerebrovascular event within 48 hours, confirmed by neuroimaging (MRI or CT); (2) Informed consent provided by patients or their families.

Exclusion criteria: (1) Age <18 years; (2) Cerebrovascular disease secondary to trauma, tumor, coagulation disorder, aneurysm, or arteriovenous malformation; (3) Renal failure; (4) Refusal to participate.

1.2 Baseline Investigation and Follow-up 1.2.1 Baseline Data Collection: (1) Basic information: age, sex, smoking, alcohol consumption, and medical history of hypertension, diabetes mellitus, and atrial fibrillation. Definitions: Smoking was defined as >5 cigarettes daily for at least 2 years; alcohol consumption as >10 g weekly for at least 2 years; hypertension as systolic blood pressure >140 mmHg (1 mmHg=0.133 kPa) according to relevant guidelines; type 2 diabetes mellitus according to American Diabetes Association guidelines; and atrial fibrillation according to American Heart Association guidelines. (2) Laboratory parameters: fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A (ApoA), apolipoprotein B (ApoB), SUA, and Scr. The SUA/Scr ratio was calculated. Fasting blood samples were collected from the antecubital vein after 8-12 hours of overnight fasting, placed in serum separator tubes, and centrifuged. TC, TG, FBG, HDL-

C, LDL-C, ApoA, ApoB, Scr, and SUA were measured within 2 hours of blood collection.

1.2.2 Follow-up and Outcome Events: Follow-up continued until September 2020 through a combination of outpatient visits and telephone contacts at 3 months, 6 months, 9 months, 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years after discharge. The primary endpoint was all-cause mortality, while secondary endpoints included recurrent cerebrovascular events, recurrent cardiovascular events, and other vascular events (such as lower extremity arteriovenous thrombosis). All patients underwent MRI or CT examination. Cerebral infarction was diagnosed when neurological deficits persisted for 24 hours with normal CT scan or when MRI showed recent infarction in the relevant brain region. TIA diagnosis followed similar criteria but with symptom duration <24 hours and no evidence of recent infarction on MRI. Intracranial hemorrhage was diagnosed based on CT findings. Cardiovascular events were defined as acute organ dysfunction due to cardiac or vascular disease, including coronary heart disease events and heart failure.

1.3 Statistical Analysis SPSS 25.0 software was used for data analysis. Continuous variables with normal distribution were expressed as mean±standard deviation, compared between two groups using independent t-tests, among multiple groups using one-way ANOVA, and between-group pairwise comparisons used LSD-t tests. Continuous variables with non-normal distribution were expressed as median (P25, P75) and compared using rank-sum tests. Categorical data were expressed as percentages and compared using ^{2} tests. Multivariate Cox proportional hazard regression models were used to investigate factors influencing mortality and recurrence in acute cerebrovascular disease, with hazard ratios (HR) and 95% confidence intervals (CI) reported. P<0.05 was considered statistically significant.

Results

2.1 Baseline Characteristics This study was approved by the Tianjin Huanhu Hospital Ethics Committee (2023-082). A total of 13,313 eligible patients were included, comprising 9,284 men (69.7%) and 4,029 women (30.3%) with a median age of 61 (54, 69) years. Diabetes mellitus was present in 3,215 patients (24.1%), hypertension in 8,271 (62.1%), atrial fibrillation in 623 (4.7%), alcohol consumption in 2,182 (16.4%), and smoking in 4,955 (37.2%). Median laboratory values were: LDL-C 2.86 (2.33, 3.41) mmol/L, HDL-C 1.07 (0.91, 1.26) mmol/L, TG 1.40 (1.03, 1.95) mmol/L, TC 4.91 (4.24, 5.63) mmol/L, ApoA 1.16 (1.03, 1.31) g/L, ApoB 1.00 (0.82, 1.08) g/L, FBG 5.60 (4.90, 7.12) mmol/L, Scr 72.18 (60.00, 86.00) mol/L, and SUA 285.10 (234.00, 345.00) mol/L.

