

ROLE OF RAISED SERUM URIC CONCENTRATION IN INDUCING THE ACUTE ISCHEMIC STROKE- A PROSPECTIVE COHORT STUDY

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Abstract

Background: The role of uric acid as a risk factor for acute ischemic stroke is controversial, and little is known about its role as a risk factor. Recent evidence suggests uric acid may be an essential causal agent in precipitating stroke. Some research also proposed uric acid as a potent antioxidant to protect the brain from free radicals generated during acute ischemic stroke. **Materials and Methods:** The study was based on 100 patients of age group 29-87 years (60.49±13.98 years) who were admitted with acute ischemic stroke in the Department of General Medicine, Father Muller's Medical College, Mangalore, for 18 months. Within 24 hours, serum uric acid (SUA) was measured and analyzed against various modifiable and non-modifiable risk factors such as age group, gender, hypertension, diabetes, and smoking habit. The NIHSS scale was employed to measure stroke severity, and the mRS Scale was used to measure stroke outcomes at day 0, 7th and 30th post-stroke. **Results:** Higher incidence of stroke occurred in patients with age groups of 41-50 and 61-70 years. However, no significant relationship ($p = 0.2947$) was established between mean SUA and age-group-associated stroke. A significant relationship ($p = 0.0003$) was observed between male mean SUA (5.84 ± 1.64) and hypertension. Hypertensive and smoking habit patients showed a significant relationship with mean SUA, $p = 0.0333$ and $p = 0.0002$. However, no significant correlation ($p = 0.4597$) between diabetic status and mean SUA was established. **Conclusion:** This study concluded that although age, hypertension, diabetes, and smoking are various risk factors associated with ischemic, there is no significant relation between baseline serum uric acid with the risk factors, except with hypertension and smoking habit.

INTRODUCTION

Stroke is the third most frequent cause of disability and the second most frequent cause of death worldwide. The prevalence of stroke ranges from 84-262/1,00,000 in rural settings to 334-424/1,00,000 in urban areas in India.^[1] Stroke is broadly classified into two major groups: Ischemic and hemorrhagic stroke.^[2] The term acute ischemic stroke (AIS) is used for a stroke that has started within the previous 24 hours or less.

The risk factors associated with stroke are classified into modifiable and non-modifiable categories. Modifiable risk factors like diabetes, hypertension, carotid stenosis, cardiac disease, lifestyle issue (e.g., smoking, tobacco use, excessive alcohol, physical inactivity), oral contraceptives, obesity, etc. Non-modifiable risk factors like age, gender, race, ethnicity, migraine history, family history of stroke,

etc.^[3] Serum uric acid has emerged as one of the risk factors for stroke in various studies.^[4]

Uric acid is derived from the enzymatic degradation of purine compounds. At physiological pH, it exists almost entirely in its ionized form as urate. Urate may play an antioxidant role in people due to its capacity to chelate transition metals and scavenge peroxynitrite, hydroxyl radicals, and singlet oxygen.^[5] Given its relatively high oxygen consumption, presence of highly peroxidizable lipids, and high concentration of iron, the brain is particularly vulnerable to damage caused by free radicals. Additionally, free radicals and other byproducts of oxidative damage are released into the bloodstream during cerebral ischemia and reperfusion.^[6]

In contrast to its antioxidant activity, uric acid can sometimes become a pro-oxidant by reacting with other oxidants to produce radicals. These radicals target lipids (LDL and membranes) more than other

cellular components. The hydrophobic environment that lipids generate makes it difficult for uric acid to exert its antioxidant properties, and damaged lipids can even cause uric acid to become an oxidant.^[7] Epidemiological studies have shown evidence that the underlying cause of gout hyperuricemia is linked to an increased risk of cerebrovascular (CV), hypertensive, and renal disease events, including stroke.^[8,9] Additionally, it has been demonstrated that therapeutic approaches that have the potential to reduce SUA reduced CV disease morbidity and mortality. The risk of stroke and all other atherosclerotic vascular disease symptoms is two to four times higher in people with NIDDM. According to one study, hyperuricemia, which is independent of other CV risk factors, is a reliable predictor of stroke occurrences in middle-aged patients with NIDDM.^[10] These observations have prompted interest in the potential impact of raised UA concentrations in the setting of acute ischemic stroke.

