

Review

The Association between Uric Acid Level and Ischemic Stroke

Yang Xu ¹, Eng Hwa Wong ^{1, 2, *}, Rusli Bin Nordin ³, Abdul Kareem Meera Mohaideen ¹, Benjamin Samraj Prakash Earnest ¹, Yin How Wong ¹

1. Taylor's University, School of Medicine, Faculty of Health and Medical Sciences, 1, Jalan Taylor's, 47500 Subang Jaya, Selangor, Malaysia; E-Mails: ywantang@gmail.com; EngHwa.Wong@taylorsonline.edu.my; AbdulKareemMeera.Mohaideen@taylorsonline.edu.my; BenjaminSamrajPrakash.Earnest@taylorsonline.edu.my; YinHow.Wong@taylorsonline.edu.my
2. Taylor's University, Medical Advancement for Better Quality of Life Impact Lab, 47500 Subang Jaya, Malaysia
3. MAHSA University, Faculty of Medicine, Level 7, Main Building, Bandar Saujana Putra, 42610 Jenjarom, Selangor, Malaysia; E-Mail: rusli@mahsa.edu.my

* **Correspondence:** Eng Hwa Wong; E-Mail: EngHwa.Wong@taylorsonline.edu.my

Academic Editor: Giuseppe Lanza

Collection: [New Developments in Brain Injury](#)

OBM Neurobiology

2024, volume 8, issue 1

doi:10.21926/obm.neurobiol.2401209

Received: July 11, 2023

Accepted: January 10, 2024

Published: January 16, 2024

Abstract

Stroke is the second and third leading cause of death and disability, respectively, all over the world. It seriously affects patients' lives and brings huge burdens to their families. Ischemic stroke accounts for most of the stroke cases. In the absence of any effective treatment, prevention measures through controlling the risk factors for ischemic stroke become crucial. While uric acid has been reported as an essential risk factor for ischemic stroke, researchers hold inconsistent views regarding the specific association between uric acid and ischemic stroke. By summarizing the association between uric acid levels and ischemic stroke, this article can guide researchers to quickly and comprehensively understand the relationship between uric acid and ischemic stroke and develop further studies for its exploration.



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Keywords

Ischemic stroke; risk factor; level; risk; association

1. Introduction

Stroke is the second and third leading cause of death and disability, respectively, all over the world [1]. It poses a substantial economic burden on patients and their families. Globally, the new incidence of stroke reached 13.7 million in 2016, with approximately 87% of cases being ischemic stroke [2]. The highest risk of the incidence of ischemic stroke is mainly found in former Soviet Union countries and developing countries, where it is on the rise year by year compared to developed countries where it has been kept stable. Since currently, there exists no very effective treatment for ischemic stroke, prevention measures through controlling the associated risk factors to reduce morbidity and mortality is a priority. Often reported as an essential risk factor for ischemic stroke, uric acid may be good for the prevention of ischemic stroke in high-risk populations and clinical treatment in stroke patients. However, researchers hold inconsistent views on the effect of uric acid levels on ischemic stroke, the specific association between them being controversial. By summarizing the association between uric acid levels and ischemic stroke according to previous reports, this article can guide researchers to quickly and comprehensively understand the relationship between uric acid and ischemic stroke and develop further studies for its exploration.

2. The Association between Uric Acid Level and Ischemic Stroke

Uric acid is the final product of purine metabolism; it is an essential natural antioxidant in the body's tissues and fluids. It is a very useful oxygen-free radical scavenger of hydroxyl extreme and peroxynitrite, which could sweep away oxygen radicals in the pathological process of ischemic stroke. Studies on the association between uric acid levels and ischemic stroke yielded consistent results in animal experiments with rats and found that uric acid is a protective factor in ischemic stroke; they also showed that uric acid could reduce cerebral infarction size and was beneficial for better prognosis of ischemic stroke. While the results for human clinical experiments were inconsistent, interventional and observational studies showed contrary results. The interventional study was mostly consistent in showing that uric acid provided a protective effect in ischemic stroke, and high uric acid levels contributed to improving patients' disease conditions and the recovery of neurological function. However, observational studies in clinical human experiments showed two opposite views: some researchers considered uric acid a protective factor. In contrast, for others, it was a risk factor for ischemic stroke (Table 1). Nonetheless, most observation studies reported uric acid as a risk rather than a protective factor.

Table 1 The articles for the association between uric acid level and ischemic stroke from pubmed and google scholar.