Based on acute-phase SUA/Scr quartiles, patients were divided into Q1 (SUA/Scr $\leq$ 3.16, n=3,520), Q2 (3.16<SUA/Scr $\leq$ 3.94, n=3,280), Q3 (3.94<SUA/Scr $\leq$ 4.92, n=3,270), and Q4 (SUA/Scr>4.92, n=3,243). Sig-

nificant differences were observed among Q1-Q4 groups in age, sex, smoking history, alcohol consumption, hypertension history, diabetes history, TC, LDL-C, TG, HDL-C, FBG, ApoA, and ApoB ($P<0.05$). Age and Scr were higher in Q1 than in Q2, Q3, and Q4, while TC, LDL-C, TG, ApoA, and ApoB were lower in Q1 than in Q2, Q3, and Q4 ($P<0.05$). Similar patterns were observed for Q2 versus Q3 and Q4, and for Q3 versus Q4 (all $P<0.05$). No significant differences were found in atrial fibrillation history among the four groups ($P>0.05$) .

2.2 Multivariate Cox Regression Analysis of Factors Influencing Cerebrovascular Disease Recurrence, Cerebral Infarction Recurrence, and TIA Recurrence in Male and Female Patients By the end of follow-up, 774 of 13,313 patients (5.8%) had died, and 2,064 (15.5%) experienced recurrent cerebrovascular events, including 1,741 cases of cerebral infarction recurrence (13.1%), 100 cases of intracerebral hemorrhage (0.8%), and 223 cases of TIA (1.7%).

2.2.1 Male Patients: Using cerebrovascular disease recurrence (yes=1, no=0) and time as dependent variables, with SUA/Scr as the independent variable (using Q1 as reference) and adjusting for age, smoking, alcohol consumption, hypertension, diabetes, TG, TC, FBG, HDL-C, LDL-C, ApoA, and ApoB (all as continuous or binary variables as appropriate), multivariate Cox regression showed that SUA/Scr quartiles were not a risk factor for cerebrovascular disease recurrence in men ($P>0.05$) .

Using cerebral infarction recurrence (yes=1, no=0) and time as dependent variables with the same adjustments, SUA/Scr in Q4 compared with Q1 was an influencing factor for acute cerebral infarction recurrence in men ($P<0.05$) .

Using TIA recurrence (yes=1, no=0) and time as dependent variables with the same adjustments, SUA/Scr quartiles were not an influencing factor for TIA recurrence in men ($P>0.05$) .

2.2.2 Female Patients: Using cerebrovascular disease recurrence, cerebral infarction recurrence, and TIA recurrence (each yes=1, no=0) with time as dependent variables, SUA/Scr as the independent variable, and the same adjustments, multivariate Cox regression showed that SUA/Scr quartiles were not influencing factors for any recurrence outcomes in women (all $P>0.05$) .

2.3 Multivariate Cox Regression Analysis of Factors Influencing All-Cause Mortality, Death from Cerebral Infarction, Death from Intracerebral Hemorrhage, and Post-Discharge Death in Male and Female Patients **2.3.1 Male Patients:** Using all-cause mortality (yes=1, no=0) and time as dependent variables, with SUA/Scr as the independent variable and adjusting for age, smoking, alcohol consumption, hypertension, diabetes, TG, TC, FBG, HDL-C, LDL-C, ApoA, and ApoB, multivariate Cox regression showed that SUA/Scr in Q4 compared with Q1 was an influencing factor for all-cause

mortality (P<0.05) .

Using death from cerebral infarction (yes=1, no=0) and time as dependent variables with the same adjustments, SUA/Scr in Q4 compared with Q1 was an influencing factor for death from cerebral infarction in men (P<0.05) .

Using death from intracerebral hemorrhage (yes=1, no=0) and time as dependent variables with the same adjustments, SUA/Scr quartiles were not an influencing factor for death from intracerebral hemorrhage in men (P>0.05) .

Using post-discharge death (yes=1, no=0) and time as dependent variables with the same adjustments, SUA/Scr in Q3 and Q4 compared with Q1 were influencing factors for post-discharge death in men (P<0.05) .

2.3.2 Female Patients: Using all-cause mortality, death from cerebral infarction, death from intracerebral hemorrhage, and post-discharge death (each yes=1, no=0) with time as dependent variables, SUA/Scr as the independent variable, and the same adjustments, multivariate Cox regression showed that SUA/Scr quartiles were not influencing factors for any mortality outcomes in women (all P>0.05) .

2.4 Multivariate Cox Regression Analysis of Death and Recurrence Risk in the Cerebral Infarction Subgroup 2.4.1 Recurrence Analysis: Using recurrence of large-artery atherosclerotic cerebral infarction (yes=1, no=0) and time as dependent variables, with SUA/Scr as the independent variable and adjusting for the same covariates, multivariate Cox regression showed that SUA/Scr in Q4 compared with Q1 was an influencing factor for recurrence of large-artery atherosclerotic cerebral infarction in the male cerebral infarction subgroup (P<0.05), but not in the female subgroup (P>0.05) .

