ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 08 | August - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

SERUM LEVELS OF URIC ACID AS A MARKER OF FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

Neurology

Fatima Saman Junior Resident, Department of Medicine, JNMC, AMU

Khan Ruhi* MD, DNB Assistant Professor, Department of Medicine, AMU Aligarh-202002 INDIA*Corresponding Author

Dr. Saif Quaiser Assistant Professor Department of Medicine, JNMC, AMU

ABSTRACT

Background: Functional outcome after stroke is subject to complex interactions with multiple factors. A direct relationship between the levels of the natural antioxidant uric acid and the risk of coronary or cerebrovascular ischemic events has been suggested. The exact association between stroke outcomes and serum uric acid levels remains to be elucidated. Materials and methods: This study was undertaken in the Department of Medicine, Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh, over a period of two years.102 patients who were admitted with the diagnosis of acute ischemic stroke on clinical as well as radiological grounds were recruited in the study. Results: Mean serum uric acid was 4.733 ± 1.511 mg/dl. Minimum uric acid 2.1 mg/dl and maximum uric acid was 7.2 mg/dl. The (mean ± SD) of serum uric acid was higher in patients with good outcome (6.20 ± 0.91mg/dl) and lower in patients with poor outcome (3.70 ± 0.82mg/dl). The difference between the two groups was statistically significant ($p<0.01$).Conclusion: Our study concluded that serum uric acid levels are independent predictors of good outcome in acute ischemic stroke and can be used as prognostic indicators of functional outcome at 3 months in patients of acute ischemic stroke.

KEYWORDS

Acute ischemic stroke, uric acid, functional outcome

Introduction:
Stroke is classically characterized by a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH), and is a major cause of disability and death worldwide.[1]

Functional outcome after stroke is subject to complex interactions with multiple factors, including age, gender, ethnicity, pre-existing morbidity, stroke severity, acute interventions, and post stroke care. Other important predictors of outcome include causal type of stroke, sedentary lifestyles, alcoholism and cigarette smoking, hypertension, diabetes, dyslipidemia, coronary artery disease, atrial fibrillation, and previous history of stroke or TIA.

A direct relationship between the levels of the natural antioxidant uric acid and the risk of coronary or cerebrovascular ischemic events has been suggested. Several studies have provided conflicting results about the relationship of high or low serum uric acid levels with good functional outcome after ischemic stroke. The exact association between stroke outcomes and serum uric acid levels remains to be elucidated.[2,3]

This study was intended to study the prognostic significance of blood levels of serum uric acid in patients of acute ischemic stroke.

Materials and methods: This study was undertaken in the Department of Medicine, Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh. 102 patients who were admitted with the diagnosis of acute ischemic stroke on clinical as well as radiological grounds were recruited in the study.

Inclusion criteria: All patients age ≥ 18 years presenting with acute ischemic stroke.

Exclusion criteria: Patients age < 18 years**,** Hemorrhagic stroke**,** Previous TIA/ ischemic attack**,** Hyperuricemia**,** known patients of gout**,** Fever at presentation**,** Patients who had surgery within last 3 weeks**,** Patients on immunosuppressive agents or steroids were excluded from the study.

Methodology: For the purpose of accuracy and consistency; the WHO definition of stroke was adapted. To qualify as an acute stroke; only patients who presented with a focal or global disturbance of cerebral function within 48 hours were considered. A detailed clinical history was taken and examination findings were recorded.

Complete blood counts, RFT, Blood sugar levels, lipid profile, ESR, TSH, serum uric acid, chest X-ray, ECG and brain imaging (NCCT head/ MRI brain) were done in all the patients.

Measurement of Outcome: Neurological and functional outcome was assessed by Modified Rankin Scale at day 90. We defined poor outcome as mRS 2 or more (m RS >2), because it was suggested that using this cutoff point makes it easier to define poor outcome[4].

