



Role of Serum Uric Acid in Acute Ischemic Stroke: A Case-Control Study in India

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ABSTRACT

Background. Stroke is a condition of quickly developing clinical signs of focal or global neurological disruption lasting for over twenty-four hours with no visible reason besides a vascular origin. Different risk factors are included for stroke development, like hyperlipidemia, hypertension, diabetes, and smoking. The current study was conducted to determine serum uric acid in acute ischemic stroke patients and evaluate its relationship with stroke severity.

Method. An Analytical, Non-interventional Prospective study was conducted among 50 cases of acute ischemic stroke admitted in the medicine ward at Sadhana Kutir Hospital, Kim, India, over six months from August 2020 to January 2021. All patients who presented within twenty-four hours of the onset of stroke and who gave consent were included. Fifty normal healthy individuals are included as controls. Serum uric acid levels, along with other blood routine tests, were done. The GCS score measured stroke severity.

Results. The mean age group in cases was 62.39 ± 11.61 and in control was 60.18 ± 14.72 . In cases, mean blood uric acid was 5.41 ± 1.26 and in control was 4.82 ± 1.26 ; this difference was statistically significant at a p-value of 0.021. There was no correlation between the severity of stroke and serum uric acid levels. (p value-0.2488).

Conclusion. This study concludes that serum uric acid can be utilized as neurotic biomarkers in acute ischemic stroke patients. But stroke severity can not be predicted by its level.

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1. Introduction:

Uric acid is a byproduct of the purine cycle. Primates tend to have high uric acid levels due to the loss of a key enzyme, uricase, which converts uric acid to water-soluble allantoin. Elevated serum uric acid concentrations (hyperuricemia, defined as a serum uric acid concentration of > 7 mg/dL in men and > 6 mg/dL in women) or elevated urinary uric acid concentrations (hyperuricosuria) can result in gout and uric acid nephrolithiasis, as well as an increased risk of hypertension, chronic kidney disease, and cardiovascular disease (Caterina et al., 2020).

Uric acid is a highly effective scavenger of reactive oxygen species and is a critical antioxidant in humans. However, elevated serum uric acid levels are associated with several diseases, including several that are associated with increased oxidative stress. Thus, the paradoxical role of uric acid as an antioxidant and/or prooxidant has been a topic of discussion. The balance between uric acid

production and excretion is regulated by genetic and dietary factors.

Stroke is further classified into two groups, ischemic and hemorrhagic, based on the nature of the cerebral circulation disturbances. Ischemic stroke occurs when a cerebral artery becomes occluded, either by an embolus or a thrombus, resulting in ischemic damage to a portion of the entire territory supplied by the occluded artery. In comparison, hemorrhagic stroke is primarily caused by arteriolar hypertension and is only rarely caused by coagulation disorders, malformations of the brain, or diet (Truelsen et al., 2006). Patients who have had a transient ischemic attack (TIA) or a minor ischemic stroke (MIS) are at a greater risk of recurrent stroke, and identifying them is critical for better adherence to preventive strategies (Weimar et al., 2010). Clinical insight rules assist clinicians in determining which patients should receive priority treatment, and stroke recurrence can provide a strong interpretation to assist clinicians in clinical



decisions (Ois et al., 2008). Prediction scores assist in subgrouping TIA patients based on their initial stroke risk, thereby ensuring conclusive triage in primary and secondary care (Coutts et al., 2008).

A stroke, also known as a cerebrovascular accident, is characterized as the sudden onset of a neurologic deficit caused by a focal vascular origin. Stroke is the third leading cause of death worldwide, after coronary heart disease and cancer, and is particularly prevalent in the elderly (Dimitroula et al., 2008; Feigin et al., 2009). The acute phase mortality risk of stroke is as high as 20%, and it continues to be higher in stroke cases for many years following the acute occurrence than in the general population (Dimitroula et al., 2008).

Ischemia of the brain initiates a complex chain of metabolic events that results in the production of nitric oxide and free oxygen radicals (Love & Jenner, 1999). These free radicals and reactive oxygen species (ROS) are responsible for a large proportion of the injuries that occur after a transient ischemic attack or during chronic ischemia, by altering macromolecules, especially DNA, and initiating apoptosis and necrosis.