Title	Year	Author	Research for stroke/ischemic stroke	Participants	Study types	Methods classification and statistical method	Effect size with 95% CI	Conclusion	Whether uric acid have association with ischemic stroke or not (Yes/No) and a Risk or Protective factor
1. Serum Uric Acid Is a Strong Predictor of Stroke in Patients With Non-Insulin-Dependent Diabetes Mellitus	1998	Seppo Lehto et al.	stroke	patients with non-insulin-dependent diabetes mellitus (NIDDM)	observational study	cohort study. Two independent samples t-test, χ^2 test, cox regression.	(hazard ratio = 1.91, 95% CI = 1.24-2.94, P = 0.003)	Hyperuricemia is a strong predictor of stroke events in middle-aged patients with NIDDM independently of other cardiovascular risk factors.	Yes (Risk)
2. Serum Urate as an Independent Predictor of Poor Outcome and Future Vascular Events After Acute Stroke	2003	Christopher J Weir et al.	stroke	patients with ischemic stroke or primary intracranial hemorrhage	observational study	retrospective study. Fisher exact test, χ^2 test, Mann-Whitney test, univariate and multivariate logistic regression, cox regression.	[adjusted odds ratio (OR) = 0.78, 95% CI = 0.67-0.91, P = 0.0012] (elevated urate level predicted a lower chance of good 90-day outcome)	Independently of other prognostic factors, higher serum urate levels predicted poor outcomes (dead or in care) and higher vascular event rates.	Yes (Risk)

3. Serum uric acid and risk of ischemic stroke: The ARIC Study	2006	Atsushi Hozawa et al.	ischemic stroke	general participants	observational study	prospective cohort study. analysis of variance (ANOVA), χ^2 test, cox regression.	[adjusted relative hazard (RH) = 1.49, 95% CI = 1.00-2.23, P = 0.02]	Uric acid is an independent predictor of ischemic stroke among subjects not using diuretics, but elevated uric acid itself may not cause ischemic stroke.	Yes (Risk)
4. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study	2006	Michiel J Bos et al.	stroke	general participants	observational study	cohort study, rotterdam study. cox regression.	(hazard ratio = 1.57, 95% CI = 1.11-2.22) for stroke	Uric acid is a strong risk factor for myocardial infarction and stroke.	Yes (Risk)
5. Study of Serum Uric Acid in Cerebrovascular Disease	2009	S Parvin et al.	cerebrovascular disease	cerebrovascular disease patients and healthy people	observational study	case control study. one way ANOVA test, bonferroni test.	5.98 ± 1.52 mg/dl for cerebrovascular disease, 6.04 ± 1.45 mg/dl for ischaemic cerebrovascular disease, 5.85 ± 1.68 for haemorrhagic cerebrovascular disease	Serum uric acid found significantly increased in cerebrovascular disease, ischaemic cerebrovascular disease and haemorrhagic cerebrovascular disease cases in comparison to control subjects.	Yes (Risk)

6. Uric Acid Levels Are Relevant in Patients With Stroke Treated With Thrombolysis	2010	Sergio Amaro et al.	stroke	patients with stroke treated with thrombolysis	observational study	prospective study. student's t-test, one way ANOVA, Mann-Whitney, Kruskal-Wallis test, χ^2 test, Fisher exact test, binary and ordinal multivariate logistic regression.	(OR = 1.23, 95% CI = 1.03-1.49, P = 0.025)	Increased UA serum levels are associated with better outcome in patients with stroke treated with reperfusion therapies.	Yes (Protective)
7. High levels of serum uric acid are associated with silent brain infarction	2010	Sung Hyuk Heo and Seung-Hoon Lee	stroke	non-stroke individuals	observational study	intensive interviews and laboratory examinations. unpaired student's t-test, χ^2 test, multivariate logistic regression.	(adjusted OR = 1.79, 95% CI = 1.11-2.91)	An increased uric acid level may be a risk factor for silent brain infarction. Uric acid level might be a good serum marker of underlying silent brain infarction or future stroke, especially in women.	Yes (Risk)
8. Acute ischemic non-embolic stroke and serum level of uric acid	2012	Farhad Iranmanesh et al.	ischemic stroke	ischemic non-embolic stroke patients	observational study	case-control study. Chi-Square test.	13.0% in the case group and 10.7% in the control group had hyperuricemia.	There was no relationship between uric acid and acute ischemic non-embolic stroke.	No (No relation)

<p>9. Association of serum uric acid level with ischemic stroke, stroke subtypes and clinical outcome</p>	<p>2013</p>	<p>Koppula, Rajeshwar et al.</p>	<p>ischemic stroke</p>	<p>ischemic stroke patients and healthy individuals</p>	<p>observational study</p>	<p>case-control study. student's t-test, Mann-Whitney U test, multivariate logistic regression.</p>	<p>(adjusted OR = 2.93, 95% CI = 1.93-4.876, P < 0.001)</p>	<p>Elevated levels of uric acid were associated with ischemic stroke and its subtypes except lacunar stroke. Patients with high uric acid levels had a significant increased risk of poor outcome. Uric acid is an independent prognostic factor of poor outcome.</p>	<p>Yes (Risk)</p>
<p>10. Serum Uric Acid and Outcome after Acute Ischemic Stroke: PREMIER Study</p>	<p>2013</p>	<p>Erwin Chiquete et al.</p>	<p>ischemic stroke</p>	<p>ischemic stroke patients</p>	<p>observational study</p>	<p>prospective study, primer registro mexicano de isquemia cerebral (PREMIER) study. student's t-test, Mann-Whitney U test, χ^2 test, Fisher's exact test, multivariate logistic regression.</p>	<p>(OR = 1.76, 95% CI = 1.05-2.95, P = 0.031)</p>	<p>A low uric acid concentration is modestly associated with a very good short-term outcome. Uric acid is more a marker of the cerebral infarction magnitude than a predictor of stroke outcome.</p>	<p>Yes (Risk)</p>
<p>11. Serum uric acid level in acute ischaemic stroke</p>	<p>2013</p>	<p>Arvind Charan Mangal, Rishi T</p>	<p>ischemic stroke</p>	<p>ischemic stroke patients</p>	<p>observational study</p>	<p>Chi square and student's t-test</p>	<p>the neurological function scores in patients with elevated serum</p>	<p>Patient with hyperuricemia were having poor neurological status</p>	<p>Yes (Risk)</p>

