Association Between Serum Uric Acid Levels and Two-Year Prognosis in First-Ever Acute Ischemic Stroke: A Postprint

Authors: Yao Huihui, Shu Lin, Yao Linli, Li Sha, Yang Xiaotong, Li Yunchun

Date: 2022-08-12T00:00:00+00:00

Abstract

Background: Recent epidemiological studies have indicated that serum uric acid (Uric acid, UA) levels are associated with outcomes in patients with acute ischemic stroke (Acute Ischemic Stroke, AIS), but whether UA exerts a beneficial effect on AIS patients remains controversial.

Objective: To investigate whether different early UA levels are associated with two-year recurrence and all-cause mortality in patients with first-ever AIS, thereby providing a scientific basis for developing public health education intervention strategies.

Methods: A retrospective cohort study was conducted selecting patients with first-ever AIS who were hospitalized in the Department of Neurology of a tertiary hospital in Shenzhen, Guangdong Province from January 1, 2018 to December 31, 2019. General information, biochemical indicators during hospitalization, and two-year recurrence and all-cause mortality data were collected. Logistic regression analysis was employed to examine whether UA levels at the time of stroke were associated with poor prognosis in AIS patients.

Results: Patients with different uric acid levels showed no statistically significant differences overall in length of stay, hospitalization costs, discharge NIHSS score, BADL (Basic Activities of Daily Living, BADL) score, or risk of recurrence and all-cause mortality within two years ($P>0.05$). However, compared with the Q1 group, the Q4 group exhibited significantly lower hospitalization costs ($P<0.05$). Older age, history of diabetes, chronic renal insufficiency, elevated fasting blood glucose, and triglyceride levels were risk factors for recurrence and all-cause mortality in male patients ($P<0.05$); older age and history of diabetes were risk factors for recurrence and all-cause mortality in female patients ($P<0.05$). Logistic regression analysis stratified by gender revealed that in males, the Q4 group had a significantly lower risk of recurrence and all-cause mortality than

the Q1 group (OR: 0.031, 95% CI: 0.087-0.892, P<0.05). After adjusting for multiple factors including age, TOAST (Trial of Org 10172 in Acute Stroke Treatment, TOAST) classification, history of diabetes, history of hypertension, hyperuricemia, and chronic renal insufficiency, this difference persisted (OR: 0.049, 95% CI: 0.187-0.990, P<0.05). However, this difference was not observed in female patients (P>0.05).

Conclusion: Compared with lower UA levels, higher UA levels are associated with lower rates of recurrence and all-cause mortality within two years in male AIS patients. However, our study does not imply that hyperuricemia can reduce recurrence and all-cause mortality in patients with first-ever acute ischemic stroke.

Full Text

Relationship Between Early Serum Uric Acid Level and Two-Year Prognosis of First Acute Ischemic Stroke

DOI: 10.12114/j.issn.1007-9572.2022.0582

Authors: YAO Huihui[1], SHU Lin[1]*, YAO Linli[1], LI Sha[1], YANG Xiaotong[1], LI Yunchun[1]

Affiliation: [1]Department of Clinical Nutrition, University of Hong Kong-Shenzhen Hospital, Shenzhen 518048, Guangdong Province, China

Corresponding Author: SHU Lin, Deputy Director, Attending Physician; E-mail: shul@hku-szh.org

---

Abstract

Background: Epidemiological studies in recent years have shown that serum uric acid (UA) levels are associated with outcomes in patients with acute ischemic stroke (AIS), but whether UA exerts a beneficial effect on AIS patients remains controversial.

Objective: To investigate whether different early UA levels are associated with recurrence and all-cause mortality within two years in patients experiencing their first AIS, and to provide a scientific basis for developing public health education intervention strategies.

Methods: We conducted a retrospective cohort study of patients with first-time AIS admitted to the Department of Neurology at a tertiary hospital in Shenzhen, Guangdong Province, between January 1, 2018, and December 31, 2019. General information, biochemical indicators, and data on recurrence and all-cause mortality within two years were collected during hospitalization. Logistic regression analysis was used to examine whether UA levels at the time of stroke were associated with poor prognosis in AIS patients.