As a major aqueous antioxidant in humans, serum uric acid can play a preventive role in stroke patients. Numerous major trials have produced contradictory findings of the medical relevance of elevated serum uric acid levels in cerebrovascular diseases.

Numerous surveys, including the National Health and Nutrition Examination Survey (NHANES), concluded that uric acid is a risk factor for the occurrence of cardiovascular and cerebrovascular diseases (Fang, & Alderman, 2000). In comparison, a prospective hospital-based study involving 881 patients discovered that a higher serum urate level was associated with improved stroke outcomes, implying that serum urate could be helpful and mitigate against worse outcomes (Chamorro et al., 2002).

Additionally, an experimental analysis demonstrated that uric acid is neuroprotective in the rat brain after a thromboembolic stroke and extends the advantages of recombinant tissue plasminogen activator (rtPA) (Romanos et al., 2007).

As a result, the effect of uric acid as a risk factor for ischaemic stroke is debatable. Against the context of this debate and a severe lack of Indian records, it was agreed to conduct the current research to examine serum uric acid levels in patients with acute ischaemic stroke and assess its possible risk factor status.

2. Materials & Methods:

It was an Analytical, Non-interventional Prospective study conducted among 50 cases of acute ischemic stroke admitted in the medicine ward at Sadhana Kutir Hospital, Kim, India, over six months from August 2020 to January 2021.

All patients who presented within twenty-four hours of the onset of stroke and who gave consent were included.

Patients' data were collected by detailed history, clinical examination, investigations, and ischemic stroke was differentiated by computer tomography (CT) scan and magnetic resonance imaging (MRI).

Only MRI brain or CT brain proved cases of acute ischemic stroke were included in the study. Apart from routine investigations, serum uric acid estimation was done. The severity of stroke was assessed as per Glasgow Coma Scale (GCS).

2.1. Exclusion criteria:

Patients with a known instance of cardio-embolic stroke, Past history of valvular heart illness, Patients taking medications that are probably going to modify levels of serum uric acid (diuretics, Losartan, Allopurinol), history of gouty arthritis or clinical evidence of gout, patients with hemorrhagic stroke, malignancy, renal or liver disease.

2.2. Selection of controls:

Consisted of 50 normal healthy individuals from the same population reporting to an out-patient department with minor complaints.

3. Results

Each group consists of an equal number of patients, i.e. 50 patients in each group. The mean age of all 100 patients was 61.28 ± 13.16 years. The mean age group in cases was 62.39 ± 11.61 and in control was 60.18 ± 14.72 . Mean blood uric acid in cases was 5.41 ± 1.26 and in control was 4.82 ± 1.26 ; this difference was statistically significant at a p-value of 0.021. There was no correlation between the severity of stroke and serum uric acid level (p-value-0.2488).

Details of cases and controls are mentioned in Table 1. Correlation between severity of stroke and serum uric acid level in cases is mentioned in Table 2. Table 3 shows serum uric acid level distribution and corresponding numbers of cases and controls.

Table 1: Differences between cases and controls

Details	Cases(n=50)	Controls(n=50)	p- value
Age	62.39 ± 11.61	60.18 ± 14.72	
Male	29	25	
Female	21	25	
Uric Acid level	5.41 ± 1.26	4.82 ± 1.26	0.021

Table 2: Severity of stroke and serum uric acid level in cases

GCS	SUA<6	SUA>6	p-value
< 12	4	4	0.2488
> 12	30	12	



Table 3: Serum Uric acid level distribution

Uric acid level	Cases	Controls	Total
0-5	12	26	38
5-5.5	20	13	33
5.5-6	11	5	16
6-6.5	4	2	6
6.5-7	1	2	3
7-7.5	1	2	3
7.5-8	1	0	1

4. Discussion

The molar mass of uric acid is 168.112 g/mol. At natural blood pH, the majority of uric acid circulates as urate, a weakly charged salt formed from uric acid. Uric acid is removed from the human body via urine as the result of purine catabolism, as long as renal function is not impaired. A Male's acceptable blood uric acid range can vary between 1.5 to 6.0 mg/dL, while a female's range is between 2.5 to 7.0 mg/dL. A possible reason for this discrepancy is estrogen's effect on females by increasing uric acid excretion and suppressing the URAT1 transporter in the proximal tubule (HakAE, 2008). Increases in the blood urate level beyond the solubility limit of 6.8 mg/dl increase the chance of uric acid crystal formation, also known as monosodium urate (Mandal & Mount, 2015).