		Guria, Manish Kumar Singh					uric acid were 38.31 ± 11.31 and 31.35 ± 12.64 in patient with normal serum uric acid, P = 0.0116	compared to patients without. Outcome was poor with rising level of uric acid but no statistically significant relationship between the outcome and hyperuricemia in ischemic stroke patients.	
12. Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromsø Study	2013	Hilde M Storhaug et al.	ischemic stroke	general participant s	observ ational study	prospective cohort study. multiple linear regression, cox regression.	(HR = 1.31, 95% CI = 1.14-1.50) in men and (HR = 1.13, 95% CI = 0.94-1.36) in women	Uric acid was associated with all-cause mortality in men and women. After adjusting confounding factors, uric acid was associated with 31% increased risk of stroke in men.	Yes (Risk)
13. Abstract P212: Elevated Uric Acid Levels and Risk of Ischemic Stroke among Women	2013	Monik Jimenez et al.	ischemic stroke	female ischemic stroke patients	observ ational study	nested case- control. matched analysis, multivariate logistic regression.	(OR = 1.92, 95% CI = 1.07-3.46)	There was suggestive evidence for an association between elevated uric acid levels and greater risk of ischemic stroke in this population of women.	Yes (Risk)

14. Uric Acid Therapy Improves Clinical Outcome in Women With Acute Ischemic Stroke	2015	Laura Llull et al.	ischemic stroke	patients with ischemic stroke	interventional study	efficacy study of combined treatment with uric acid and rtPA in acute ischemic stroke (URICO-ICTUS) trial. student's t-test, one way ANOVA, Mann-Whitney, Kruskal-Wallis tests, χ^2 test, Fisher exact test, binary logistic regression.	UA therapy doubled the effect of placebo to attain an excellent outcome in women (OR = 2.088, 95% CI = 1.050-4.150, P = 0.036)	In women with ischemic stroke treated with alteplase, the administration of UA reduced infarct growth in selected patients and was better than placebo to reach excellent outcome.	Yes (Protective)
15. Uric acid improves glucose-driven oxidative stress in human ischemic stroke	2015	Sergio Amaro et al.	ischemic stroke	ischemic stroke patients treated with alteplase	interventional study	URICO-ICTUS trial. student's t test, one-way ANOVA, Mann-Whitney, Kruskal-Wallis test, χ^2 test, Fisher exact test, binary logistic regression.	uric acid was associated with an increased rate of excellent outcomes in patients with glucose levels in the upper tertile range (OR = 2.9, 95% CI = 1.0-8.3)	Uric acid therapy was associated with reduced infarct growth and improved outcomes in patients with hyperglycemia during acute stroke.	Yes (Protective)
16. Prognostic Significance of	2015	Dhrubajyoti Bandyopa	stroke	stroke patients including	observational study	cross-sectional study. correlation	B = 9.307, 95% CI = 4.882-13.732, P < 0.001	High uric acid level is associated with good neurological outcome in	Yes (Protective)

Serum Uric Acid at the Time of Admission in Patients with Acute Stroke		dhyay et al.	ischemic and hemorrhagic stroke		analysis, simple linear regression.		ischemic stroke patients.		
17. Serum uric acid as an independent predictor of recurrence in ischemic stroke patients	2015	Akbar Hamzei Moghaddam et al.	ischemic stroke	ischemic stroke patients	observational study	cohort study. t test, multivariate logistic regression	(OR = 1.29, 95% CI = 1.12-1.73, P = 0.01)	Elevated uric acid concentration is significantly and independently associated with increased risk of stroke recurrence in ischemic stroke patients.	Yes (Positive with recurrence)
18. Association of serum uric acid and cardioembolic stroke in patients with acute ischemic stroke	2016	Xiu-Li Yang et al.	ischemic stroke	ischemic stroke patients	observational study	retrospective study. χ^2 tests, unpaired t-test, one way ANOVA, Kruskal-Wallis test, binary logistic regression.	(OR = 2.59, 95% CI = 1.35-4.97, P < 0.001)	SUA level is associated with the risk of cardioembolic stroke in acute ischemic stroke patients of both sexes.	Yes (Risk)
19. Sex-specific Association Between Uric Acid and Outcomes After Acute Ischemic Stroke: A	2016	Li-Hua Chen et al.	ischemic stroke	ischemic stroke patients	observational study	prospective study. multivariate logistic regression.	a high serum UA was associated with a decreased risk of primary outcome in men (OR = 0.63, 95% CI = 0.44-0.91, P =	There was a sex-specific association between uric acid and the prognosis of ischemic stroke. Elevated uric acid was positively associated with better	Yes (Protective only in men)