Given the above discrepancies, we used a prospective cohort study design to investigate the relationship between serum uric acid and acute ischemic stroke severity and its outcome up to one month. Age group and gender were taken as non-modifiable risk factors, whereas hypertension, diabetes, and smoking habit were taken as modifiable risk factors. The vascular territory was used to classify the stroke area. The NIHSS scale was used to measure stroke severity, and a modified Rankin scale was employed to measure the stroke outcomes. Serum uric acid was measured using a urate oxidase reagent and a Dax analyzer (Bayer-Technichon) at the time of admission.

MATERIALS AND METHODS

Study Population

This study was conducted among 100 subjects of the age group 29-87 years in the Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai for 18 months. A written, voluntarily informed consent was acquired from each subject after the study's ethical approval by DMCH, Darbhanga. Each subject was informed of their participation in the study in their native tongue. The subjects were included and excluded based on 'Inclusion & Exclusion Criteria'.

Inclusion Criteria

Participants were included, if they had a confirmed stroke history as described by the World Health Organization (WHO) or as defined by clinical criteria (confirmed by imaging, when possible), such as cerebral infarction, intracerebral haemorrhage, subarachnoid haemorrhage, or uncertain pathological subtypes. Age, sexual orientation, and other factors like protein folding and misfolding were not constrained (e.g., degree of impairment post-stroke or interventions received).^[11,12]

- Patients diagnosed with an acute ischemic stroke within 48 hrs of onset.
- Age > 18 years to 65 years.

Exclusion Criteria

- Patients who have experienced a transient ischemic attack or cerebrovascular accident in the past.
- Patients with other identified risk factors such renal failure, leukemia, lymphoma, hemolytic anemia, psoriasis, or hyperparathyroidism that are known to raise serum uric acid levels.
- Patients taking drugs that are known to raise serum uric acid levels like aspirin, diuretics, vitamin B-3, chemotherapeutic agents, immune-suppressing drugs, angiotensin receptor blockers, anti-tuberculosis drug like pyrazinamide, dopamine precursors i.e., levodopa, and on regular antioxidant/ multivitamin supplement therapy prior to the stroke.
- Patients diagnosed to have gout.

On admission, a complete medical history, including a history of smoking, cardiovascular event, renal problems, gout, and diabetes, was recorded in the Master Chart. The National Institute of Health Stroke Scale (NIHSS Score) was used to determine the severity of the stroke.^[13,14] Different biochemical tests such as serum creatinine, blood urea, uric acid, and HbA1C were carried out. Modified Rankin Scale (mRS) was used to evaluate the stroke outcome using a follow-up questionnaire and clinical examination on days zero, 7, and 30 post-strokes.^[15] The subjects were then divided into the following modifiable and non-modifiable risk factors (variables), their serum uric acid was determined at each level, and any relationship with variables was established:

1. Age and Gender Distribution: The subjects were distributed in an age group of 10 years each. Further, they were also divided on the basis of sex.
2. Risk Factor: The chosen patients were screened for hypertensive status, diabetic status and smoking history. HbA1c value $\leq 6\%$ were assigned non-diabetic while $> 6\%$ were assigned diabetic.
3. Vascular Territory of Brain: Subjects were divided into on the basis of various vascular territory of brain as follows:
 - MCA - Middle cerebral artery territory infarct
 - PCA - Posterior cerebral artery territory
 - ACA - Anterior cerebral artery territory
 - Mix - Multiple territories - 5% of cases
4. NIH Stroke Scale measurement: The NIH Stroke Scale is a widely used tool built to assess a stroke's cognitive effects. In more scientific terms, it "provides a quantitative measure of the stroke-related neurologic deficit".^[16] The scale consists of 11 factors: Level of consciousness, Best gaze, Visual, Facial Palsy, Motor Arm, Motor Leg, Limb Ataxia, Sensory, Best Language, Dysarthria, Extinction and

