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Prognostic Significance of Serum Uric Acid at the Time of Admission in Patients with Acute Stroke

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Abstract **Background & objectives**: Stroke is the one of the important causes of death.Uric acid is described as a strong endogenous antioxidant that is consumed early in acute stroke. Uric acid being an aqueous antioxidant can become a pro-oxidant under certain circumstances, particularly, if other antioxidants such as ascorbate are low. This work was conducted to find an association between serum uric acid levels at the time of admission with functional outcome in patients with acute stroke. **Method**: This study was carried out on 96 patients of stroke including both ischemic and hemorrhagic stroke. Sampling scheduled one day of the week by rotation to avoid selection bias and the study design was descriptive, observational, cross-sectional study. **Result**: we found statistically significant positive correlation between serum uric acid level and change in Mathew score in ischemic stroke patients and poor positive correlation between uric acid level and change of Mathew score in hemorrhagic stroke patients. **Conclusion**: High serum uric acid level is associated with good neurological outcome in patients with acute ischemic stroke. A high serum uric acid level is associated with insignificant poor neurological outcome in patients with hemorrhagic stroke.

Keywords: *acute stroke, mathew score, Uric acid (UA)*

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1. Background and Main Text

Worldwide, stroke is the second most common cause of death behind disease of the heart. [1] Between 1998 and 2008 the annual strokedeath rate decreased by 35%, but stroke remains a leading causeof long-term disability [2].

Cerebrovascular diseases include some of the most common and devastating disorders: ischemic stroke, hemorrhagic stroke, and cerebrovascular anomalies, such as intracranial aneurysms and arteriovenous malformations. [3] The oxidative stress that follows acute strokes has more recently been implicated in the neuronal injury, which to a large extent influences the severity and outcome. [4] Oxidative stress is caused by reactive intermediate oxygen and nitrogen species called free radicals, which have largely deleterious effects in biologic tissues and antioxidants, are known to counteract, or in the least, mitigate their deleterious effects [5].

The catabolic steps that generate uric acid from nucleic acid and free purine nucleotides involve degradation to hypoxanthine and xanthine through purine nucleoside intermediates. Some of the hypoxanthine formed by the nucleoside turnover is diverted to the liver and metabolized in sequential reaction catalyzed by Xanthine oxidase to uric acid: the remainder is salvaged to Hypoxanthine-Guanine phosphoribosyltransferase (HGPRT). Serum uric acid reflects the interactions of four major processes: dietary purine intake, endogenous purine metabolism, urinary urate excretion, and intestinal uricolysis. [6] Once thought to be a metabolically inert product of purine metabolism, uric acid is now being recognized as a potent antioxidant with a concentration in plasma that is nearly 10 times higher than other antioxidants, including vitamins C and E, therefore accounting for a substantial part of the antioxidant property of plasma. [7] It is particularly effective in neutralizing hydroxyl, superoxide and peroxynitrite radicals and may serve a protective physiological role by preventing lipid peroxidation [8,9].

In a variety of organs and vascular beds, local uric acid concentration might be a compensatory mechanism that confers protection against free radical injury. [10] In animal models, local uric acid concentration significantly increases in acute brain injury. [11] Uric acid is described as a strong endogenous antioxidant that is consumed early in acute stroke and presently its combination with recombinant tissue plasminogen activator is believed to be synergistic in experimental models of acute ischemic strokes. [12,13] In ischemic rat brain, the administration

of uric acid resulted in neuro-protection and improved behavioral outcome. The severity of neurological impairment and the volume of infarction in patients with stroke have been found to be inversely related to the concentration of uric acid [14].

However, uric acid being an aqueous antioxidant can become a pro-oxidant under certain circumstances, particularly, if other antioxidants such as ascorbate are low. [15] Thus, the fall in ascorbate level with acute stroke could predispose the serum uric acid to take on pro-oxidant properties. Consistent with this hypothesis is the observation that in acute stroke, those with high uric acid and low ascorbate levels have the worst outcome [16].