Prospective Study from CATIS Trial						0.01) but not in women (OR = 1.29, 95% CI = 0.83-2.01, P = 0.15)	prognosis in men, but not in women.		
20. Uric Acid Therapy Prevents Early Ischemic Stroke Progression: A Tertiary Analysis of the URICO-ICTUS Trial (Efficacy Study of Combined Treatment With Uric Acid and r-tPA in Acute Ischemic Stroke)	2016	Sergio Amaro et al.	ischemic stroke	ischemic stroke patients treated with alteplase	interventional study	URICO-ICTUS trial. χ^2 test, Fisher exact test, Mann-Whitney, logistic regression.	early ischemic worsening (EIW) occurred in 7 of 204 (3%) patients treated with UA and in 18 of 200 (9%) patients treated with placebo (P = 0.01)	Uric acid therapy may prevent early ischemic worsening after acute stroke in thrombolysed patients. Optimal access of uric acid to its molecular targets through appropriate collaterals may modify the magnitude of the neuroprotective effect.	Yes (Protective)
21. Uric acid therapy improves the outcomes of stroke patients treated with intravenous tissue plasminogen activator and	2017	Ángel Chamorro et al.	ischemic stroke	ischemic stroke patients treated with intravenous thrombolysis and	interventional study	randomized and placebo-controlled study, URICO-ICTUS trial. multivariate binary logistic regression, multivariate cumulative	(adjusted OR = 6.12, 95% CI = 1.08-34.56)	Uric acid therapy was safe and improved stroke outcomes in stroke patients receiving intravenous thrombolysis followed by thrombectomy.	Yes (Protective)

mechanical thrombectomy				mechanical thrombectomy		ordinal logistic regression, linear regression.			
22. Association between serum uric acid and ischemic stroke in patients with nonvalvular paroxysmal atrial fibrillation	2017	Nermin Bayar et al.	ischemic stroke	patients with paroxysmal AF	observational study	prospective study. χ^2 test, Fisher's exact test, Kolmogorov-Smirnov test, student's t-test, Mann-Whitney U test, multivariate logistic regression.	uric acid level higher than 6.35 mg/dl was independently associated with having a history of stroke/transient ischemic attack (OR = 81.623, 95% CI = 17.33-384.26, P < 0.001)	Assessment of uric acid levels might be useful in patients with paroxysmal atrial fibrillation to select patients with higher risk of stroke.	Yes (Risk)
23. Relationship between serum uric acid and ischemic stroke in a large type 2 diabetes population in China: A cross-sectional study	2017	Lijun Wang et al.	ischemic stroke	general participants	observational study	cross-sectional study. student's t-test, Chi-square test, ANOVA analysis, binary logistic regression.	in the age group of <60 years (adjusted OR = 1.765, 95% CI = 1.097-2.840); in the age group of \geq 60 years (OR = 0.767, 95% CI = 0.630-0.934) and (OR = 0.782, 95% CI = 0.640-0.957)	Uric acid levels were independently positively associated with ischemic stroke in patients aged <60 years, but the association was U-shaped in patients aged \geq 60 years.	Yes (Risk)

<p>24. U-Shaped Relationship Between Functional Outcome and Serum Uric Acid in Ischemic Stroke</p>	<p>2018</p>	<p>Yimin Yang et al.</p>	<p>ischemic stroke</p>	<p>patients with ischemic stroke</p>	<p>observational study</p>	<p>prospective study. Fisher exact test, Mann-Whitney U test, multivariate logistic regression.</p>	<p>uric acid concentration had a strong association with functional outcome (adjusted OR = 0.996, 95% CI = 0.993-0.998, P < 0.001)</p>	<p>The association between uric acid and ischemic stroke was the U-shaped relationship. Uric acid was significantly associated with the risk of poor functional outcomes in stroke patients.</p>	<p>Yes (Risk)</p>
<p>25. The association between serum uric acid levels and ischemic stroke in essential hypertension patients</p>	<p>2020</p>	<p>Shuo Zhang et al.</p>	<p>ischemic stroke</p>	<p>essential hypertension patients</p>	<p>observational study</p>	<p>retrospective study. cox regression.</p>	<p>(HR = 1.41, 95% CI = 1.16-1.84, P < 0.01)</p>	<p>Uric acid was an independent risk factor for ischemic stroke, and also have a good predictive value for ischemic stroke among hypertensive patients.</p>	<p>Yes (Risk)</p>
<p>26. J-shaped relationship between serum uric acid levels and the risk of ischemic stroke in high-risk individuals: A hospital-based</p>	<p>2020</p>	<p>Gaifeng Hu et al.</p>	<p>ischemic stroke</p>	<p>patients with acute stroke</p>	<p>observational study</p>	<p>cross-sectional study. retrospective study. student's t-test, Mann-Whitney U-test, Chi-square test, multiple linear regression, binary</p>	<p>patients in both the bottom (OR = 1.521, 95% CI = 1.025-2.258, P = 0.037) and upper (OR = 2.004, 95% CI = 1.370-2.932, P < 0.001) uric acid quartiles</p>	<p>A J-shaped, independent association between uric acid levels and the risk of ischemic stroke in high-risk individuals.</p>	<p>Yes (Risk)</p>

