Prognostic Significance of Uric Acid Levels in Intracerebral Hemorrhage Patients

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Background and Purpose: The role of serum uric acid (UA) level in patients suffering from stroke remains controversial. Our aim was to investigate the effect of UA level on clinical outcomes in patients with intracerebral hemorrhage (ICH).

Methods: In the retrospective cohort study, we analyzed data from 250 patients with intracerebral hemorrhage (85 women and 165 men) to investigate the difference in UA levels between patients with a good prognosis and those with a poor prognosis. Additionally, we analyzed the impact of UA levels on the risk of short-time prognosis of ICH patients.

Results: Patients with a good prognosis presented with significantly lower levels of UA (348.71 ± 84.97 μmol/L) than those with poor prognosis (393.06 ± 148.46 μmol/L). Furthermore, multivariate logistic regression model demonstrated that a high UA level was a likely risk factor for worse prognosis among patients suffering in ICH (odds ratio [95% confidence interval], 1.006 [1.0012, 1.0108]; P = 0.015). Additionally, UA has a threshold effect value of 363.9 μmol/L and was presented in levels that were in a nonlinear relationship with incidence rate of short-time prognosis outcome of ICH patients.

Conclusion: Our findings indicate that higher UA levels can increase the risk of poor clinical prognosis in patients with ICH and high UA levels are not conductive to the clinical prognosis of patients with ICH. These findings provide a new perspective on the treatment and prevention of ICH.

Keywords: intracerebral hemorrhage, uric acid, oxidative stress, follow-up, nonlinear relationship, prognosis

Introduction

Stroke has become the leading cause of death and disability in China, and in a cross-sectional study of 676,394 participants aged 40 years and older, it was estimated that in 2020, 17.8 (95% CI, 17.5–18.0) million adults in China had experienced a stroke, of whom 3.4 (95% CI, 3.3–3.6) million experienced a first stroke and another 2.3 (95% CI, 2.2–2.4) million died as a result.1 According to the China Stroke Surveillance Report 2021, ICH accounts for 10.8–4.9% of all stroke events.

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UA is the terminal product of purine metabolism, and it is highly soluble and is excreted by the kidneys. Abnormal UA levels are known to be closely associated with many chronic diseases, such as gout, coronary heart disease and ischemic stroke. In addition, it has been demonstrated that elevated UA is associated with increased risk of adverse functional outcomes and death in atherosclerotic disease. Uric acid has also been suggested to be neuroprotective due to its role in scavenging oxygen free radicals. Numerous studies indicated that elevated baseline uric acid (UA) levels during the onset of acute ischemic stroke (AIS) typically correlated with a more favorable prognosis for AIS patients. Conversely, AIS patients with low UA levels face an elevated risk of hemorrhagic transformation, irrespective of whether they have undergone revascularization therapy.

While there is an extensive body of literature investigating the association between uric acid and stroke, the mechanism of uric acid’s involvement remains elusive. Furthermore, prior studies have focused on ischemic stroke, and only a small body of literature has explored the association between blood uric acid levels and cerebral hemorrhage, and the findings have not been agreed upon. As a result, it is unknown if UA is an effective neuroprotective agent that promotes or protects against unfavorable outcomes in ICH, or if it simply acts as a marker indicating an elevated risk of ICH development or adverse functional outcomes. Previous meta-analyses have found support for UA’s dual role as a pro-oxidant and antioxidant, implying a potential association between UA and the pathogenesis of ICH. Nevertheless, this analysis failed to uncover substantial evidence connecting UA to the risk of ICH. A study of hemorrhagic stroke in black Africans indicated that high blood uric acid levels were not an independent predictor of death and poor outcome (mRS > 2 points) in ICH. Liu et al found that higher levels of uric acid were a protective factor for ICH severity and in-hospital complications based on ICH data from the Chinese Stroke Centre Consortium, but the article did not mention the relationship between uric acid levels and ICH patient prognosis. A recent study on uric acid and early neurological deterioration (END) in ICH patients discovered that ICH patients with higher serum UA levels had a significantly increased risk of END, potentially leading to a poor neurological prognosis in ICH patients. Based on the above, the relationship between UA level and cerebral hemorrhage has not been well studied and remains controversial. We believe that hyperuricemia has a negative effect on the prognosis of cerebral hemorrhage. Thus, in this study, we aimed to investigate the relationship between UA levels and the prognosis of patients with ICH.