2. Aims and Objectives

Although, a lot of research has been done to find out an easily available biochemical parameter like serum uric acid for stroke outcome across the globe; such information from India is very scanty. Therefore, this work will be conducted to find an association between serum uric acid level at the time of admission with functional outcome (Mathew scoring) in patients with acute stroke.

3. Materials and Methods:

1). STUDY SETTING: R.G. Kar Medical College & Hospital, Kolkata, a tertiary care academic hospital in eastern India.

2). TIMELINES: 12 months (from 1st November 2013 to 31st October 2014).

3). DEFINITION OF PROBLEM: The role of serum uric acid as a prognostic indicator in acute stroke, an important cause of mortality, morbidity and disability, has been observed by many researchers.

4). DEFINITION OF POPULATION: Indoor patients of Department of General Medicine, R.G. Kar Medical College & Hospital, Kolkata presenting with acute stroke.

5). STUDY VARIABLES:

Independent variables:

- Serum Uric Acid at the time of admission.
- **Socio demographic variables:** age, sex.

Dependent variable: Outcome of the patients as per Mathew scale.

6) INCLUSION CRITERIA:

All patients with first attack of stroke admitted to the hospital within 48 hrs of onset of symptoms were included in the study.

EXCLUSION CRITERIA:

- All patients with prior history of stroke
- Strokes secondary to trauma, neoplasms, coagulation disorders or aneurysms.
- Patients with subarachnoid or primary intraventricular hemorrhage.
- Patients on iron or antioxidant vitamins, or diuretics.

7) SAMPLE SIZE: From hospital records the average number of patients with stroke, admitted in R.G.Kar Medical College three years prior to this study was approximately 600. Considering the feasibility of a single researcher, 15% of this value (approximately 90) was considered as the sample size.

8) SAMPLING DESIGN: Scheduled sampling. One day of the week was selected by rotation to avoid selection bias. All patients admitted on that day with stroke and fulfilling the inclusion criteria were selected for the study after taking informed consent from them or their caregivers.

9) STUDY DESIGN: Descriptive, observational, cross-sectional study.

10) CONTROL: Not required.

11) METHODS OF DATA COLLECTION: On admission the following activities will be performed:

- Informed consent from patient/caregiver.
- Comprehensive history of stroke, diabetes, cardiovascular events, hypertension, renal disease, gout, use of diuretics, smoking, alcohol.
- Detailed general examination and vitals recording.
- The Mathew score at the time of admission and discharge/ death were calculated.
- We labeled them as good clinical outcome when the Mathew score was> 75 and poor neurological outcome when the Mathew score was ≤ 75.
- Serum uric acid within 48 hrs of admission.
- Hemoglobin%, Total leukocyte count, Differential Count, Random blood glucose/ Fasting blood glucose, Blood urea, Serum Creatinine, Serum Sodium, Serum Potassium, lipid profile.
- All the patients presented to the hospital within 48 hours of onset of symptoms.
- Baseline computed tomography (CT) scan of brain in all patients within 24 hr of admission.
- The patients with ischemic stroke were divided into 3 groups according to the size of lesions. Serum uric acid levels were compared between each group.
- **Estimation of uric acid** [17]**:**

3.1. Method

Uricase / PAP method

3.1.1. Principle:

Uricase convert uric acid into allantoin and hydrogen peroxide. In presence of peroxidase, hydrogen peroxide oxidatively couples with phenolic chromogens (4-aminoantipyrine (4-AAP) and 3, 5-dichloro-2-hydroxybenzenesulfonic acid (DHBSA)) to form a red colored compound (red quinoneimine dye), which has maximum absorbance at 510 nm (500 – 530 nm). Sodium ferrocyanide and ascorbate oxidase are added to the reaction mixture to minimize the potential interference of bilirubin and ascorbic acid. The concentration of the red colored compound is proportional to the amount of uric acid in specimen.