observational study						logistic regression.	have a significantly elevated the risk of ischemic stroke		
27. Lower uric acid level may be associated with hemorrhagic transformation but not functional outcomes in patients with anterior circulation acute ischemic stroke undergoing endovascular thrombectomy	2020	Zhongyun Chen et al.	ischemic stroke	ischemic stroke patients who underwent endovascular thrombectomy	observational study	retrospective study. Chi Square test, Fisher's exact test, Kolmogorov-Smirnov test, independent samples t-test, Wilcoxon rank sum test, one way ANOVA, Kruskal-Wallis H test, multivariate logistic regression.	(OR = 0.383, 95% CI = 0.173-0.848, P = 0.018)	A lower UA level is an independent risk factor of hemorrhagic transformation (HT) post- endovascular thrombectomy (EVT) in anterior circulation AIS patients, but is not associated with the short-term functional outcomes.	No (No relation)
28. Association Between Hyperuricemia and Acute Ischemic Stroke in Patients at a Tertiary Care Hospital	2020	Muhammad Irfan et al.	ischemic stroke	participants	observational study	case-control study. Chi-Square test, logistic regression.	elevated uric acid could be taken as a predictor of ischemic stroke (OR = 2.95, P = 0.002)	The prevalence of hyperuricemia in patients with ischemic stroke was significantly higher compared to the healthy population. Hyperuricemia can be considered as a risk	Yes (Risk)

								factor for ischemic stroke.	
29. Combined effect of hypertension and hyperuricemia on ischemic stroke in a rural Chinese population	2021	Peng Sun et al.	ischemic stroke	participants	observational study	cross-sectional epidemiological survey. student's t-test or Mann-Whitney test, Chi-square test, rank-sum test, or multivariate logistic regression.	in women (OR = 1.888, 95% CI = 1.244, 2.864)	The positive correlations between hypertension, hyperuricemia, and ischemic stroke. The joint effect between hypertension and hyperuricemia towards ischemic stroke only in women, not in men.	Yes (Risk)
30. The Relationship between Serum Uric Acid Level and Ischemic Stroke and its Subtypes	2021	Nurhan Kaya Tutar et al.	ischemic stroke	ischemic stroke patients and healthy individuals	observational study	case-control study, retrospective study. independent-samples t-test, Mann-Whitney U test, Chi-Square test, Fisher exact test, logistic regression.	UA levels higher than 5.6 mg/dL were identified as independent risk factors for ischemic stroke (OR = 3.107, 95% CI = 1.424-6.789, P = 0.004)	High uric acid levels were seen as an independent risk factor for stroke.	Yes (Risk)
31. Uric Acid and Gluconic Acid as Predictors of Hyperglycemia and Cytotoxic	2021	Zsuzsanna Ament et al.	stroke	patients with acute stroke	observational study	cohort study. ordered logistic regression, linear regression analysis.	uric acid was associated with poor outcome (OR = 2.3, 95% CI	Both uric acid and gluconic acid were associated with hyperglycemia and cytotoxic brain injury.	Yes (Risk)

Injury after Stroke							= 1.02-5.3, P = 0.043)	Both metabolites are linked to oxidative stress.	
32. Relationship Between Change in Serum Uric Acid and Ischemic Stroke in Chinese Hypertensive Patients	2021	Qiu-hong Tan et al.	ischemic stroke	hypertensive patients	observational study	retrospective cohort study. Kaplan-Meier analysis and log-rank test, cox regression	(HR = 1.76, 95% CI = 1.01-3.06, P = 0.0451)	Uric acid increase substantially was significantly correlated with an elevated risk of ischemic stroke among hypertension patients.	Yes (Risk)
33. Prevalence of Hyperuricemia in Patients with Ischemic Stroke	2022	Obaid Ur Rehman et al.	ischemic stroke	ischemic stroke patients	observational study	cross-sectional study. Chi-Square.	the majority of the patients were male gender (70%). sixty patients were found to have hyperuricemia (40%)	Hyperuricemia was found in a more significant percentage of acute stroke patients than in the general population.	Yes (Risk)
34. Serum Uric Acid Levels and Their Changes and Risk of Stroke: A 7-Year Prospective Cohort Study in Northwest China	2022	Shan Zheng et al.	stroke	individuals without cardiovascular disease	observational study	prospective cohort study. cox regression	(HR = 1.046, 95% CI = 1.007-1.086)	High initial uric acid concentration and an increase in uric acid concentration over time would increase the risk of stroke, there is no safe increase in uric acid.	Yes (Risk)