Using recurrence of small-artery occlusion cerebral infarction and time as dependent variables with the same adjustments, SUA/Scr quartiles were not influencing factors for recurrence in either male or female cerebral infarction subgroups (P>0.05) .

Using cardioembolic stroke recurrence and time as dependent variables with the same adjustments, SUA/Scr quartiles were not influencing factors for recurrence in either male or female cerebral infarction subgroups (P>0.05) .

2.4.2 Mortality Analysis: Using death from large-artery atherosclerotic cerebral infarction (yes=1, no=0) and time as dependent variables, with SUA/Scr as the independent variable and adjusting for the same covariates, multivariate Cox regression showed that SUA/Scr in Q4 compared with Q1 was an influencing factor for death from large-artery atherosclerotic cerebral infarction in the male cerebral infarction subgroup (P<0.05), but not in the female subgroup (P>0.05) .

Using death from small-artery occlusion cerebral infarction and time as dependent variables with the same adjustments, SUA/Scr quartiles were not influenc-

ing factors for mortality in either male or female cerebral infarction subgroups (P>0.05) .

Using death from cardioembolic stroke and time as dependent variables with the same adjustments, SUA/Scr quartiles were not influencing factors for mortality in either male or female cerebral infarction subgroups (P>0.05) .

Discussion

The prevalence of stroke has been increasing in recent years, and identifying factors associated with poor prognosis will facilitate closer patient monitoring and optimal preventive management. Accumulating evidence indicates that SUA is an independent predictor of mortality and recurrence in acute cerebrovascular disease. To exclude the influence of renal function and more accurately investigate the relationship between SUA and cerebrovascular disease prognosis, this study examined whether SUA/Scr is a influencing factor.

We found that elevated SUA/Scr during the acute phase of cerebrovascular disease may reduce mortality and recurrence rates of cerebrovascular events in male patients. However, this association was not significant for intracerebral hemorrhage, small-artery occlusion cerebral infarction, or cardioembolic stroke subtypes. SUA/Scr levels were not associated with increased risk of cerebrovascular disease recurrence or mortality in female patients. These results may be related to the interaction between uric acid and estrogen or to the smaller number of outcome events in women. As this study did not investigate hormone-related indicators, this aspect was not explored. Previous studies have reported that higher SUA affects blood lipids and blood pressure, which is consistent with our findings that LDL-C, HDL-C, TG, TC, FBG, ApoA, and ApoB levels were also associated with SUA levels.

High SUA levels may have neuroprotective effects in acute large-artery atherosclerotic cerebral infarction and improve long-term prognosis, thereby reducing mortality and recurrence rates. However, this neuroprotective effect appears to occur only in men, possibly explained by the antioxidant properties of uric acid. SUA acts as an antioxidant that scavenges hydrogen peroxide and hydroxyl free radicals, prevents peroxynitrite synthesis of nitrotyrosine, and maintains extracellular superoxide dismutase activity. Furthermore, Leinonen et al. reported that severe neurological injury is associated with low plasma antioxidant activity. Acute cerebral infarction leads to rapid consumption of SUA, and higher SUA levels correlate with better prognosis. Therefore, it is reasonable to expect that higher SUA would be beneficial during acute stroke. In this context, high SUA may represent a compensatory mechanism to mitigate oxidative damage caused by atherosclerosis and aging. In our study, patients with higher SUA/Scr levels did not have higher rates of atrial fibrillation, and SUA/Scr levels did not predict cardioembolic stroke risk, contrasting with Yang et al.' s report of a relationship between SUA levels and cardioembolic stroke risk in different sexes. SUA/Scr levels are influenced by

many factors, and the role of SUA cannot be simply explained—further research is needed.

The role of SUA in the development and progression of cardiovascular and cerebrovascular disease remains controversial. The relationship between SUA/Scr and acute ischemic stroke has not been fully described. Our study provides additional evidence for the neuroprotective effect of SUA in patients with large-artery atherosclerotic cerebral infarction. A study of 12,739 patients found that high SUA levels at disease onset may have neuroprotective effects in acute cerebral infarction. Sun et al.' s study of a Chinese population showed that higher SUA levels predicted favorable outcomes in acute ischemic stroke. However, other studies have suggested that higher SUA levels predict poor prognosis (death or hospitalization) and higher rates of vascular events, possibly due to differences in endpoint events and follow-up duration. Future clinical studies should further examine the impact of SUA on cerebrovascular disease prognosis.