Results: There were no statistically significant differences across UA level groups in hospitalization days, medical costs, discharge NIHSS scores, BADL (Basic Activities of Daily Living) scores, or two-year recurrence and all-cause mortality risk (P>0.05). However, compared with the Q1 group, the Q4 group showed significantly lower hospitalization costs (P<0.05). Older age, diabetes history, chronic renal insufficiency, and higher fasting blood glucose and triglyceride levels were risk factors for recurrence and all-cause mortality in male patients (P<0.05), while older age and diabetes history were risk factors in female patients (P<0.05). Logistic regression analysis stratified by sex revealed that in men, the Q4 group had significantly lower risk of recurrence and all-cause mortality compared with the Q1 group (OR: 0.031, 95% CI: 0.087-0.892, P<0.05). This difference persisted after adjusting for multiple factors including age, TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, diabetes history, hypertension history, hyperuricemia, and chronic renal insufficiency (OR: 0.049, 95% CI: 0.187-0.990, P<0.05). However, no such difference was observed in female patients (P>0.05).

Conclusion: Higher UA levels, compared with lower levels, were associated with lower two-year recurrence and all-cause mortality in male AIS patients. However, our study does not imply that hyperuricemia can reduce recurrence and all-cause mortality in patients with first-time acute cerebral infarction.

Keywords: uric acid; acute ischemic stroke; recurrence and all-cause mortality; prognosis

Introduction

Stroke remains one of the leading causes of disability, mortality, and cognitive impairment worldwide. According to the 2020 China Stroke Report, acute ischemic stroke (AIS) accounts for approximately 81.9% of all stroke cases [1]. The disease status and functional outcomes of AIS have a major impact on patients' future quality of life. Approximately 80% of serum uric acid (UA) in the human body is the final product of purine metabolism, while 20% derives from exogenous sources such as meat, seafood, and organ meats [2]. UA is an important endogenous antioxidant in blood, with concentrations nearly ten times higher than other antioxidants. However, research also indicates that UA can promote oxidative stress by generating reactive oxygen species (ROS), thereby triggering endothelial dysfunction and accelerating the atherosclerotic process [3]. Recent epidemiological studies have demonstrated an association between UA levels and outcomes in AIS patients, yet whether UA exerts a beneficial effect remains controversial [4-8], and whether this relationship exhibits sex specificity remains unclear [9,10]. Therefore, this study aims to explore the impact of early UA levels on prognosis in AIS patients to provide further insights.

Methods

1.1 Study Population

We conducted a retrospective cohort study of patients with first-time AIS admitted to the Department of Neurology at a tertiary hospital in Shenzhen, Guangdong Province, between January 1, 2018, and December 31, 2019. A total of 513 patients were included (364 men and 149 women), all meeting the following inclusion and exclusion criteria.

Inclusion Criteria: (1) Met the diagnostic criteria for AIS according to the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (2018) [11], confirmed by head CT or MRI; (2) Age $ $18 years; (3) Complete clinical data available.

Exclusion Criteria: (1) Previous stroke history; (2) Diffusion-Weighted Imaging (DWI)-negative AIS; (3) Time from onset >3 days; (4) Severe organ dysfunction of heart, liver, or kidney; (5) Alzheimer' s disease or severe psychiatric disorders; (6) Major surgery within the past 3 months.

1.2 Data Collection

During hospitalization, we collected the following information: demographic data (sex, age, occupation, education level), smoking history, alcohol consumption history, disease history (diabetes, hypertension, gout/hyperuricemia, hyperlipidemia, chronic renal insufficiency, chronic hepatic insufficiency, arrhythmia, coronary heart disease, atrial fibrillation, coronary artery stenosis, atherosclerosis), medication history (antihypertensive drugs, hypoglycemic agents, lipid-lowering drugs, urate-lowering drugs, anticoagulants), medical insurance type (self-pay, medical insurance), AIS TOAST classification (Trial of Org 10172 in Acute Stroke Treatment) (Large Artery Atherosclerosis (LAA), Small Vessel Occlusion (SVO), Cardioembolic (CE), Stroke of Undetermined Etiology (SUE), or Stroke of Other Determined Etiology (SOE)), NIHSS (National Institutes of Health Stroke Scale) score, BADL (Basic Activities of Daily Living) score, Body Mass Index (BMI, weight (kg)/height^2 (m^2)), and biochemical indicators (creatinine (CREA), urea (UREA), UA, fasting blood glucose (FPG), C-reactive protein (CRP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)). TOAST classification was determined by licensed physicians according to the Org 10172 trial criteria based on infarct location.