<p>35. Relationship of Serum Uric Acid Level with Acute Ischemic Stroke: A Single-Center, Hospital-Based Study from Bangladesh</p>	<p>2022</p>	<p>Rahman MM et al.</p>	<p>ischemic stroke</p>	<p>ischemic stroke patients and healthy individuals</p>	<p>observational study</p>	<p>cross-sectional study. multivariate logistic regression.</p>	<p>(OR = 4.51, 95% CI = 1.67-12.16, P < 0.05)</p>	<p>Uric acid levels among ischemic stroke patients were significantly higher than in healthy subjects. Hyperuricemia and hypertension were independent risk factors of ischemic stroke. Uric acid normalization may be good for the prevention of ischemic stroke.</p>	<p>Yes (Risk)</p>
<p>36. Role of Serum Homocysteine, C-Reactive Protein (CRP), Uric Acid & Pro-Brain Natriuretic Peptide (Pro-BNP) in Predicting the Functional Outcome in Patients with Ischemic Stroke- A Prospective Observational Study from North India</p>	<p>2022</p>	<p>Himanshu Chauhan et al.</p>	<p>ischemic stroke</p>	<p>patients with ischemic stroke</p>	<p>observational study</p>	<p>prospective study. multivariate logistic regression.</p>	<p>the mean serum uric acid level was 6.1 ± 3.3 mg/dl</p>	<p>Uric acid levels had no obvious association with the risk of ischemic stroke</p>	<p>No (No relation)</p>

37. Elevated Serum Uric Acid Increases the Risk of Ischemic Stroke Recurrence and Its Inflammatory Mechanism in Older Adults	2022	Han-Yu Zhu et al.	ischemic stroke	ischemic stroke patients	observational study	Chi Square test, ANOVA, Mann-Whitney U-test, cox regression. mediation analysis and interaction and joint analysis.	(OR = 1.432, 95% CI = 1.220-1.682, P < 0.0001) and (OR = 1.965, 95% CI = 1.681-2.297, P < 0.0001)	UA level is non-linearly associated with recurrence.	Yes (Risk)
38. A Study on the Role of Serum Calcium, Serum Albumin and Serum Uric Acid as Markers of Initial Neurological Severity and Short Term Outcome Indicators in Acute Ischemic Stroke	2022	Pavan Kumar Bc, Vijay G Somanna var	ischemic stroke	patients with ischemic stroke	observational study	cross sectional study. Chi-Square, logistic regression.	the positive correlation was seen only with low calcium levels and other two parameters did not show any positive correlation	Uric acid did not have association with short term outcome (mRS grades) of ischemic stroke	No (No relation)
39. Elevated Serum uric level is a risk factor for Acute Ischemic Stroke: A case	2022	A Garg, MDA Bashar, S Kapila	ischemic stroke	ischemic stroke patients and normal individuals	observational study	case-control study. Chi-Square test, independent t-test, Pearson	mean uric acid level of cases was 6.49 ± 2.36 mg/dL and mean uric acid level of	Elevated uric acid level is significantly associated with the occurrence of ischemic stroke and may be a risk	Yes (Risk)

control study
from Northern
India

correlation
coefficient.

controls was 5.59
± 0.98 mg/dL (p =
0.01)
44.0% of the
cases were
hyperuricemic
and only 16.0% of
the controls were
hyperuricemic (p
= 0.002)

factor for ischemic
stroke.

*39 articles from Pubmed and Google scholar: search keywords (uric acid and ischemic stroke) with setting filters applied: clinical Study, clinical trial, controlled clinical trial, observational study, randomized controlled trial in Pubmed. And search keywords ("uric acid and ischemic stroke") in Google scholar.

In an earlier research, Bansal et al. [3] reported that ischemic cerebrovascular disease patients with thrombus showed noticeable elevated uric acid levels among those under 40 or with abnormal angiograms. On the contrary, a study by Sridharan et al. in 1992 found lower levels of uric acid in stroke patients [4]. This research indicated that the uric acid level was obviously decreased in stroke patients, and a low level of uric acid increased the risk of ischemic stroke. A study of the association between the uric acid level and the prognosis for ischemic stroke in 2002 pointed out that for every 12-milligram increase in uric acid, the probability of a good outcome for ischemic stroke patients would increase 12%. The higher uric acid level of ischemic stroke patients at admission was dependently associated with good prognosis and functional outcome of patients at discharge, while lower level with bad clinical outcomes. This study pointed out that the role of uric acid in ischemic stroke was consistent with animal experiments [5].

Subsequent studies have reported that high levels of uric acid could increase the risk of ischemic stroke. Weir et al. demonstrated that a high level of uric acid predicted bad prognosis and clinical outcomes of stroke patients and a higher incidence of vascular events [6]. A study in 2006 indicated that a high level of uric acid could increase the risk of ischemic stroke, even among patients with diabetes [7]. However, this result contradicted almost all interventional studies, which showed that uric acid has a beneficial role in ischemic stroke. For instance, Amaro et al. used recombinant tissue plasminogen activator (rt-PA) to treat ischemic stroke and found that simultaneously adding uric acid for stroke treatment achieved good results; uric acid could reduce the peroxidation of lipids, and it prevented the level of uric acid from declining in the early acute period. The uric acid level in stroke patients treated only by rt-PA experienced the most significant decline in the 6 or 7 hours after stroke onset; uric acid was consumed quickly and had more lipid peroxidation. Conversely, the uric acid level in stroke patients treated by rt-PA and 500 mg uric acid did not show an obvious decline in uric acid level, while stroke patients treated by rt-PA 1 g uric acid showed an increase in uric acid level and maintained this high level within 24 hours. Stroke patients who were given a larger dose of uric acid had lower lipid peroxidation. This proved uric acid's protective role and antioxidation in ischemic stroke [8]. Despite having anti-oxidation solid function, the uric acid would be consumed quickly, and its antioxidative capacity would be less if ischemic stroke is severe. Uric acid's level and antioxidation capacity were negatively associated with the degree of damage to neurological function and cerebral infarction size. Supplementing uric acid may enhance its antioxidation capacity to confer better neuroprotective effects in ischemic stroke [9]. The study by Zhang et al. also proved the protective effect of high uric acid levels on ischemic stroke and pointed out that an elevated uric acid on admission is positively associated with a better prognosis after discharge [10].