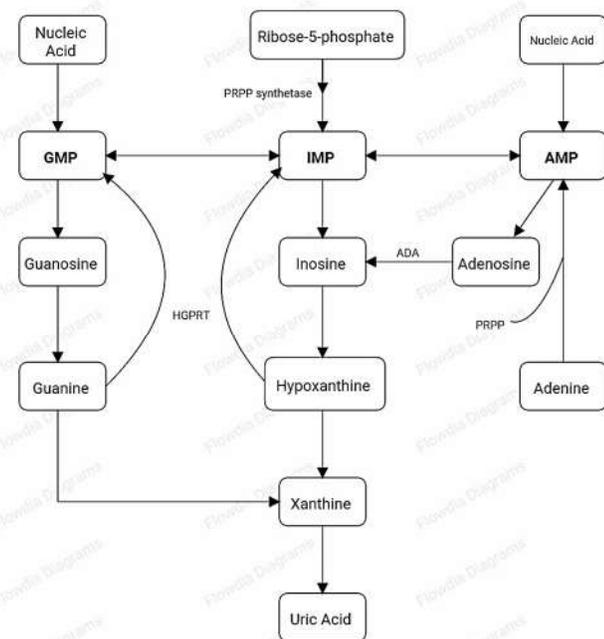
The early phases of hominoid evolution result in a functional mutation in the UOX gene, which encodes the urate oxidase enzyme. As a result, humans cannot eliminate uric acid effectively via the kidney due to a deficiency in the conversion of uric acid to more polar molecules such as allantoic acid and ammonia. Due to a lack of urate oxidase combined with considerable reabsorption of filtered urate by the renal glomerulus,

humans have higher serum uric acid levels than other animals (Mandal & Mount, 2015).

Purine metabolism is the process by which purine nucleotides such as guanosine monophosphate (GMP), inosine monophosphate (IMP), and adenosine monophosphate (AMP) are deaminated and dephosphorylated to form inosine, xanthosine, and guanosine nucleosides. These nucleosides are then further processed into purine bases hypoxanthine, xanthine, and guanine via the purine nucleoside phosphorylase (PNP) enzyme.

Meanwhile, the xanthine oxidoreductase (XOR), also known as xanthine oxidase (XAO), catalyzes the conversion of hypoxanthine to xanthine, while the guanine deaminase enzyme catalyzes the conversion of guanine to xanthine. Finally, the enzyme XOR oxidizes xanthine irreversibly to create uric acid, the final metabolite (Maiuolo et al., 2016).

Uric acid is a heterocyclic compound composed of carbon, nitrogen, hydrogen, and oxygen that is formed through the oxidation of purine in blood circulation. Uric acid is an antioxidant that aids in the prevention of inflammation, aging, and cancer. At physiological pH, uric acid occurs as a urate anion, and these urate ions are membrane-impermeable and require a transporter. The body maintains uric acid volumes by a balance of processing and excretion. The liver is the primary site of urate production, and it is excreted in the proximal tubule of the kidneys, where 90% of it is reabsorbed into the blood, aided by multiple transporters. The kidneys are critical in controlling uric acid levels, excreting 60-70% of uric acid, while the remaining 30-40% is secreted into the intestine, where it is acted upon by bacteria and then excreted from the body (Bobulescu & Moe, 2012). In the kidneys, uric acid is excreted through secretion and absorption. The resorption of uric acid is aided by numerous urate transporters (UT) present around the renal tubules (Bo et al., 2001). It has been estimated that 90% of uric acid filtered by the kidneys is reabsorbed. All of these UTs are proteins encoded by chromosomes, and any difference in these genes increases the risk of hyperuricemia and its associated complications, which include lifestyle diseases such as obesity, chronic kidney disease (CKD), cardiovascular disease, gout, and type 2 diabetes (T2DM) (Dong et al., 2017). Serum uric acid elevation is a strong indicator of vascular disorders such as peripheral neuropathy (Facchini et al., 1991). Uric acid is a strong antioxidant and a free radical scavenger. It accounts for approximately 60% of the blood's capacity to scavenge free radicals, with its concentration dramatically increasing during a stroke. Uric acid has an antioxidant activity equal to or greater than that of ascorbate, another significant antioxidant in plasma (AMES et al., 1981). Ischemic stroke is an oxidative stress-related syndrome in which a thrombus obstructs a brain artery, initiating an ischemic cascade. The infarct center is an area of the brain





that lacks blood flow and perfusion, causing irreversible damage to neural tissues and cells. The infarct center is covered by an ischemic penumbra, a region of hypoperfused but clinically viable tissue, which makes it an excellent candidate for neuroprotective therapies (Liu et al., 2010). The most common treatment for stroke at the moment is recanalization and reperfusion of thrombosed arteries using a thrombolytic agent such as recombinant tissue plasminogen activator (rtPA) (Berkhemer et al., 2015).