This study has several limitations. First, we did not collect data on gout history or urate-lowering medications (such as allopurinol). Second, information on patients' long-term residence and dietary habits was not collected, so the influence of these factors cannot be excluded. Third, SUA and Scr levels in this study may have been affected by patients' stress levels. Fourth, the follow-up period was relatively short. Future studies should enroll more patients and extend follow-up duration to address these limitations.

Conclusion

Within a certain range, low SUA/Scr is associated with increased risk of death and recurrence in male patients with large-artery atherosclerotic cerebral infarction. However, SUA/Scr is not associated with increased risk of recurrence and mortality in small-artery occlusion or cardioembolic stroke. This trend was not observed in female patients. Assessment of SUA/Scr may play an important role in early prognosis determination for cerebrovascular disease patients, and attention to SUA/Scr may provide clinicians with new insights for improving medium- and long-term outcomes, reducing patients'psychological and economic burden, and enhancing quality of life.

References

[1] CHO S K, CHANG Y, KIM I, et al. U-shaped association between serum uric acid level and risk of mortality: a cohort study[J]. Arthritis Rheumatol, 2018, 70(7): 1122-1132. DOI: 10.1002/art.40472.

[2] CULLETON B F, LARSON M G, KANNEL W B, et al. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study[J]. Ann Intern Med, 1999, 131(1): 7-13. DOI: 10.7326/0003-4819-131-1-199907060-00003.

[3] JOHNSON R J, KANG D H, FEIG D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?[J]. Hypertension, 2003, 41(6): 1183-1190. DOI: 10.1161/01.HYP.0000069700.62727.C5.

[4] CHAMORRO A, OBACH V, CERVERA A, et al. Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke[J]. Stroke, 2002, 33(4): 1048-1052. DOI: 10.1161/hs0402.105927.

[5] ONG G, DAVIS W A, DAVIS T M E. Serum uric acid does not predict cardiovascular or all-cause mortality in type 2 diabetes: the Fremantle Diabetes Study[J]. Diabetologia, 2010, 53(7): 1288-1294. DOI: 10.1007/s00125-010-1735-7.

[6] WANG A X, TIAN X, WU S L, et al. Metabolic factors mediate the association between serum uric acid to serum creatinine ratio and cardiovascular disease[J]. J Am Heart Assoc, 2021, 10(23): e023054. DOI: 10.1161/JAHA.121.023054.

[7] DURMUS KOCAK N, SASAK G, AKA AKTURK U, et al. Serum uric acid levels and uric acid/creatinine ratios in stable chronic obstructive pulmonary disease (COPD) patients: are these parameters efficient predictors of patients at risk for exacerbation and/or severity of disease?[J]. Med Sci Monit, 2016, 22: 4169-4176. DOI: 10.12659/msm.897759.

[8] GU L B, HUANG L J, WU H D, et al. Serum uric acid to creatinine ratio: a predictor of incident chronic kidney disease in type 2 diabetes mellitus patients with preserved kidney function[J]. DOI: 10.1177/1479164116680318.

[9] TAO J, SHEN X, LI J, et al. Serum uric acid to creatinine ratio and metabolic syndrome in postmenopausal Chinese women[J]. DOI: 10.2337/dc09-0625.

[10] WHITWORTH J A, International Society of Hypertension Writing Group, World Health Organization. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension[J]. J Hypertens, 2003, 21(11): 1983-1992. DOI: 10.1097/00004872-200311000-00002.

[11] AMERICAN DIABETES ASSOCIATION. Diagnosis and classification of diabetes mellitus[J]. Diabetes Care, 2009, 32(Suppl 1): S62-67. DOI: 10.2337/dc09-S062.

[12] JANUARY C T, WANN L S, ALPERT J S, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society[J]. J Am Coll Cardiol, 2014, 64(21): e1-e76. DOI: 10.1016/j.jacc.2014.03.022.

[13] SON M, SEO J, YANG S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017[J]. PLoS One, 2020, 15(2): e0228684. DOI: 10.1371/journal.pone.0228684.