Biochemical parameters:
Complete blood counts: By automated machine (NIKOH KOHDEN Celltac hematology analyser)

Serum uric acid: By VITROS 4600 chemistry analyser

Principle: The VITROS URIC Slide is a multilayered, analytical element coated on a polyester support. A drop of patient sample is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. Uric acid from the sample migrates to the reagent layer, where it is oxidized in the presence of uricase to form allantoin and hydrogen peroxide. Hydrogen peroxide oxidizes a leuco dye in the presence of peroxidase to generate a coloured dye. The reflection density of the dye is measured by reflectance spectrophotometry.

Specimen collection: Using standard laboratory procedure, sample should be centrifuged to separate serum within 4 hours of collection.
Normal values: Male 3.5-8.5 mg/dl, Female 2.5-6.2 mg/dl

CT scan head: was done by SOMATOM Emotion eco (16-slice configuration) which has increased efficacy with linked database, fast reconstruction, workstream 4D, and dose reduction with CARE Dose 4D.
MRI Brain: was done by the Magnetom Avanto with Tim+ Dot Fit model of Siemens with 48 channels, the most updated of 1.5 Tesla MRI scanners. A Tim+ Dot System is the landmark in 1.5T imaging. In combination with a dramatic reduction in acoustic noise and a comprehensive application range upto 205cm, whole body imaging offers a high level of flexibility with high diagnostic confidence due to exceptional magnet homogeneity for excellent fat saturation.

Statistical Analyses:
Statistical analysis was done using SPSS version 20. Results were expressed as mean ± standard deviation and percentage. Univariate analysis was performed using Independent T test for continuous variables and Chi Square test for categorical variables. Spearman's correlation coefficient (r) was used to show correlation between variables. Logistic regression analysis was used to assess the independent contribution of variables statistically significant on univariate analysis in the prediction of outcome.

Results:
Mean age of the patients was 64.69 ± 8.735 years, minimum age was 43 years and maximum age was 82 years. Out of 102 patients, 60 (59%) were males and 42 (41%) were females.

TOAST Classification: When patients were classified according to TOAST subtype, maximum number of patients were found to be of large vessel disease stroke (n =28). There were 24 patients each in the small vessel disease and undetermined etiology group. 22 patients suffered from cardio embolic stroke and 4 patients were classified as having other subtype of stroke.

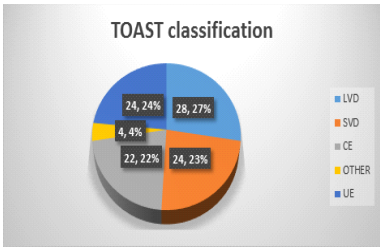

Figure 1: Distribution according to TOAST classification in study group

OCSP Classification: When patients were classified according to OCSP classification, maximum number of patients were found to be having PACS subtype of stroke (n=38). There were 22 patients each of TACS and POCS subtype and 20 patients of LACS subtype.

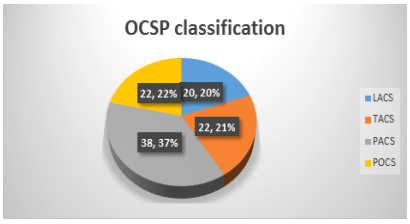

Figure 2: Distribution according to OCSP classification in study group.

Serum uric acid: Mean serum uric acid was 4.733 ± 1.511 mg/dl. Minimum uric acid 2.1 mg/dl and maximum uric acid was 7.2 mg/dl.

Table 1: Mean uric acid in study group.

	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM
S. URIC ACID	4.733	1.511	2.1	7.2

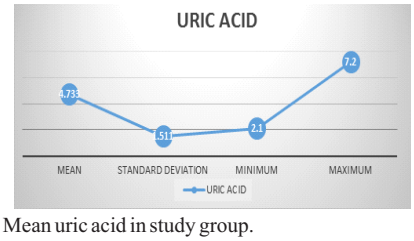

Figure 3: Mean uric acid in study group.

Modified rankin scale (m RS):
Out of 102 patients, 60 patients had poor outcome (m RS >2) and 42 patients had good outcome (m RS ≤ 2).