Uric acid or uric acid analogs have been shown in animal experiments to prevent the brain from ischemic injury by reducing infarct size and neurofunctional dysfunction (Aliena-Valero et al., 2018). Romanos et al. raised doubts on the efficacy of combining uric acid and recombinant tissue plasminogen activator therapy (rtPA). The combination procedure was shown to be superior, as it resulted in decreased post-ischemic brain neutrophil recruitment, cerebral edema, and infarct volume (Romanos et al., 2007). Clinical studies on humans were initiated as a result of the reported neuroprotective properties of uric acid. However, in humans, a mixture of negative and positive outcomes has been published. A pilot trial with stroke patients treated with rtPA showed that the administration of uric acid is completely healthy and has beneficial effects such as a decrease in oxidative stress agents (Amaro et al., 2007).

In the phase 2b/3 URICO-ICTUS clinical trial, 421 stroke patients were randomly allocated to receive either 1000 mg of uric acid or a placebo intravenously along with alteplase infusion. Although the study demonstrated that uric acid is well tolerated by patients, it did not significantly improve the proportion of patients who reached beneficial follow-up three months after stroke as compared to placebo (Chamorro, 2014). Overall, these results are corroborated by a 2016 meta-analysis of ten trials including 8,131 patients with ischemic stroke (Wang et al., 2016). The study revealed that patients with elevated serum uric acid levels at the onset of stroke had a favorable clinical result, indicating uric acid's defensive properties. Numerous mechanisms have been suggested to explain why uric acid acts as a neurotoxin. Increased uric acid levels promote smooth muscle wall proliferation, thereby increasing LDL (low-density lipoprotein) oxidation, inhibit endothelial nitric oxide synthase, resulting in endothelial dysfunction, and increase platelet-derived growth factors development, thereby optimizing platelet adhesion (Glantzounis et al., 2005). Any of these causes can initiate a cascade of coagulation, resulting in the development of thrombus and arterial occlusion, and ultimately intracranial atherosclerosis. Patetsios et al. demonstrated the direct function of uric acid in the formation of atherosclerotic plaques by comparing various samples of atherosclerotic plaques to control specimens and discovered a higher concentration of uric acid and xanthine oxidase in atherosclerotic plaque

specimens (Patetsios et al., 2001). The explanation that elevated uric acid levels are often associated with cerebrovascular morbidity is that inflammation is involved. Hyperuricemia has been shown in experimental trials to result in increased levels of inflammatory mediators such as interleukin 6 (IL-6), tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP) (Lyngdoh et al., 2011). Although more recent data indicates that uric acid can also cause systemic inflammation through the NF- κ B signaling pathway (Spiga et al., 2017). In recent years, meta-analyses conducted by Kim et al. in 2009 and Li et al. in 2013 have bolstered the case for a causal connection between stroke and elevated uric acid levels (KimsY & Km, 2009; Li et al., 2014). In our study, the mean blood uric acid level in cases was 5.41 ± 1.26 , and in control, it was 4.82 ± 1.26 mg/dl; this difference was statistically significant. Srikrishna et al. found that serum uric acid levels were significantly higher in cases as compared to controls (6.56 ± 0.73 versus 4.66 ± 0.47 , $p < 0.05$) (Srikrishna & Suresh, 2009). In the Rotterdam study, high serum uric acid levels were associated with stroke risk (Bos et al., 2006).

Longo-Mbenza et al. found significantly higher serum uric acid in males (6.6 ± 7 versus 5.8 ± 6 mg/dl, $p < 0.01$), which is contrasting to the present study where we found no significant difference (Longo-Mbenza et al., 1999). The correlation between the severity of stroke based on GCS score and uric acid levels was not statistically significant in our study (p -value being 0.2488). This finding contrasts with Kaur I et al, 2017 where they reported a statistical difference in serum uric acid level finding when the GCS score is severe (Kaur et al., 2017).