[14] CHOI Y J, YOON Y, LEE K Y, et al. Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis[J]. FASEB J, 2014, 28(7): 3197-3204. DOI: 10.1096/fj.13-247148.

[15] LI Q, YANG Z, LU B, et al. Serum uric acid level and its association with metabolic syndrome and carotid atherosclerosis in patients with type 2 diabetes[J]. Cardiovasc Diabetol, 2011, 10: 72. DOI: 10.1186/1475-2840-10-72.

[16] SQUADRITO G L, CUETO R, SPLENSER A E, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid[J]. Arch Biochem Biophys, 2000, 376(2): 333-337. DOI: 10.1006/abbi.2000.1721.

[17] HINK H U, SANTANAM N, DIKALOV S, et al. Peroxidase properties of extracellular superoxide dismutase: role of uric acid in modulating in vivo activity[J]. Arterioscler Thromb Vasc Biol, 2002, 22(9): 1402-1408. DOI: 10.1161/01.atv.0000027524.86752.02.

[18] LEINONEN J S, AHONEN J P, LÖNNROT K, et al. Low plasma antioxidant activity is associated with high lesion volume and neurological impairment in stroke[J]. Stroke, 2000, 31(1): 33-39. DOI: 10.1161/01.str.31.1.33.

[19] LLULL L, AMARO S, CHAMORRO Á. Administration of uric acid in the emergency treatment of acute ischemic stroke[J]. Curr Neurol Neurosci Rep, 2016, 16(1): 4. DOI: 10.1007/s11910-015-0604-7.

[20] NIETO F J, IRIBARREN C, GROSS M D, et al. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis?[J]. Atherosclerosis, 2000, 148(1): 131-139. DOI: 10.1016/s0021-9150(99)00214-2.

[21] YANG X L, KIM Y, KIM T J, et al. Association of serum uric acid and cardioembolic stroke in patients with acute ischemic stroke[J]. J Neurol Sci, 2016, 370: 57-62. DOI: 10.1016/j.jns.2016.09.019.

[22] HOLME I, AASTVEIT A H, HAMMAR N, et al. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417,734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS)[J]. J Intern Med, 2009, 266(6): 558-570. DOI: 10.1111/j.1365-2796.2009.02133.x.

[23] ZOPPINI G, TARGHER G, NEGRI C, et al. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients[J]. Diabetes Care, 2009, 32(9): 1716-1720. DOI: 10.2337/dc09-0625.

[24] LEI Z H, CAI J J, HONG H, et al. Serum uric acid level and outcome of patients with ischemic stroke: a systematic review and meta-analysis[J]. Neurologist, 2019, 24(4): 121-131. DOI: 10.1097/NRL.0000000000000234.

[25] SUN Z J, FENG J Y, HE M L, et al. Higher uric acid is associated with better discharge recovery and short-term outcome in stroke patients treated with thrombolysis[J]. Neurol Sci, 2021, 42(8): 3225-3231. DOI: 10.1007/s10072-020-04919-z.

Author Contributions

Ren Xiaoqiao: data collection and organization, manuscript writing and revision, statistical analysis and data processing. Wang Pan: conceptual design, editorial assistance and revision. Wu Hao: feasibility analysis, data collection and organization. Ji Yong: project management and conceptual guidance. Shi Zhihong: conceptual guidance and resource provision, manuscript supervision and review.

Funding: National Natural Science Foundation of China (82171182); Tianjin Municipal Health Science and Technology Project (TJWJ2023QN060, TJWJ2022MS032); Tianjin Municipal Education Commission Research Project (2023KJ060); Tianjin Key Medical Specialty (Neurology) Construction Unit (TJYXZDXK-052B).

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: Approved by the Tianjin Huanhu Hospital Ethics Committee (2023-082).

Conflict of Interest: The authors declare no conflicts of interest.

ORCID: Shi Zhihong: https://orcid.org/0000-0001-5235-6349

Citation: Ren XQ, Wang P, Wu H, et al. Correlation of serum uric acid to serum creatinine ratio with the recurrence and mortality of cerebrovascular events in patients with acute cerebrovascular disease: a prospective cohort study[J]. Chinese General Practice, 2024. DOI: 10.12114/j.issn.1007-9572.2024.0073. [Epub ahead of print].

Received: 2024-05-10
Revised: 2024-08-10
Accepted for publication: 2024-XX-XX

Note: Figure translations are in progress. See original paper for figures.