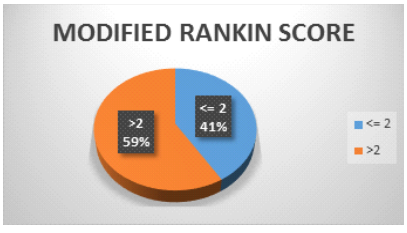

Figure 4: Distribution of poor and good outcome in study group.

For the purpose of correlation of various variables with outcome, patients were divided into 2 groups: Good outcome: m RS ≤ 2, Poor outcome: m RS > 2

TOAST Classification:
As shown in table 2, amongst patients with LVD, majority had poor outcome (n=24) and 4 had good outcome. Similarly, greater number of patients of cardio embolic stroke had poor outcome (n=16). Amongst patients of SVD, greater number (n=18) had good outcome and 6 had poor outcome. There were 4 patients of other subtype and all had good outcome. 10 patients of undetermined etiology subtype had good outcome and 14 patients had poor outcome.

The difference between the 2 outcome groups with respect to TOAST classification was statistically significant (p<0.05).

Table 2: Distribution of TOAST stroke subtypes in the 2 outcome groups.

	m RS ≤ 2	m RS > 2	X^2	p value
LVD	4(14%)	24(86%)	27.167	<0.05
SVD	18(75%)	6(25%)		
CE	6(27%)	16(73%)		
OTHER	4(100%)	0		
UE	10(41%)	14(59%)		

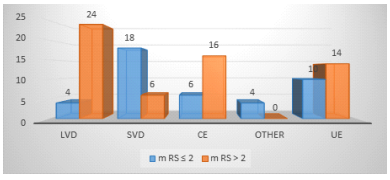

Figure 5: Distribution of TOAST stroke subtypes in the 2 outcome groups.

Serum uric acid:
As shown in table 3, the (mean ± SD) of serum uric acid was higher in patients with good outcome (6.20 ± 0.91mg/dl) and lower in patients with poor outcome (3.70 ± 0.82mg/dl). The difference between the two groups was statistically significant (p<0.01).

Table 3: Difference in mean serum uric acid in the 2 outcome groups.

	Serum Uric acid (mean ± SD)	p value
m RS ≤ 2	6.20 ± 0.91	<0.01
m RS > 2	3.70 ± 0.82	

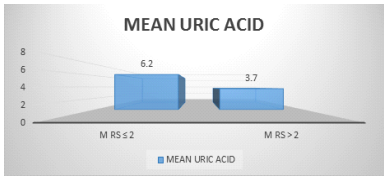

Figure 6: Difference in mean serum uric acid in the 2 outcome groups.
Also, as depicted in table 4, there was a negative correlation between serum uric acid and functional outcome according to m RS. As serum uric acid increased, m RS grade decreased with a correlation coefficient of -0.768 and the result was statistically significant (p <0.01)

Table 4: Correlation between serum uric acid and functional outcome according to m RS.

	SPEARMAN CORRELATION COEFFICIENT (r)	p value
m RS	-0.768	<0.01

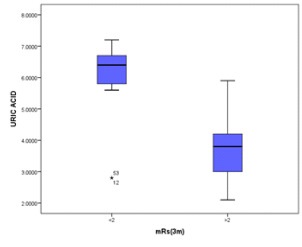

Figure 7: Box plot showing correlation between serum uric acid and functional outcome according to m RS.

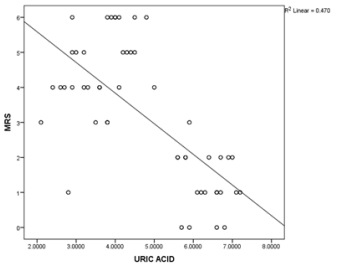

Figure 8: Scatter plot showing correlation between serum uric acid and functional outcome according to m RS.

Discussion

Studying long term stroke outcomes regarding neurological impairments as well as activity limitations, and the factors affecting them is important to guide further improvements in treatment protocol. A number of clinical variables like age, sex, initial stroke severity, subtype of stroke, smoking, alcoholism, diabetes mellitus, hypertension, CAD, and atrial fibrillation are associated with stroke. Biochemical variables like dyslipidemia, raised ESR, deranged TSH, and uncontrolled blood sugar also affect stroke outcome.