Inattention. Each ability is given a score between 0 and 4, with 0 representing normal functioning and 4 representing severe impairment. The patient's NIHSS score is determined by summing the values for each component of the scale (Table 1); the maximum score that may be achieved is 42.^[16]

5. The modified Rankin Scale (mRS) is a frequently used scale for assessing the level of dependency or disability in daily activities in individuals who have experienced a stroke or other neurological condition.^[17,18] The modified Rankin Scale (mRS) range is 0-6, which indicates the stroke outcomes (Table 2).

Laboratory Measurement

On the first day of presentation, blood samples from all study participants were collected, and the blood was centrifuged for 10 minutes at 3000 rpm to separate the serum as supernatant. Using urate oxidase reagent and a Dax analyzer (Bayer-Technichon), uric acid was determined in the serum according to accepted laboratory practices. The interassay coefficient of variation was 3.5%, according to an external quality control program.^{19, 20} The classification of the SUA level under low, normal and high group is shown in Table 3. Statistical Analysis

The Statistical Package for the Social sciences (SPSS) (v25, SPSS Inc., Chicago. IL, USA) and Microsoft Excel 2016 (Microsoft Corporation, NY, USA) were used to calculate frequencies, percentages, means, standard deviations (S.D.). Based on the number of test group either Unpaired t-test or one-way ANOVA were applied to calculate the 'p' value. A significant relationship is deemed to exist when the "p" value is less than 0.05.

RESULTS

100 subjects were included in this study based on inclusion and exclusion criteria. The age of patients was ranged from 29-87 years with mean age 60.49±13.98 years. The patients were grouped in various age groups as shown in Table 4 with their mean SUA concentration. Higher incidence of stroke was occurred in patients with age group of 41-50 and 61-70 years. However, no significant relationship ($p = 0.2947$) was established between mean SUA and stroke incidence.

Most male and female patients presented with acute ischemic stroke belonged to normal SUA level (3.1-6.9 mg/dl) measured at presentation with 74% in the male group and 84% in the female groups. Mean serum uric acid of the male group was found higher than female group. A significant correlation ($p = 0.0003$) was observed between mean SUA and stroke occurrence (Table 5).

Regardless of the type of stroke, hypertension is one of the main causes of morbidity and mortality.^{21, 22} Along with hypertension, age, diabetes, and smoking habit is also a risk factor for stroke. In this

study, hypertension was 2nd major risk factor after diabetes. Among 100 patients presented with acute ischemic stroke, most of them belonged to normal SUA level (3.1-6.9 mg/dl) measured at presentation with 39 patients in non-hypertensive group and 40 patients in hypertensive groups (Figure 1). The mean uric acid level in hypertensive group is 5.60 mg/dl and in non-hypertensive group is 4.92 mg/dl. The current study shows significant association ($p = 0.0333$) between hypertension and serum uric acid concentration (Table 5).

One of the major risk factors for an ischemic stroke is undoubtedly diabetes, particularly in people under the age of 65.²³ In this study, diabetes was found a leading risk factor among the hypertension, diabetes and smoking condition with 65% patients who were admitted with acute ischemic stroke. Among those, 50 patients were associated with normal SUA level (3.1-6.9 mg/dl), 10 patients found with level of SUA (> 7 mg/dl), and 5 patients were found with low level of SUA (Figure 2). The mean uric acid level in diabetic group is 5.19 mg/dl and in non-diabetic group is 5.44 mg/dl with no significant association ($p = 0.4597$) between diabetes and serum uric acid concentration.