$$\text{Uric acid} + H_2O \xrightarrow{\text{Uricase}} \text{Allantoin} + H_2O_2$$

$$H_2O_2 + \text{Phenolic chromogens} \xrightarrow{\text{Peroxidase}} \text{Red colored compound}$$

3.1.2. Reagents

1) Buffer	100mMol/L
2) Peroxidase	140 IU/L
3) Uricase	100 IU/L

4) Ascorbate oxidase	100 IU/L
5) Chromogen	2.5 µ Mol/L
6) Surfactants/ Stabilizers	
7) Standard	6mg%

3.1.3. Preparation of Working Solutions:

The required amount of working reagent is pre-warmed at room temperature before use.

3.1.4. Storage and Stability of the Reagents

The reagent kit was stored at 2°- 8°C and was used within 15 months of manufacturing.

3.1.5. Instruments

1. Pipettes 3. Hard glass tubes 5. Centrifuge tubes
2. Centrifuge machine 4. Hitachi Auto Analyzer

3.1.6. Procedure

Blood was collected in a clean dry container and serum was separated from the cells within 60 minutes. 1 ml of working reagent was mixed the required amount of working reagent with 0.025 ml of serum and incubated at room temperature (not less than 25º C) for 10 minutes. After completion of the incubation the absorbance of the assay mixture was measured against blank at 510 nm. The concentration was calculated in mg % as

$$\frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 6$$

The normal range in male was 3.4 – 7.0 mg % and Female 2.4 – 5.7 mg %

4. Result

The present study was carried out on 96 patients of stroke including both ischemic (66) and hemorrhagic (30) stroke (Figure 1) admitted to the wards of medicine department of R G KAR Medical College and hospital, Kolkata from 1st November 2013 to 31st October 2014.

The diagnosis was made by CT scan of brain. All the patients presented to the hospital within 48 hours of onset of symptoms. 52 patients of stroke had a good clinical outcome (Mathew score > 75) and 44 patients had poor neurological outcome (Mathew score ≤ 75) and 8 patients died during the hospital stay but after their blood sample was collected and CT scan done.

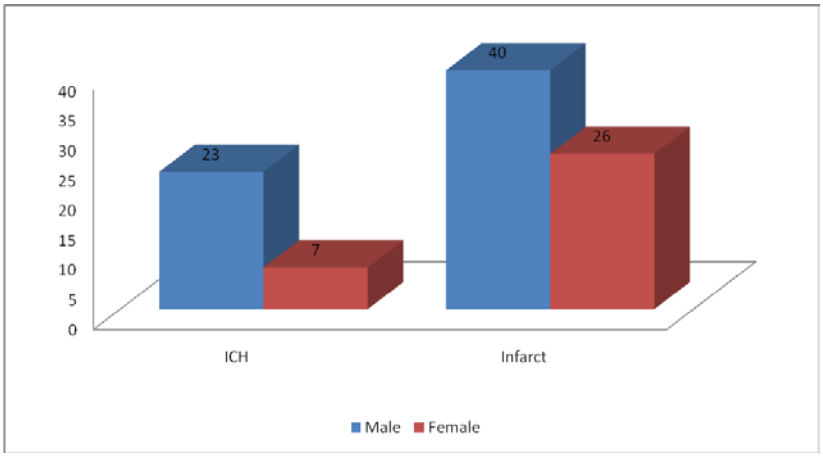

Figure 1. Distribution of Ischemic and hemorrhagic stroke in patients under study