Serum uric acid, an end product of purine metabolism, has recently been studied for its anti-oxidant properties as well as a risk factor for cardiovascular and cerebrovascular atherothrombotic events.

In our study, mean age of the patients was 64.69 ± 8.735 years, minimum age was 43 years and maximum age was 82 years. Maximum patients were in the age group 60-69 years. Ginsberg et al (2013) conducted a study on 841 subjects and the mean age was 64.1 ± 12.9 years[5].

The TOAST (Trial of Org 10 172 in Acute Stroke Treatment) classification was based on clinical findings detected by history and examination, the results of brain imaging, and the findings of ancillary testing including vascular and cardiac imaging. Given in 1993, this classification system is important in determining the cause of stroke which helps in guiding further treatment. In our study, amongst patients with LVD, majority had poor outcome (n=24, 85%) and 4 had good outcome. Similarly, greater number of patients of cardio embolic stroke had poor outcome (n=16, 72%). Amongst patients of SVD, greater number (n=18, 75%) had good outcome and 6 had poor outcome. There were 4 patients of other subtype and all had good outcome. 10 (41%) patients of undetermined etiology subtype had good outcome and 14 (59%) patients had poor outcome. The difference between the 2 outcome groups with respect to TOAST classification was statistically significant ($p<0.05$). Also, on application of regression analysis, LVD was found to be an independent predictor of poor outcome and SVD was found to be an independent predictor of good outcome. Shuolin wu (2017) conducted a study on 2907 patients and found that subtype of stroke according to TOAST classification significantly affected long term functional outcomes. It was reported that 67% patients of cardio embolic stroke had poor outcomes, 59% patients of LVD had poor outcomes, and 65% patients of SVD had good outcomes. In the Tinzaparin in Acute Ischemic Stroke Trial (TAIST) trial conducted by (Sprigg et al., 2007), it was found that recovery differs amongst stroke subtypes, with SVD stroke improving most and CE the least.6 Consistent with other work, it was shown that most recovery occurs early and early recovery was associated with good functional outcome. Omori et al (2012) conducted a study on 2052 patients and found that statistically significant difference was found in m RS grades according to causal subtypes. Poor outcomes were seen the most in CE stroke (41%), and LVD (36.7%) and least in SVD stroke (20%).[7]

In our study, the (mean ± SD) of serum uric acid was higher in patients with good outcome (6.20 ± 0.91mg/dl) and lower in patients with poor outcome (3.70 ± 0.82mg/dl). The difference between the two groups was statistically significant ($p<0.01$). High uric acid levels at baseline were found to be an independent predictor of good outcome on regression analysis. Chamorro et al (2002) studied 881 subjects and found that the mean serum uric acid levels were higher in patients with no/mild disability (5.30 mg/dl) and significantly lower in patients with moderate/severe disability (4.84 mg/dl). It was also found that there was a 12% increase in the odds of good clinical outcome for each milligram per decilitre increase of uric acid.[8] Wu et al (2014) studied 1452 patients and found similar results. Wu et al (2017) conducted a study on 2907 patients and concluded that those with serum uric acid levels <3.71 mg/dl had poor functional outcome.[9,10] Wang et al(2018) divided a cohort of 1167 patients into 4 quartiles according to uric acid levels and showed that patients with uric acid levels >6.2mg/dl had the best neurological outcomes and those with serum uric acid levels <3.98 mg/dl had the worst neurological outcomes. [11]Aditya et al (2016) studied 193 ischemic stroke patients and found that higher serum uric acid level was associated with good clinical outcome.12 Similar findings were also reported by Bandyopadhyay et al (2015)[13].