1.3 Patient Follow-up

At 24 months post-AIS, trained researchers collected prognostic information for all patients through telephone follow-up and review of readmission medical records. For patients whose prognostic information was obtained through the hospital system query, informed consent was waived by the Ethics Committee of the University of Hong Kong-Shenzhen Hospital, as these patients may have

already been discharged. For patients contacted via telephone, the study purpose was explained and informed consent was obtained. The primary outcome measures were all-cause mortality and stroke recurrence within 24 months after discharge. Stroke recurrence included both ischemic and hemorrhagic stroke.

1.4 Statistical Analysis

Continuous variables were described as mean ± standard deviation ($\bar{x} \pm s$) and analyzed using ANOVA. Categorical variables were described as percentages (%) and analyzed using chi-square (^{2}) tests. Logistic regression analysis was used to calculate odds ratios (OR) to assess the association between different UA levels and adverse outcomes in acute cerebral infarction. Data analysis was performed using SPSS 25.0. $P<0.05$ was considered statistically significant.

1.5 Quality Control

Patient diagnosis and treatment were determined by licensed physicians based on individual patient conditions. Demographic information, smoking and alcohol history, disease history, medication history, medical insurance type, and NIHSS scores were collected and entered by professionally trained nurses with valid nursing licenses. For blood biochemical indicators, all patients were required to fast for at least 8 hours, with blood samples collected at 7:00 AM. All blood samples were immediately sent to the hospital laboratory for testing. Data entry was performed using double-entry to ensure accuracy.

Results

2.1 Baseline Characteristics

Given the sex differences in normal UA level ranges, we stratified patients by sex and divided them into four groups based on UA quartiles: Q1, Q2, Q3, and Q4. Significant differences were observed among the four groups in smoking status, TOAST classification, hyperuricemia, chronic renal insufficiency, weight, BMI, DBP (Diastolic Blood Pressure), UREA, CREA, UA, AST (Aspartate Transaminase), HDL-C, and LDL-C ($P<0.05$). No significant differences were found in sex distribution, age, alcohol consumption, infarct location, diabetes history, or hypertension history ($P>0.05$). See Table 1 .

2.2 Comparison of Uric Acid Levels and Discharge Outcomes

Analysis revealed no statistically significant differences among groups in hospitalization days, medical costs, discharge NIHSS scores, or BADL scores at discharge ($P>0.05$). However, in male patients, the Q4 group showed significantly lower hospitalization costs and discharge NIHSS scores compared with the Q1 group ($P<0.05$). See Table 2 .

2.3 Logistic Regression Analysis

Univariate logistic regression analysis showed that older age, diabetes history, chronic renal insufficiency, and higher fasting blood glucose and triglyceride levels significantly increased the risk of adverse outcomes in male patients ($P<0.05$). In female patients, only older age and diabetes history were identified as risk factors for adverse outcomes ($P<0.05$). See Table 4 .

As shown in Table 5 , sex-stratified logistic regression analysis revealed that in men, the Q4 group had significantly lower risk of adverse outcomes compared with the Q1 group (OR: 0.031, 95% CI: 0.087-0.892, $P<0.05$). This difference remained significant after adjusting for multiple factors including age, TOAST classification, diabetes history, hypertension history, hyperuricemia, and chronic renal insufficiency (OR: 0.049, 95% CI: 0.187-0.990, $P<0.05$). However, no such difference was observed in female patients ($P>0.05$).

Discussion

Uric acid circulates as urate and is excreted through urine. When renal function is impaired, urate cannot be efficiently eliminated, leading to hyperuricemia. UA exhibits paradoxical antioxidant and pro-oxidant properties. On one hand, it serves as a potent antioxidant and scavenger of singlet oxygen and free radicals, providing approximately 60% of blood free radical scavenging capacity. On the other hand, it can cause endothelial dysfunction through oxidative stress, triggering inflammation and reactive oxygen species release, thereby contributing to cardiovascular diseases such as stroke [12].