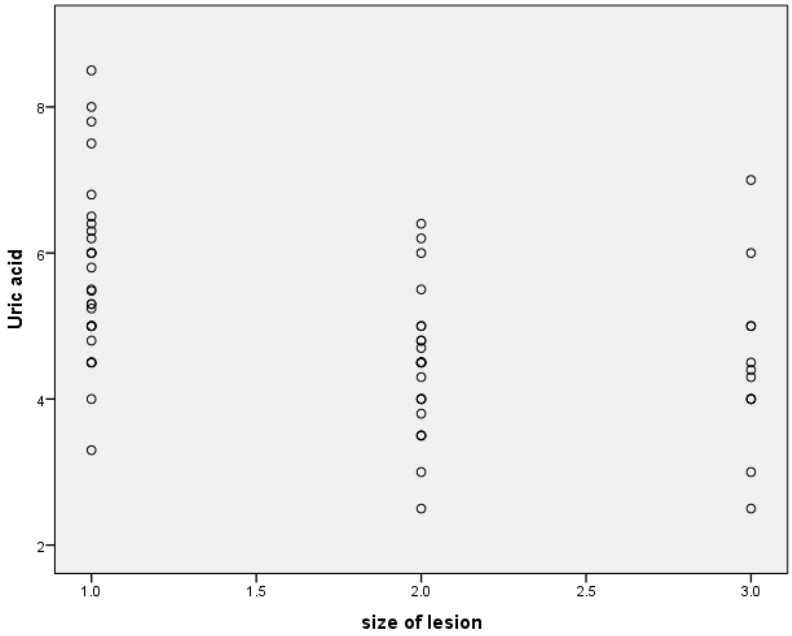

Figure 2. Higher uric acid level at the time of admission associated with smaller infarct

4.1. Ischemic Stroke

In patients with ischemic stroke 38 patients (58%) had good outcome, 28 patients (42%) had poor neurological outcome and 3 patients (5 %) of the 28 patients died during the stay in hospital.

Higher Serum uric acid level at the time of admission is associated with smaller infarct (Figure 2).

Level of uric acid and Mathew score at discharge showed a significant positive correlation. 21.6 % (R^2=0.216) variation in dependant variable (Mathew score at discharge) can be explained by independent variable (uric acid) (Figure 3, Table 1).

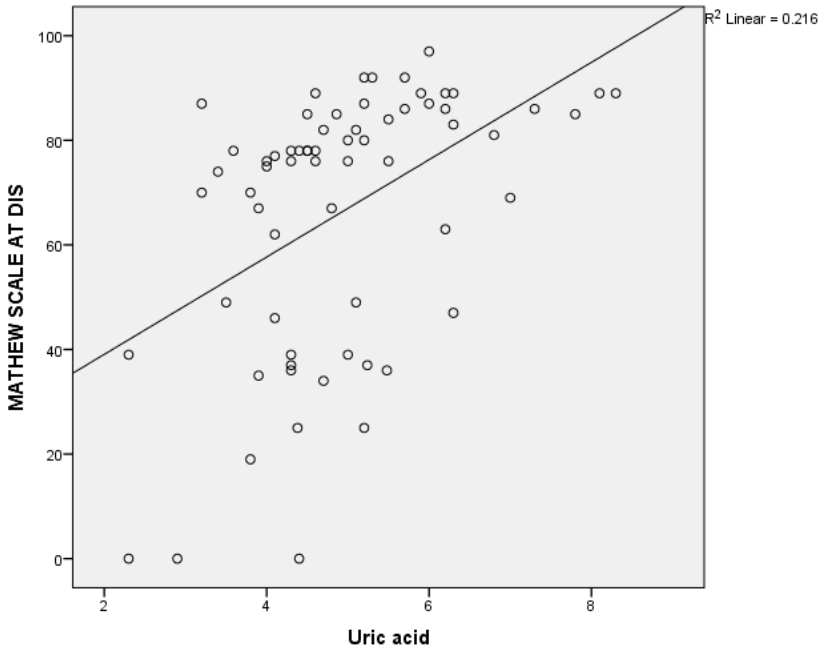

Figure 3. Scattered diagram shows correlation between uric acid levels at the time of admission with Mathew score at discharge in ischemic stroke patients

Table 1. Correlations between serum uric acid level and Mathew score at discharge

Pearson correlation coefficient	P
0.465	.000

One unit change in uric acid give rise to 9.307 times increase in Mathew score and it is statistically significant (Table 2). About 14% (R^2=0.140) change in dependent variable (change in Mathew score) can be explained by independent variable (uric acid) (Figure 4).