Cigarette smoking is one of the most significant, and preventable, risk factors for stroke; it is believed that up to 25% of all strokes are caused by smoking. In men and women of all examined races, smoking is positively correlated with an elevated risk of stroke.²⁴ In this study 32% patients who were admitted with acute ischemic stroke were found to be smoker. Smoking was 3rd leading risk factor for stroke after diabetes and hypertension in our study. The mean uric acid level in smoking habit group is 6.13 mg/dl and in non-smoking habit group is 4.87 mg/dl. A significant association ($p = 0.0002$) was found between smoking history and serum uric acid concentration (Figure 3).

Vascular territory was utilized to categories strokes because it is practical and often used by clinicians, and primary objective of this prospective study of the stroke database is to offer baseline and comparative demographic, clinical, and functional outcome data of ischemic stroke.²⁵ The distribution of vascular territory and with a number of patients associated with those infarct regions are shown in Table 5. A maximum number of infarcts ($n = 54$) were shown in a middle cerebral artery (MCA) with 40 patients out of these in the normal range of SUA (Figure 4).

The NIH Stroke Scale is a widely used tool built to assess a stroke's cognitive effects. In more scientific terms, it "provides a quantitative measure of stroke-related neurologic deficit".¹⁶ The distribution of NIHSS score with serum uric acid level is given in Figure 5. Among 100 cases of ischemic stroke in this study, 50 patients belonging to minor stroke had a mean uric acid of 5.39 mg/dl, 37 patients with moderate stroke were associated with 5.06 mg/dl mean SUA, nine patients moderate to severe stroke were found with 5.76 mg/dl mean SUA, and 4

patients belonging to severe stroke had a mean uric acid level of 4.7 mg/dl (Table 5). Statistically no significant relationship was established between mean uric acid values and NIHSS score on admission ($p = 0.5235$).

The modified Rankin Scale (mRS) is a frequently used scale for assessing the level of dependency or disability in daily activities in individuals who have experienced a stroke or other neurological condition.^{17, 18} The distribution of cases of 100 patient of ischemic stroke with levels of uric acid and mRS score on day 7 and day 30 since admission was studied for any significance relationship. The results are given in Table 5 and SUA level distribution is shown in Figure 6 and Figure 7. However, on both days, i.e., 7th and 30th there is no statistically significant relationship was established between mean uric acid values and mRS Score on admission.