Previous clinical studies reported that the association between uric acid level and the risk of ischemic stroke was either a positive or negative relationship. That is because those studies tested uric acid levels mainly at the time of admission, with the uric acid levels of stroke patients tested only one or two times. The researchers were unaware of the changes in uric acid levels in the intermediate stage after stroke onset and the dynamic changes of uric acid level throughout the acute phase of stroke. Hong et al. researched the active detection of uric acid levels in the beginning, in 24 hours, in 48 hours, on the seventh day, and the fourteenth day in ischemic stroke patients (five times test) and found that uric acid levels declined in 48 hours and then gradually rose within 14 days after stroke onset, finally returning to the baseline level or above. The uric acid level was reflected in a U-shape change in ischemic stroke patients, and it fluctuated after acute ischemic

stroke. There was a difference in the change of uric acid levels among ischemic stroke patients with or without vessel recanalisation. The correlation between the change of uric acid levels and the volume of cerebral infarction became more robust and the levels were higher in ischemic stroke patients who had vessel recanalisation [11]. Brouns et al. studied uric acid levels at 24 h, 72 h, 7th day, after 1 month and 3 months, and found that uric acid levels significantly decreased within the first seven days and then rose up to return to the baseline level or above, and remained at this level to 3 months after ischemic stroke [12]. Contrary to previous studies, the study by Seet et al. categorized uric acid levels in quartiles: less than 280 $\mu\text{mol/L}$, 280 to 340 $\mu\text{mol/L}$, 340 to 410 $\mu\text{mol/L}$ and above 410 $\mu\text{mol/L}$. They found that ischemic stroke patients with uric acid levels in the fourth quartile ($>410 \mu\text{mol/L}$) or the first quartile ($<280 \mu\text{mol/L}$) had worse outcomes and prognosis and higher risk of ischemic stroke while those in the third quarter (340 to 410 $\mu\text{mol/L}$) had the lowest risk of ischemic stroke. A U-shaped relationship was observed between poor functional outcomes and uric acid levels in stroke patients. There were more patients with poor functional outcomes at both higher and lower uric acid levels, and the lowest incidence of poor outcomes for ischemic stroke was in the intermediate uric acid levels [13].

Subsequent studies paid more focus on the clinical outcome of ischemic stroke. The study by Chiquete et al. related to the association between uric acid levels and the result of ischemic stroke mainly focused on the prognosis and outcome of ischemic stroke with modified Rankin Scale (mRS) neurological function scores; it tested uric acid levels at admission and assessed neurological function with modified Rankin Scale scores in thirtieth day, third month, sixth month and twelfth month. Results indicated that low uric acid levels had a correlation with good short outcomes. Lower uric acid levels at admission were associated with better clinical outcomes on the thirtieth day after stroke onset compared with higher levels [14].

Besides studying the outcome of ischemic stroke, more researchers have paid attention to the gender difference in the uric acid levels and ischemic stroke. The study by Storhaug et al. pointed out that uric acid levels were associated with all-cause mortality in both women and men. An increase in serum uric acid levels per 87 $\mu\text{mol/L}$ were associated with a 31% increased risk of ischemic stroke in men and an increased risk of all-cause mortality in both women and men, with a 16% and 11% risk of death in women and men respectively [15]. The study by Zhang et al. focused on the role of gender factors in the clinical prognosis and outcomes of ischemic stroke. Uric acid levels were measured on the day after admission to the hospital, and patients' prognosis was assessed using the mRS score in the third month after the onset of ischemic stroke. Patients were divided into four groups with uric acid levels $>380 \mu\text{mol/L}$, 316-380 $\mu\text{mol/L}$, 251-315 $\mu\text{mol/L}$, and $\leq 250 \mu\text{mol/L}$. Patients with high uric acid levels $>380 \mu\text{mol/L}$ or low uric acid levels $\leq 250 \mu\text{mol/L}$ on admission had a worse prognosis at 3 months after stroke, while those with moderate uric acid levels of 316-380 $\mu\text{mol/L}$ had the lowest incidence of adverse functional outcome. This also differed significantly between men and women, with male patients having the worst prognosis for ischemic stroke at high levels of uric acid on admission and the best prognosis at intermediate levels. However, opposite results were obtained for female patients who had the best prognosis for ischemic stroke at high levels of uric acid on admission and the worst prognosis at intermediate levels. Therefore, uric acid may play a dual role after the onset of ischemic stroke, and the relationship between uric acid levels and stroke prognosis was not linear but rather an inverted U-shaped curve. Patients with low uric acid levels on admission tended to have a poor prognosis after stroke. However, high uric acid levels were also associated with a poor prognosis: either too high or