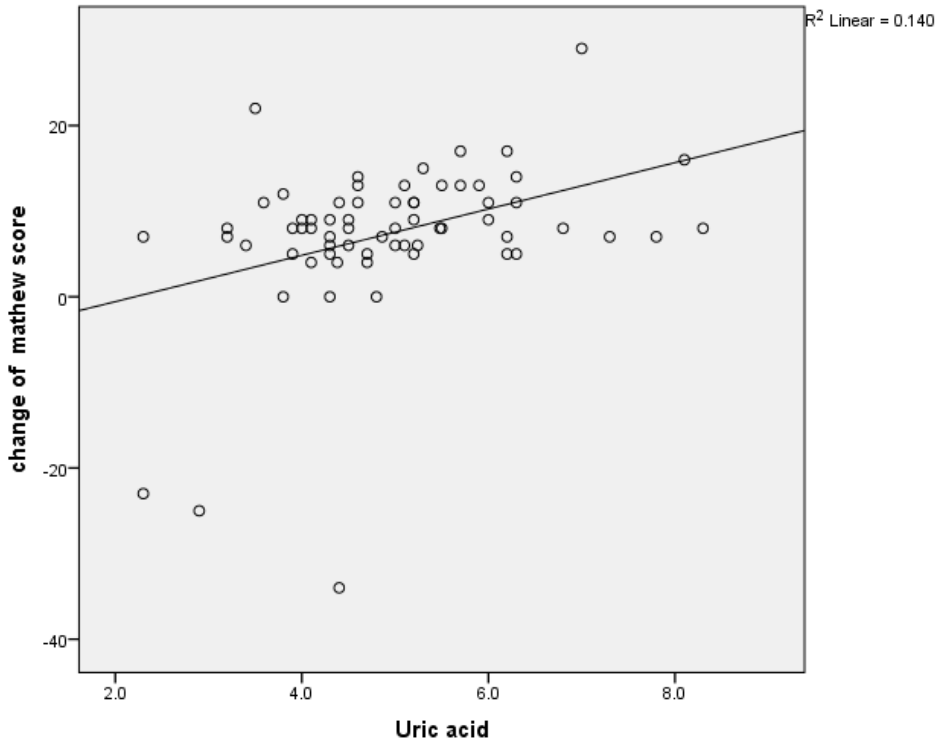

Figure 4. scattered diagram shows correlation between uric acid and change of Mathew score

Table 2. Simple linear regression analysis between uric acid and Mathew score at discharge

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% confidence interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	20.464	11.289		1.813	.075	-2.089	43.016
	Uricacid	9.307	2.215	.465	4.202	.000	4.882	13.732

4.2. Hemorrhagic Stroke

In patients with hemorrhagic stroke, 14 patients (47%) had good neurological outcome, 16 patients (53%) had poor outcome and 5 patients (17%) patients died during their hospital stay.

Level of uric acid and Mathew score at discharge showed a poor negative correlation which is not statistically significant. (Figure 5, Table 3)