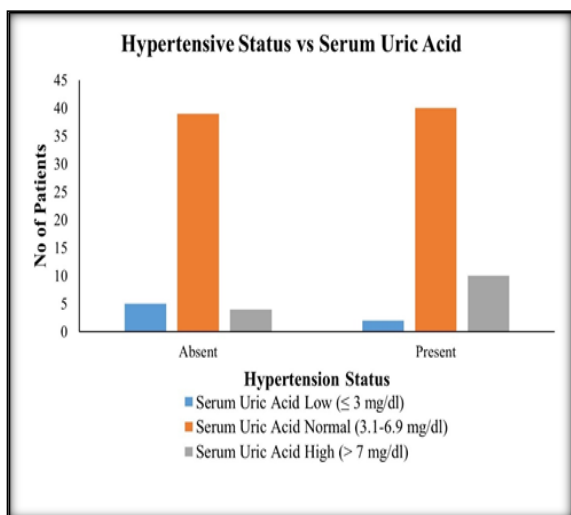


Figure 1: Serum uric acid level variation in hypertensive patients

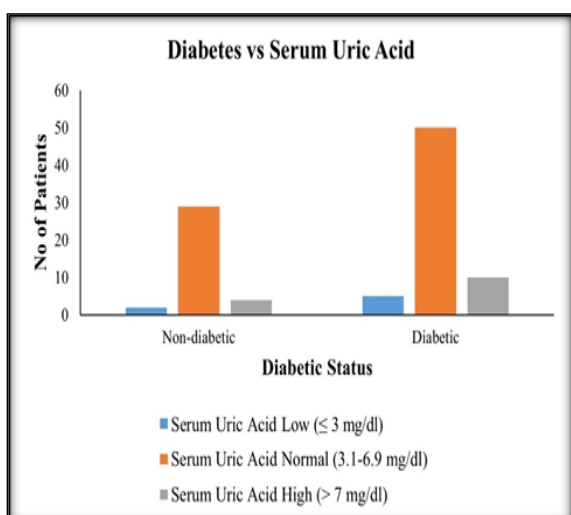


Figure 2: Serum uric acid level variation in diabetic patients

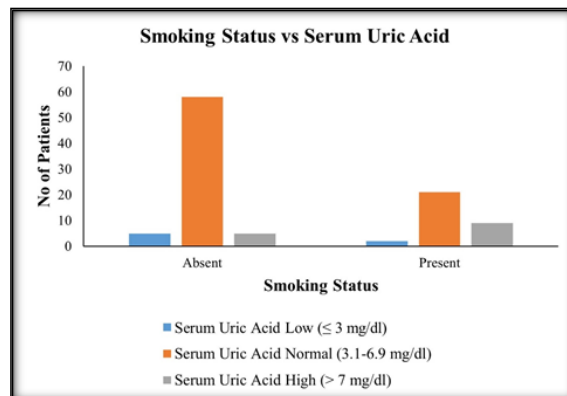


Figure 3: Serum uric acid level in patients with smoking history

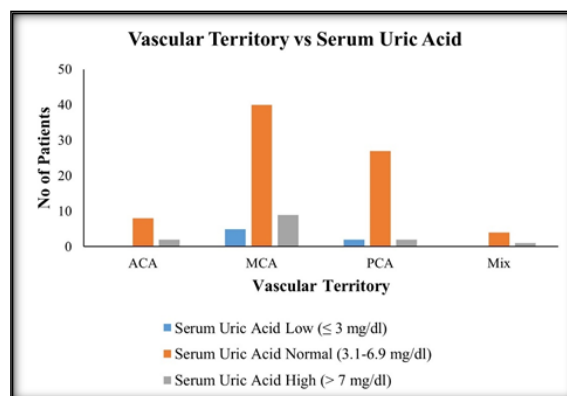


Figure 4: Serum uric acid level in patient with vascular territory infarct

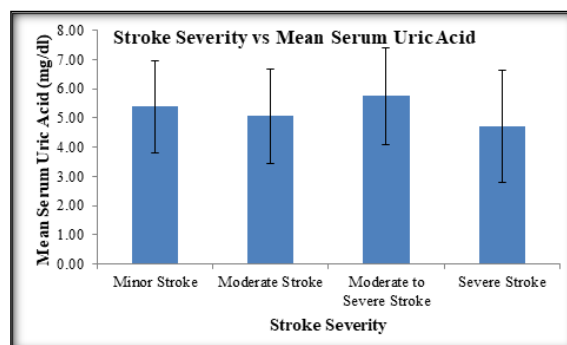


Figure 5: Mean uric acid levels with NIHSS

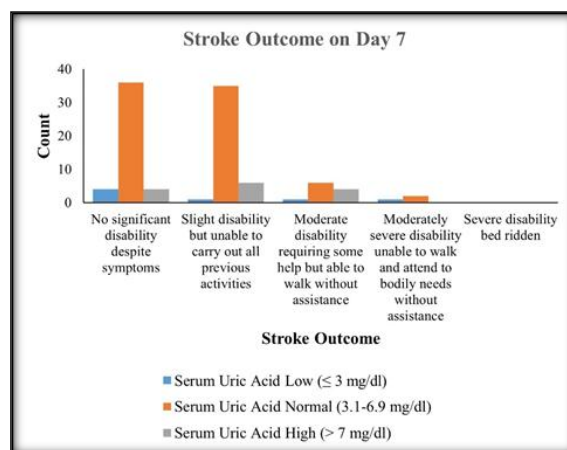


Figure 6: mRS Score (day 7) with serum uric acid level distribution

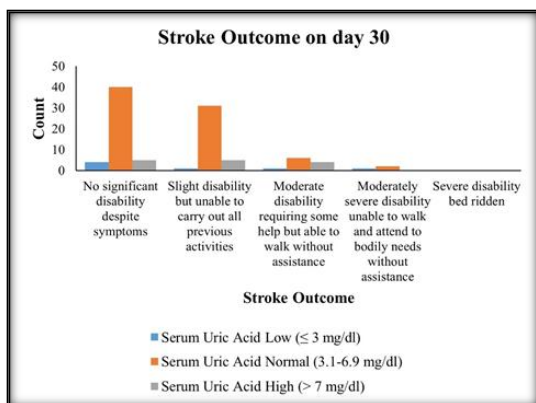


Figure 7: mRS Score (day 30) with serum uric acid level distribution

Table 1: Stroke score and related severity as per NIH Stroke Scale

S. No.	Score	Stroke Severity
1.	0	No Stroke Symptoms
2.	1-4	Minor Stroke
3.	5-15	Moderate Stroke
4.	16-20	Moderate to severe stroke
5.	21-42	Severe Stroke

Table 2: modified Rankin Scale (mRS) range and associated explanation

mRS Range	Stroke Outcome
0	No symptoms
1	No obvious disability. Despite minor symptoms, able to perform all daily tasks.
2	Slight disability. Able to manage one's affairs on their own without help, yet unable to perform all prior activities.
3	Moderate disability. Able to walk without assistance, but needs some assistance.
4	Moderately Severe Disability. Unable to walk without assistance and unable to care for one's own physical requirements.
5	Severe disability. A bedridden and incontinent, and requires ongoing nursing care.
6	Death

Table 3: Classification of serum uric acid level

Serum Uric Acid Level	Range
Low	≤ 3 mg/dl
Normal	3.1-6.9 mg/dl
High	> 7 mg/dl