However, conflicting results were reported by Weir et al (2003) who studied 3731 patients and found that higher serum uric acid levels predicted poor outcome14. Behera et al (2017) also reported same results.[15] Regarding the role of uric acid as a risk factor of cardiovascular and cerebrovascular diseases, it has been found that uric acid was an independent predictor of stroke or excess mortality in patients with non–insulin-dependent diabetes mellitus, isolated systolic hypertension, or essential hypertension. The Atherosclerosis Risk in Communities (ARIC) Study observed that the level of uric acid was directly and significantly associated with B-mode ultrasound carotid intimal-medial thickness[16]. The Framingham cohort also found a greater risk for developing cardiovascular disease in male subjects with gout [17]. Contrarily, the Framingham Heart Study did not find uric acid to be an independent risk factor for cardiovascular disease[18]. Therefore, it has been argued that hyperuricemia could be a compensatory mechanism to counteract oxidative damage related to atherosclerosis and aging in humans. Our findings further suggest that increased uric acid concentration provides a more efficient antioxidant capacity that decreases the adverse effects of brain ischemia.

Assuming the importance of oxidative stress in patients with brain ischemia, antioxidant property of uric acid is recently being evaluated as therapeutic intervention in ischemic stroke. Romanos et al (2007) reported that urate exerts additive neuroprotection to the benefits of recombinant tissue plasminogen activator in a rat model of thromboembolic stroke[19]. Waring et al (2003) showed that high UA concentrations are associated with increased serum antioxidant capacity and reduced oxidative stress during acute physical exercise in healthy subjects[20]. These findings indicate that the antioxidant properties of UA are of biological importance in vivo. Llull et al (2015) conducted a study which showed that in women with acute ischemic stroke treated with alteplase, the administration of UA reduced infarct growth in selected patients and was better than placebo to reach excellent outcome[21]. Chamorro et al (2017) showed in a cohort of 45 patients that uric acid therapy was safe and improved outcomes in stroke patients receiving intravenous thrombolysis followed by thrombectomy[22]. With even more emerging evidence, it is quite probable that uric acid can be used as a potential future therapy for ischemic stroke patients.

Conclusion

Our study concludes that serum uric acid levels are independent predictors of good outcome in acute ischemic stroke and can be used as prognostic indicators of functional outcome at 3 months in patients of acute ischemic stroke.

REFERENCES

1. Sacco, R.L., Kasner, S.E., Broderick, J.P., Caplan, L.R., Connors, J.J., Culebras, A., Elkind, M.S., George, M.G., Hamdan, A.D., Higashida, R.T. and Hoh, B.L., (2013). An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 44(7), pp.2064-2089.
2. Zhang, Q., Lei, Y.X., Wang, Q., Jin, Y.P., Fu, R.L., Geng, H.H., Huang, L.L., Wang, X.X. and Wang, P.X., (2016). Serum albumin level is associated with the recurrence of acute ischemic stroke. The American journal of emergency medicine, 34(9), pp.1812-1816.
3. Zhang, X., Huang, Z.-C., Lu, T.-S., You, S.-J., Cao, Y.-J., & Liu, C.-F. (2016). Prognostic Significance of Uric Acid Levels in Ischemic Stroke Patients. Neurotoxicity Research, 29(1), 10–20.
4. Sulter, G., Steen, C., & De, J. K. (1999). Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke, 30(8), 1538–1541.
5. Ginsberg, M.D., Palesch, Y.Y., Hill, M.D., Martin, R.H., Moy, C.S., Barsan, W.G., Waldman, B.D., Tamariz, D. and Ryckborst, K.J., (2013). High-dose albumin treatment for acute ischaemic stroke (ALIAS) Part 2: a randomised, double-blind, phase 3, placebo-controlled trial. The Lancet Neurology, 12(11), pp.1049-1058.
6. Sprigg, N., Gray, L.J., Bath, P.M., Lindenstrøm, E., Boysen, G., De Deyn, P.P., Friis, P., Leys, D., Marttila, R., Olsson, J.E. and O'Neill, D., (2007). Early recovery and functional outcome are related with causal stroke subtype: data from the tinzaparin in acute ischemic stroke trial. Journal of Stroke and Cerebrovascular Diseases, 16(4), pp.180-184.
7. Omori, T., Kawagoe, M., Moriyama, M., Yasuda, T., Ito, Y., Hyakuta, T., Ebara, T. and