Current research on the relationship between UA levels and stroke incidence and outcomes remains controversial. A recent systematic review and meta-analysis by Zhang M et al. found no significant association between serum UA levels and ischemic stroke prognosis [7]. However, some scholars suggest that patients with high UA levels at the time of stroke experience better clinical outcomes. Wang et al. concluded that serum UA levels have a neuroprotective effect after acute ischemic stroke [4], while Sun et al. found that higher UA levels were associated with better discharge recovery and 3-month outcomes in ischemic stroke patients receiving thrombolytic therapy [8]. Studies have confirmed that UA administration in stroke patients receiving rt-PA treatment is safe, reduces oxidative stress markers, and prevents premature decline in serum UA [13,14]. A 2021 meta-analysis demonstrated that in rodent experiments, UA improved ischemic stroke outcomes by reducing infarct size, improving blood-brain barrier integrity, and enhancing neurological function [15]. Conversely, Tu W et al. found that asymptomatic hyperuricemia doubled the risk of stroke within three years, making it a significant predictor of stroke [5]. A 2017 meta-analysis revealed a significant dose-response relationship between elevated UA levels and stroke risk, with each 1 mg/dL increase in UA level associated with approximately 10% higher stroke risk [9]. A 2019 review including 33,580 stroke cases and 1,100,888 participants found insufficient evidence to support the hypothe-

sis of UA' s neuroprotective effects in ischemic stroke, concluding that elevated UA levels increase stroke incidence [16]. A 2020 case-control study not only confirmed hyperuricemia as an independent risk factor for ischemic stroke but also found that hypertension severity may mediate the effect of hyperuricemia on stroke, suggesting that the combination of hyperuricemia and hypertension severity and treatment resistance increases ischemic stroke risk [17].

Furthermore, the mechanisms underlying the sex-specific predictive role of UA remain inadequately explained. In this study, we defined recurrence as the occurrence of acute cerebral infarction, transient ischemic attack, or cerebral hemorrhage after discharge from initial AIS treatment. Due to the small number of deaths (only 8 cases), we combined recurrence and all-cause mortality as a composite adverse outcome to reduce bias. We observed that in male patients, the probabilities of recurrence and all-cause mortality within two years for Q1-Q4 groups were 14.3%, 11.0%, 13.0%, and 4.4%, respectively; in female patients, these probabilities were 10.5%, 13.2%, 13.9%, and 10.8%, respectively. Through multivariate logistic regression analysis, we found that compared with the Q1 quartile (UA: 250.76$\$\pm$35.38), $male patients in the Q4 quartile (UA: 492.07\pm71.00) had significantly lower likelihood of AIS recurrence and all-cause mortality (OR: 0.021, 95\pm14.36) or Q3 (UA: 373.93\pm\$21.21)$ quartiles in terms of AIS recurrence and all-cause mortality, nor did we observe such differences in female patients. These findings suggest that compared with lower UA levels, only higher UA levels in male AIS patients are associated with lower two-year recurrence and all-cause mortality, while intermediate UA levels show no such relationship with adverse outcomes. A recent study also indicated that higher UA levels in male AIS patients were associated with lower risk of large artery occlusion stroke, but not in females [9]. In contrast, another case-control study concluded that elevated UA levels significantly increased ischemic stroke risk in women but not in men [10]. Therefore, further animal experiments and larger population studies are needed to investigate the mechanisms underlying sex differences in the relationship between UA levels and adverse outcomes in AIS patients.

In summary, our study found that higher UA levels, compared with lower levels, were associated with lower two-year recurrence and all-cause mortality in male AIS patients. This may partially reflect the antioxidant properties of high uric acid levels in vivo, but it does not imply that hyperuricemia can reduce recurrence and all-cause mortality in acute cerebral infarction patients.

Author Contributions

SHU Lin and YAO Huihui conceptualized the overall research objectives. YAO Huihui designed the study, performed statistical analysis, interpreted results, and drafted the manuscript. YAO Linli contributed to theoretical interpretation, quality control, and manuscript revision. YAO Huihui, LI Sha, and YANG Xiaotong collected data. LI Yunchun, LI Sha, and YANG Xiaotong completed data organization and entry. SHU Lin supervised study implementation and

feasibility analysis, and was responsible for quality control and final approval. All authors read and approved the final manuscript.

The authors declare no conflicts of interest related to this article.

References

1. WANG Y J, LI Z X, GU H Q, et al. China Stroke Statistics 2019: A Report From the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations [J]. Stroke Vasc Neurol, 2020, 5(3): 211-39. DOI: 10.1136/svn-2020-000457.