Table 4: Age distribution of patients and their mean serum uric acid

Age Group	No of Patients	Percentage	Mean Serum Uric Acid (mg/dl)
21-30	2	2%	4.96±1.64
31-40	4	4%	5.38±1.32
41-50	24	24%	4.87±1.49
51-60	22	22%	5.64±2.15
61-70	24	24%	5.43±1.46
71-80	17	17%	4.76±1.26
81-90	7	7%	6.24±0.82
Grand Total	100	100%	5.27±1.60

Table 5: Serum uric acid concentration on admission in relation to gender and other risk factors

Variables	No of Subjects				p value
	Low Serum Uric Acid (≤ 3 mg/dl)	Normal Serum Uric Acid (3.1-6.9 mg/dl)	High Serum Uric Acid (> 7 mg/dl)	Serum Uric Acid (mg/dl) (Mean ± S.D.)	
Gender					
Male	2	37	11	5.84±1.64	0.0003
Female	5	42	3	4.71±1.35	
Hypertensive Status					
Present	2	40	10	5.6±1.74	0.0333
Absent	5	39	4	4.92±1.37	
Diabetic Status					
Present	5	50	10	5.19±1.50	0.4597
Absent	2	29	4	5.44±1.79	
Smoking History					
Present	2	21	9	6.13±1.85	0.0002
Absent	5	58	5	4.87±1.30	
Vascular Territory Infarct					
ACA	0	8	2	5.24±1.14	0.5948
MCA	5	40	9	5.21±1.86	
PCA	2	27	2	5.24±1.24	
Mix	0	4	1	6.24±1.40	
NIHSS Range					
1-4	1	43	6	5.39±1.57	0.5235
5-15	4	26	7	5.06±1.61	
16-20	1	7	1	5.76±1.66	
21-42	1	3	0	4.70±1.91	
mRS Score (Day 0)					
1	0	13	1	5.27±1.45	0.5437
2	5	34	7	5.06±1.77	
3	1	24	5	5.51±1.37	
4	0	6	1	5.93±1.43	
5	1	2	0	4.63±2.34	

mRS Score (Day 7)					
1	4	36	4	4.87±1.34	0.0832
2	1	35	6	5.57±1.71	
3	1	6	4	5.94±1.71	
4	1	2	0	4.63±2.34	
5	0	0	0	0±0	
mRS Score (Day 30)					
1	4	40	5	4.90±1.31	0.0769
2	1	31	5	5.62±1.78	
3	1	6	4	5.94±1.71	
4	1	2	0	4.63±2.34	
5	0	0	0	0±0	

DISCUSSION

In this study, 100 cases with acute ischemic stroke were chosen based on the inclusion and exclusion criteria over a period of 18 months. This study was conducted to study the role of serum uric acid in acute ischemic stroke and its effect on stroke outcomes.