5. Limitations

This study has several limitations. Firstly, the level of serum uric acid was measured only on admission and did not include the changes to the levels of uric acid afterward including the follow-up period. Thus, repeated measurements after a certain period of time decided with patient consent are therefore imperative to precisely notice the changes in uric acid levels over time and their association with stroke outcomes. Secondly, the sample size of our study is small and it included only the Indian population so the external validity of the study is unknown. Thirdly, we also used a relatively short duration. Future studies with larger populations and longer durations will help mitigate these limitations.

6. Conclusions

In the present study, the mean serum uric acid level was higher in cases than in controls. However, the severity of stroke did not relate to serum uric acid level. Given this discovery, We can consequently report that high uric acid levels or hyperuricemia are associated with an increased stroke occurrence. Thus we can infer that serum uric acid can be utilized as neurotic biomarkers in acute ischemic stroke patients. Despite it ought not to be used to decide the



severity of acute ischemic stroke. Further long-term prospective investigations are expected to set up the role of serum uric acid in acute ischemic stroke. Additionally, the trial of serum uric acid lowering medications in stroke patients can merit considering.

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References:

- Caterina, R. D., Martinez, J. A., & Kohlmeier, M. (2020). Principles of nutrigenetics and nutrigenomics.
- Aliena-Valero, A., López-Morales, M. A., Burguete, M. C., Castelló-Ruiz, M., Jover-Mengual, T., Hervás, D., ... & Salom, J. B. (2018). Emergent uric acid treatment is synergistic with mechanical recanalization in improving stroke outcomes in male and female rats. *Neuroscience*, 388, 263-273.
- Amaro, S., Soy, D., Obach, V., Cervera, A., Planas, A. M., & Chamorro, A. (2007). A pilot study of dual treatment with recombinant tissue plasminogen activator and uric acid in acute ischemic stroke. *Stroke*, 38(7), 2173-2175.
- AMES, B. R. CATHCART, E. SCHIRRERS & P. HOCHSTEIN. (1981). Uric acid provides an antioxidant defense in humans against oxidant-and radical-caused aging and cancer: A hypothesis. *Roc. Natl. Acad. Sci. USA*, 78, 6858-6862.
- Berkhemer, O. A., Fransen, P. S., Beumer, D., Van Den Berg, L. A., Lingsma, H. F., Yoo, A. J., ... & Dippel, D. W. (2015). A randomized trial of intraarterial treatment for acute ischemic stroke. *n Engl J Med*, 372, 11-20.
- Bo, S., Cavallo - Perin, P., Gentile, L., Repetti, E., & Pagano, G. (2001). Hypouricemia and hyperuricemia in type 2 diabetes: two different phenotypes. *European journal of clinical investigation*, 31(4), 318-321.
- Bobulescu, I. A., & Moe, O. W. (2012). Renal transport of uric acid: evolving concepts and uncertainties. *Advances in chronic kidney disease*, 19(6), 358-371.
- Bos, M. J., Koudstaal, P. J., Hofman, A., Witteman, J. C., & Breteler, M. M. (2006). Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. *stroke*, 37(6), 1503-1507.
- Chamorro, A. (2014). Amaro S. Castellanos M; URICO-ICTUS Investigators. Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomized, double-blind phase 2b/3 trial. *Lancet Neurol*, 13(5), 453-60.
- Chamorro, A., Obach, V., Cervera, Á., Revilla, M., Deulofeu, R., & Aponte, J. H. (2002). Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke. *Stroke*, 33(4), 1048-1052.
- Coutts, S. B., Eliasziw, M., Hill, M. D., Scott, J. N., Subramaniam, S., Buchan, A. M., & Demchuk, A. M. (2008). An improved scoring system for identifying patients at high early risk of stroke and functional impairment after an acute transient ischemic attack or minor stroke. *International Journal of Stroke*, 3(1), 3-10.
- Dimitroula, H. V., Hatzitolios, A. I., & Karvounis, H. I. (2008). The role of uric acid in stroke: the issue remains unresolved. *The neurologist*, 14(4), 238-242.
- Dong, Z., Zhou, J., Jiang, S., Li, Y., Zhao, D., Yang, C., ... & Wang, J. (2017). Effects of multiple genetic loci on the pathogenesis from serum urate to gout. *Scientific reports*, 7(1), 1-12.
- Facchini, F., Chen, Y. D. I., Hollenbeck, C. B., & Reaven, G. M. (1991). Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *Jama*, 266(21), 3008-3011.
- Fang, J., & Alderman, M. H. (2000). Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow-up study, 1971-1992. *Jama*, 283(18), 2404-2410.
- Feigin, V. L., Lawes, C. M., Bennett, D. A., Barker-Collo, S. L., & Parag, V. (2009). *The Lancet Neurology*.
- Glantzounis, G. K., Tsimoyiannis, E. C., Kappas, A. M., & Galaris, D. A. (2005). Uric acid and oxidative stress. *Current pharmaceutical design*, 11(32), 4145-4151.
- HakAE, C. (2008). Menopause, postmenopausal hormone use, and serum uric acid levels in US women- the third National Health and Nutrition examination survey. *ArthritisRes Ther*, 10(5), 116.
- Kaur, I., Khurana, A., Sachdev, J. K., & Mohan, G. (2017). Evaluation of serum uric acid in acute ischaemic stroke. *Int J Adv Med*, 4(1), 60-65.
- KimsY, G., & Km, K. (2009). Hyperuricemiaand riskofstroke: asystematicreviewandmeta