too low uric acid levels on admission may be detrimental [16]. Another study on gender differences showed that men had significantly higher uric acid levels than women. In male patients, higher uric acid levels were associated with a lower risk of adverse stroke outcomes, and good clinical prognosis was associated with higher uric acid levels. Higher uric acid levels as predictors of good prognosis had a protective effect on male ischemic stroke patients, but this association was not found in women. Taken together, a good prognosis in female stroke patients tends to be associated with higher uric acid levels, while an excellent clinical prognosis in male patients is at least not significantly associated with very high uric acid levels and may not even be associated with deficient uric acid levels. Male ischemic stroke patients tend to have relatively high uric acid levels, and they are usually in the middle range, which is more conducive to good functional outcomes [17].

In addition to the study for the clinical outcome and gender difference, some researchers have investigated the association between uric acid levels and its subtypes of ischemic stroke. High uric acid levels in ischemic stroke patients were positively associated with the risk of cardioembolic stroke, which is the subtype of ischemic stroke. Nonetheless, the correlation was more evident in women than men [18].

Researchers also observed the association between uric acid and ischemic stroke among patients with other medical conditions, such as hypertension or diabetes. A study with patients having hypertension showed that a significant increase in their uric acid was associated with a considerable increase in the risk of ischemic stroke, while a substantial decrease in uric acid levels was also associated with an increased risk of ischemic stroke, though the risk of stroke was not significant [19].

Although uric acid had been reported to have neuroprotective effects in previous studies, some studies during that period also showed that the uric acid levels of patients with poor prognosis were significantly lower than those with good prognosis. The study by Liu et al. indicated that lower uric acid is associated with poor short-term outcomes of ischemic stroke [20]. Another multicentre study further explored their relationship and confirmed that uric acid levels were significantly lower in patients with poor prognoses than in their counterparts with good prognoses. However, their study indicated that a U-shaped relationship exists between uric acid levels and poor functional outcomes of ischemic stroke. Poor functional outcomes were distributed between 50.6% (first quartile) and 12.4% (third quartile) in quartiles of uric acid levels, and patients at intermediate uric acid levels had the lowest risk of poor functional outcomes [21].

Although findings for uric acid and ischemic stroke abound, the effect of uric acid levels on ischemic stroke remains disputable and inconsistent. Overall, reports of uric acid as a risk factor for ischemic stroke outweigh those reporting it as a protective factor. A study by Lai et al. showed a higher incidence of ischemic stroke in male patients as the uric acid level is increased. Indeed, the incidence of ischemic stroke in male patients with higher uric acid levels and older age between 45 and 65 years increased significantly, suggesting that high uric acid level was a risk factor for ischemic stroke [22]. In terms of the pattern of the association between uric acid levels and ischemic stroke, some studies showed that their relationship was linear, while in others, it was either U-shaped or J-shaped. The study by Hu et al. indicated that uric acid levels in ischemic stroke patients were higher than those in the control group consisting of non-ischemic stroke patients. Both low and high levels of uric acid were independently associated with an increased risk of ischemic stroke. The risk of ischemic stroke was lowest in patients with intermediate uric acid levels compared with those higher in the bottom and upper quartiles. The results suggested a J-shaped relationship between

uric acid levels and the risk of ischemic stroke [23]. The study by Khalil et al. showed that elevated uric acid levels were significantly associated with the risk of ischemic stroke. In a further sex-specific analysis, elevated uric acid levels were significantly associated with an increased risk of ischemic stroke only in women but lost significance and association in men [1]. The uric acid levels also affected the recurrence of ischemic stroke. Recurrent ischemic stroke was associated with higher uric acid levels, older age, and male gender. A nonlinear relationship was observed between uric acid level and the risk of stroke recurrence [24].

3. Conclusions

Uric acid is a standard indicator of renal function in clinical tests. As an important influencing factor for ischemic stroke, uric acid has great significance in the prevention and clinical treatment of ischemic stroke. Despite an increasing number of studies on the association between uric acid levels and ischemic stroke in recent years, the specific mechanism of the dual effect of uric acid on the pathogenesis of ischemic stroke remains unclear, such that the influence of uric acid levels on ischemic stroke is still inconsistent among researchers. Given the fluctuations in uric acid levels. Therefore, more prospective experiments for testing uric acid levels repeatedly at other times in acute ischemic stroke patients are needed to observe the change of levels by simultaneously combining neurological function scores such as the National Institute of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score. Additionally, cerebral imaging examinations at admission and discharge can be used to compare cerebral infarct size and neurological function under different uric acid levels. There is also a need for more focused studies on gender differences and the association in subtypes, not to mention stratification studies on their levels in ischemic stroke, together with appropriate animal experiments. Only then can we know the association between uric acid and ischemic stroke profoundly and comprehensively.

Author Contributions

Each author contributed equally to the research and the article.

Competing Interests

The authors have declared that no competing interests exist.

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