The most common, non-moveable risk factor for stroke is age. The majority of stroke patients were among the 5th decade and 7th decade of life. The mean age group of the patients in this study was 60.49 (S.D. = 13.98) years. Murray et al. investigated the relationship between SUA and stroke in 163 people over the age of 70 and came to the conclusion that SUA raises the risk of acute ischemic stroke in elderly patients.^[26] This study, however, did not show evidence of a significant association between SUA and elderly stroke patients, as most of them belonged to the normal range of SUA.

Both male and female subjects were selected equally in this study, i.e., 50% each. Among the male and female patients presented with acute ischemic stroke, most of them belonged to normal SUA level (3.1-6.9 mg/dl) measured at presentation with 74% in male group and 84% in the female group. A significant variation ($p = 0.0003$) in the mean uric acid level was found between the male (5.84 mg/dl) and female group (4.71 mg/dl).

The most frequent modifiable risk factor for stroke is hypertension. Hypertension is frequently linked to high SUA.^[22] 52% of the stroke patients in the current study had hypertension. Patients with hypertension had mean serum uric acid levels of 5.60 mg/dl, compared to 4.92 mg/dl in non-hypertensive individuals. As a result, this study found a statistically significant link between serum uric acid and hypertension ($p = 0.0333$).

This study found that 65% of the patients had diabetes, making it the primary risk factor. According to a study by Lehtos et al. that involved 1017 people with NIDDM, hyperuricemia is a significant independent predictor of stroke occurrences in middle-aged people with NIDDM.¹⁰ In this study, no statistically significant association ($p=0.4597$) was found between the level of uric acid and diabetes mellitus. Among diabetics, the mean serum uric acid value is 5.19 mg/dl while among non-diabetic its 5.44 mg/dl.

In this study 32% patients who were admitted with acute ischemic stroke were found to be smoker, making the smoking habit as the 3rd leading risk factor for stroke after diabetes and hypertension in our study. In the present study mean SUA level in smokers (6.13 mg/dl) was significantly higher ($p = 0.0002$) as compared to non-smokers (4.87 mg/dl). In a related study, Strasak et al. found that SUA and smoking had a positive connection ($r = 0.11$, $P < 0.001$).²⁷ Similarly, Mozos et al. found, SUA levels were significantly higher ($P < 0.05$) in smokers (5.7±1.3 mg/dl) compared to non-smokers (5.0±1.1 mg/dl).^[28]

Among the various vascular territory, infarcts severely affected the middle cerebral artery region (54% of patients). Almost 40 patients who were diagnosed with middle cerebral artery infarction were also associated with normal SUA (3.1-6.9 mg/dl). The mean SUA in these 54% of patients were found 5.21 mg/dl. However, no significant difference between SUA level was found among ACA, MCA and PCA.

The National Institute of Health Stroke Scale (NIHSS) was used to quantify stroke severity. Higher NIHSS scores have been shown to predict a poor prognosis after stroke in prior investigations.^[28,29] There was no relationship between SUA level and NIHSS score upon admission in the current study ($P 0.5235$).

The modified Rankin Scale (mRS) is a frequently used scale for assessing the level of dependency or disability in daily activities in individuals who have experienced a stroke or other neurological condition. However, no significant relationship was found between serum uric acid and stroke outcome measured by mRSS scale methodology on 0, 7th and 30th day after stroke.

CONCLUSION

This study concluded that although age, hypertension, diabetes, and smoking are risk factors associated with ischemic stroke, there was no significant relation of baseline serum uric acid with the risk factors, except hypertension and smoking.

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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