24. Love, S., & Jenner, P. (1999). Oxidative stress in neurological disease. *Brain Pathology*, 9(1), 55-56.
25. Lyngdoh, T., Marques-Vidal, P., Paccaud, F., Preisig, M., Waeber, G., Bochud, M., & Vollenweider, P. (2011). Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. *PloS one*, 6(5), e19901.
26. Maiuolo, J., Oppedisano, F., Gratteri, S., Muscoli, C., & Mollace, V. (2016). Regulation of uric acid metabolism and excretion. *International journal of cardiology*, 213, 8-14.
27. Mandal, A. K., & Mount, D. B. (2015). The molecular physiology of uric acid homeostasis. *Annual review of physiology*, 77, 323-345.
28. Ois, A., Gomis, M., Rodríguez-Campello, A., Cuadrado-Godia, E., Jiménez-Conde, J., Pont-Sunyer, C., ... & Roquer, J. (2008). Factors associated with a high risk of recurrence in patients with a transient ischemic attack or minor stroke. *Stroke*, 39(6), 1717-1721.
29. Patetsios, P., Song, M., Shutze, W. P., Pappas, C., Rodino, W., Ramirez, J. A., & Panetta, T. F. (2001). Identification of uric acid and xanthine oxidase in atherosclerotic plaque¹. *American Journal of Cardiology*, 88(2), 188-191.
30. Romanos, E., Planas, A. M., Amaro, S., & Chamorro, A. (2007). Uric acid reduces brain damage and improves the benefits of rt-PA in a rat model of thromboembolic stroke. *Journal of Cerebral Blood Flow & Metabolism*, 27(1), 14-20.
31. Spiga, R., Marini, M. A., Mancuso, E., Di Fatta, C., Fuoco, A., Perticone, F., ... & Sesti, G. (2017). Uric acid is associated with inflammatory biomarkers and induces inflammation via activating the NF-κB signaling pathway in HepG2 cells. *Arteriosclerosis, thrombosis, and vascular biology*, 37(6), 1241-1249.
32. Srikrishna, R., & Suresh, D. R. (2009). Biochemical study of antioxidant profile in acute ischemic stroke. *BJMP*, 2(1), 35-37.
33. Truelsen, T., Begg, S., & Mathers, C. (2006). The global burden of cerebrovascular. In *Who Int*.
34. Wang, Z., Lin, Y., Liu, Y., Chen, Y., Wang, B., Li, C., ... & Zhao, W. (2016). Serum uric acid levels and outcomes after acute ischemic stroke. *Molecular neurobiology*, 53(3), 1753-1759.
35. Weimar, C., Benemann, J., Michalski, D., Müller, M., Luckner, K., Katsarava, Z., ... & Diener, H. C. (2010). Prediction of recurrent stroke and vascular death in patients with a transient ischemic attack or non-disabling stroke: a prospective comparison of validated prognostic scores. *Stroke*, 41(3), 487-493.

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