Matsumoto, M., (2013). Difference in prognoses among subtypes after first-ever ischemic stroke. Nagoya Med. J, 53, pp.1-10.
8. Chamorro, A., Obach, V., Cervera, A., 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.
9. Wu et al (2017) Wu, H., Jia, Q., Liu, G., Liu, L., Pu, Y., Zhao, X., Wang, C., Wang, Y. and Wang, Y., (2014). Decreased uric acid levels correlate with poor outcomes in acute ischemic stroke patients, but not in cerebral hemorrhage patients. Journal of Stroke and Cerebrovascular Diseases, 23(3), pp.469-475.
10. Wu, S., Pan, Y., Zhang, N., Jun, W. Y., Wang, C., & Investigators for the Survey on Abnormal Glucose Regulation in Patients With Acute Stroke Across China (ACROSS-China). (2017). Lower serum uric acid level strongly predict short-term poor functional outcome in acute stroke with normoglycaemia: a cohort study in China. BMC Neurology, 17(1), 21.
11. Wang, Y.-F., Li, J.-X., Sun, X.-S., Lai, R., & Sheng, W.-L. (2018). High serum uric acid levels are a protective factor against unfavourable neurological functional outcome in patients with ischaemic stroke. Journal of International Medical Research, 46(5), 1826–1838.
12. Aditya, S., Ghosh, S., Banerjee, J., Saha, S., Sengupta, S., & Ganguly, S. (2016). Prognostic Importance of Serum Uric Acid in Acute Ischaemic Stroke, Indian Journal of Basic and Applied Medical Research: 5(2), 6.
13. Bandyopadhyay, D., Hajra, A., Mukhopadhyay, S., Layek, M., Bhowmick, D., Ganeshan, V., Karmakar, P. S. (2015). Prognostic Significance of Serum Uric Acid at the Time of Admission in Patients with Acute Stroke. American Journal of Clinical Medicine Research, 3(2), 24–30.
14. Weir, C. J., Muir, S. W., Walters, M. R., & Lees, K. R. (2003). Serum Urate as an Independent Predictor of Poor Outcome and Future Vascular Events After Acute Stroke. Stroke, 34(8), 1951–1956.
15. Behera, B. K., Hui, P. K., & Simethy, R. (2017). Serum uric acid level in acute ischemic stroke in eastern India. International Journal of Research in Medical Sciences, 5(6), 2353.
16. Iribarren, C., Folsom, A. R., Eckfeldt, J. H., McGovern, P. G., & Nieto, F. J. (1996). Correlates of uric acid and its association with asymptomatic carotid atherosclerosis: The ARIC study. Annals of Epidemiology, 6(4), 331–340.
17. Abbott, R. D., Brand, F. N., Kannel, W. B., & Castelli, W. P. (1988). Gout and coronary heart disease: The Framingham study. Journal of Clinical Epidemiology, 41(3), 237–242.
18. Culleton, B. F., Larson, M. G., Kannel, W. B., & Levy, D. (1999). Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study. Annals of Internal Medicine, 131(1), 7.
19. Romanos, E., Planas, A. M., Amaro, S., & Chamorro, Á. (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.
20. Waring, W. S., Convery, A., Mishra, V., Shenkin, A., Webb, D. J., & Maxwell, S. R. J. (2003). Uric acid reduces exercise-induced oxidative stress in healthy adults. Clinical Science, 105(4), 425–430.
21. Llull, L., Laredo, C., Renú, A., Pérez, B., Vila, E., Obach, V., Urra, X., Planas, A., Amaro, S. and Chamorro, Á., (2015). Uric acid therapy improves clinical outcome in women with acute ischemic stroke. Stroke, pp.STROKEAHA-115.
22. Chamorro, Á., Amaro, S., Castellanos, M., Gomis, M., Urra, X., Blasco, J., Arenillas, J.F., Román, L.S., Muñoz, R., Macho, J. and Cánovas, D., (2017). Uric acid therapy improves the outcomes of stroke patients treated with intravenous tissue plasminogen activator and mechanical thrombectomy. International Journal of Stroke, 12(4), pp.377-382.