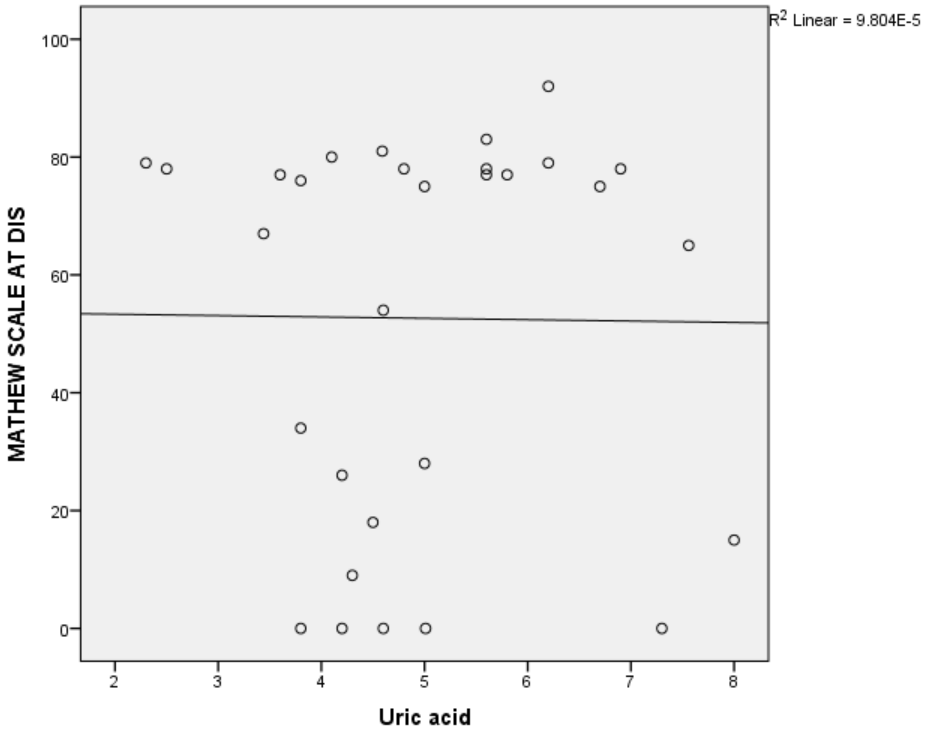

Figure 5. Scattered diagram showing correlation between uric acid levels at the time of admission with Mathew score at discharge in patients with hemorrhagic stroke

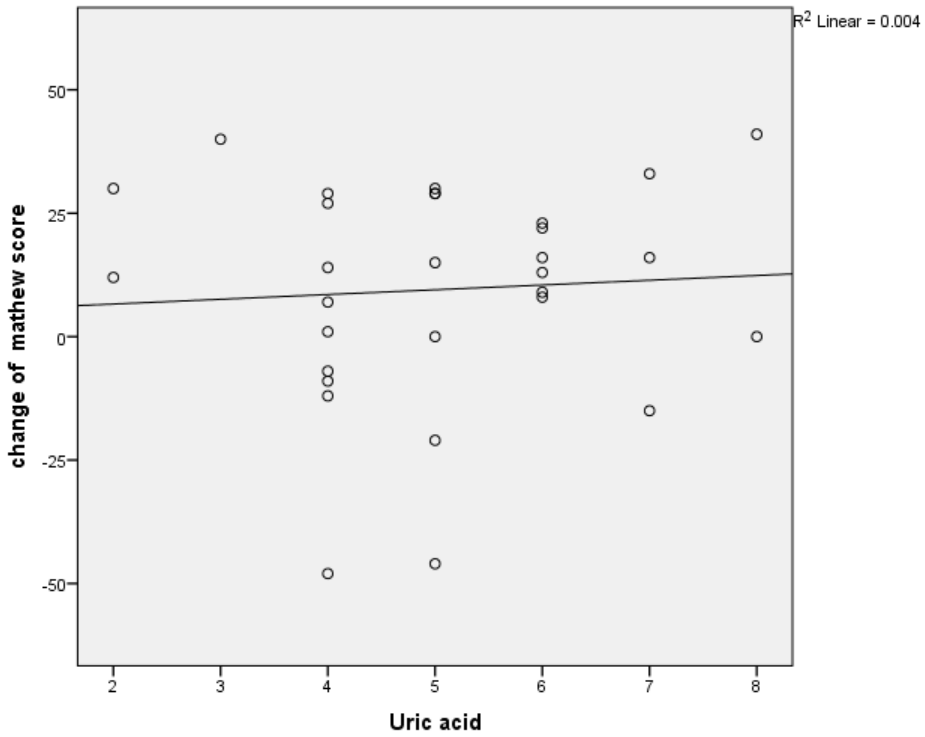

Figure 6. scattered diagram showing correlation between change of Mathew score and uric acid in hemorrhagic stroke