2. 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): 1402-8. DOI: 10.1161/01.atv.0000027524.86752.02.

3. MARUHASHI T, HISATOME I, KIHARA Y, et al. Hyperuricemia and endothelial function: From molecular background to clinical perspectives [J]. Atherosclerosis, 2018, 278: 226-31. DOI: 10.1016/j.atherosclerosis.2018.10.007.

4. WANG Z, LIN Y, LIU Y, et al. Serum Uric Acid Levels and Outcomes After Acute Ischemic Stroke [J]. Mol Neurobiol, 2016, 53(3): 1753-9. DOI: 10.1007/s12035-015-9134-1.

5. TU W, WU J, JIAN G, et al. Asymptomatic hyperuricemia and incident stroke in elderly Chinese patients without comorbidities [J]. Eur J Clin Nutr, 2019, 73(10): 1392-402. DOI: 10.1038/s41430-019-0405-1.

6. ZHONG C, ZHONG X, XU T, et al. Sex-Specific Relationship Between Serum Uric Acid and Risk of Stroke: A Dose-Response Meta-Analysis of Prospective Studies [J]. J Am Heart Assoc, 2017, 6(4). DOI: 10.1161/JAHA.116.005042.

7. ZHANG M, WANG Y, WANG K, et al. Association between uric acid and the prognosis of acute ischemic stroke: A systematic review and meta-analysis [J]. Nutr Metab Cardiovasc Dis, 2021, 31(11): 3016-23. DOI: 10.1016/j.numecd.2021.07.031.

8. SUN Z, FENG J, HE M, 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): 3225-31. DOI: 10.1007/s10072-020-04919-z.

9. WEI J, YIN R, LI X, et al. Sex-specific relationship between serum uric acid levels and the prevalence of large vessel occlusion in acute ischemic stroke [J]. Clin Exp Hypertens, 2022, 44(2): 154-8. DOI: 10.1080/10641963.2021.2013490.

10. KHALIL M I, SALWA M, SULTANA S, et al. Role of serum uric acid in ischemic stroke: A case-control study in Bangladesh [J]. PLoS One, 2020, 15(8): e0236747. DOI: 10.1371/journal.pone.0236747.

11. PENG B, WU B. Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 [J]. Chinese Journal of Neurology, 2018, 51(9): 666-682. DOI: 10.3760/cma.j.issn.1006-7876.2018.09.004.

12. ZHOU Y, ZHAO M, PU Z, et al. Relationship between oxidative stress and inflammation in hyperuricemia: Analysis based on asymptomatic young patients with primary hyperuricemia [J]. Medicine (Baltimore), 2018, 97(49): e13108. DOI: 10.1097/MD.0000000000013108.

13. AMARO S, SOY D, OBACH V, et al. A pilot study of dual treatment with recombinant tissue plasminogen activator and uric acid in acute ischemic stroke [J]. Stroke, 2007, 38(7): 2173-5. DOI: 10.1161/STROKEAHA.106.480699.

14. AMARO S, OBACH V, CERVERA A, et al. Course of matrix metalloproteinase-9 isoforms after the administration of uric acid in patients with acute stroke: a proof-of-concept study [J]. J Neurol, 2009, 256(4): 651-6. DOI: 10.1007/s00415-009-0111-3.

15. ALIENA-VALERO A, BAIXAULI-MARTIN J, CASTELLO-RUIZ M, et al. Effect of uric acid in animal models of ischemic stroke: A systematic review and meta-analysis [J]. J Cereb Blood Flow Metab, 2021, 41(4): 707-22. DOI: 10.1177/0271678X20967459.

16. TARIQ M A, SHAMIM S A, RANA K F, et al. Serum Uric Acid - Risk Factor for Acute Ischemic Stroke and Poor Outcomes [J]. Cureus, 2019, 11(10): e6007. DOI: 10.7759/cureus.6007.

17. CHAUDHARY N S, BRIDGES S L, JR., SAAG K G, et al. Severity of Hypertension Mediates the Association of Hyperuricemia With Stroke in the REGARDS Case Cohort Study [J]. Hypertension, 2020, 75(1): 246-56. DOI: 10.1161/HYPERTENSIONAHA.119.13580.

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