Table 3. Correlation between uric acid and Mathew score at discharge

Pearson correlation coefficient	P
-0.010	0.959

One unit increase in uric acid give rise to 0.232 times decrease in Mathew score at discharge considering the constant is zero and it is statistically not significant (Table 4). There is poor positive correlation between uric acid level and change of Mathew score in hemorrhagic stroke patients. About 0.4% (R^2=0.004) change in dependent variable (change in Mathew score) can be explained by independent variable (uric acid). (Figure 6).

Table 4. Simple linear regression analysis between uric acid and Mathew score at discharge

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% confidence interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	53.79	22.958		2.343	.026	6.764	100.821
	Uricacid	-.232	4.436	-.010	-.052	.959	-9.319	8.854

Uric acid level was significantly different in diabetic patients with small sized infarct compare to large size infarct. Difference did not differ significantly between patients with small and medium or medium and large sized infarct.

5. Discussion and Conclusion

The Pearson's coefficient of correlation between change of Mathew score at the time of discharge and serum uric acid was calculated among patients of ischemic stroke and was found to be significant at 0.01 levels. About 14% (R^2=0.140) change in dependent variable (change in Mathew score) can be explained by independent variable (uric acid). There is a significant positive correlation between serum uric acid level at the time of admission and Mathew score at the time of discharge. In our study population of ischemic stroke patients one unit increment in uric acid level gives 9.307 times increase of Mathew stroke score at discharge.

Mean uric acid level was significantly lower in diabetic patients than in non-diabetic patients (Table 5).

Table 5. Average uric acid level in patients with ischemic stroke according to their Glycemic status

Glycemic status	Mean	Standard deviaeion	T	df	P
Diabetic	4.2712	0.90780	3.583	64	0.001
Nondiabetic	5.3271	1.26814			

The Pearson's coefficient of correlation between change of Mathew score at the time of discharge and serum uric acid was calculated and was found to be insignificant at 0.959 levels in hemorrhagic stroke. Only about 0.4% (R^2=0.004) change in dependent variable (change in Mathew score) can be explained by independent variable (uric acid). In our study population of hemorrhagic stroke patient one unit increase in uric acid value we get 0.232 times decrease in Mathew score at discharge and it is statistically not significant.

Thus, high serum uric acid at the time of admission is associated with good outcome in patients with ischemic stroke and it is statistically significant but in hemorrhagic stroke patients level of uric acid and Mathew score at discharge showed a poor negative correlation which was not statistically significant.

In patients with acute ischemic stroke, those with small lesions in CT scan had a significantly higher serum uric acid levels and a better outcome at the time of discharge (a higher Mathew score at discharge) than those with large lesion.

In a study carried out by Sergio Amaro et al., 2011 showed that higher UA levels were associated with an increased rate of excellent recovery independently of baseline variables. Moreover, increased serum levels of UA were significantly associated with smaller infarction volumes [18].

Wu H et al, 2013 conducted a study on 1351 ischemic and 380 cerebral hemorrhage patients, showed decreased uric acid levels correlate with poor outcomes in acute ischemic stroke patients, but not in cerebral hemorrhage patients. [19] Chamorro et al (2002) found diabetic patients had lower serum uric acid values. The study also found serum uric acid to be inversely correlated with non fasting glucose and size of infarct at follow up [11].

From the above observations, it is concluded that:

High serum uric acid level is associated with good neurological outcome at the time of hospital discharge in patients with acute ischemic stroke.

A high serum uric acid level is associated with insignificant poor neurological outcome in patients with hemorrhagic stroke. Diabetic patients with ischemic stroke tended to have a lower serum uric level than non-diabetics. The present study reinforces the relevance of oxidative damage in patients with ischemic stroke.

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