Materials and Methods

Study Population

The design of this investigation was a retrospective cohort study. This retrospective analysis was performed on data collected from ICH patients consecutively admitted to the Second People’s Hospital of Hefei City, Anhui Province, between January 2018 and March 2021. The inclusion criteria were as follows: (1) ICH confirmed by cranial CT within 24 hours, (2) age ≥ 18 years, (3) signs and symptoms of focal neurological deficits present on admission. The exclusion criteria for the study were as follows: (1) other causes such as cerebral hemorrhage such as that caused by aneurysm, cerebrovascular malformation, brain trauma or brain tumor, (2) severe abnormal blood coagulation, cardiac insufficiency, and renal and pulmonary insufficiency prior to admission, (3) hemorrhagic transformation after cerebral infarction, (4) related surgical treatment receipt within 48 hours, and (5) study visit miss.

Data Acquisition

We collected demographic information, medical history, systolic blood pressure (SBP) on admission, diastolic blood pressure (DBP) on admission and other relevant clinical information from patients at admission. In addition, we also collected Glasgow Coma Scale (GCS) Scores and National Institutes of Health Stroke Scale (NIHSS) scores. ABC/2 method (A, greatest hemorrhage diameter; B, diameter perpendicular to A; C, thickness of hematoma) was used to measure the hematoma volume of ICH patient. The UA level and other related test indices were measured early in the morning on day 2 after admission. UA levels were measured with uric acid oxidase reagent using the DAX analyzer from Bayer.

Outcome

The primary outcome of our study was the modified Rankin Scale (mRS) score 90 days after onset of disease. We followed each patient for at least 3 months through outpatient, telephone, and inpatient visits. We defined an mRS score of 0–2 as an
outcome with a good prognosis, and that of ≥3 as an outcome with a poor prognosis. This score is a marker of neurological functional outcome and is often used as an endpoint in clinical trials of stroke.7

The study was reviewed and approved by the Clinical Trial Ethics Committee of the Second People’s Hospital of Hefei City (Grant No. 2023-Scientific Research-018) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. And because this was a retrospective cohort study, the Ethics Committee authorized the exemption of patients from informed consent.

**Statistical Analysis**
Continuous variables are presented as mean ± standard deviation, categorical variables are given as numbers or percentages. The normal distribution of each variable was tested by Kolmogorov–Smirnov test. For normally distributed data, we examined intergroup differences using a two-tailed Student’s t-test. For non-parametric data, we examined intergroup differences using the Mann–Whitney U-test. We incorporated the related variables from univariate analysis (p < 0.05) into multiple regression analysis. Binary logistic regression models were used to explore the association between UA levels and ICH outcomes. Moreover, piecewise linear regression was applied to analyze the threshold effect of UA levels and outcome of short-time prognosis of ICH patients. Results were considered statistically significant if the two-tailed P-value was <0.05. Empower (R) (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) and R 3.6.3 (http://www.R-project.org) were used for all the statistical analyses.

**Results**
From January 2018 to March 2021, a total of 347 patients were diagnosed with spontaneous ICH, and based on the inclusion exclusion criteria, a total of 250 patients with spontaneous ICH were finally included in our study analysis (Figure 1). The demographic information and related risk factors are listed in Table 1. Based on our study design, we divided our study cohort into good and poor prognosis groups. The poor prognosis group included 37 women (32.46%) and 77 men (67.54%) with a mean age of 66 years. In addition, compared with the good outcome group, the poor prognosis was comprised of patients who were older (p = 0.004), had a higher proportion of patients with intraventricular hemorrhage (IVH) (p < 0.001), and had patients with significantly higher values for baseline hemorrhage volume (p < 0.001), NIHSS scores (p < 0.001), blood urea nitrogen (BUN) level (p=0.008), and higher UA levels (p = 0.003).

![Flowchart of patient inclusion and analysis.](https://example.com/flowchart.png)
Table 2 presents that the results of univariate analysis between the different variables and the poor outcome. Poor outcomes were associated with age (p = 0.004), intraventricular hemorrhage (p < 0.001), hemorrhage volume (p < 0.001), Glasgow Coma Scale (GCS) scores (p < 0.001), NIHSS scores (p < 0.001), BUN level (p = 0.011), CREA level (p<0.003), and UA level (p = 0.004).
Table 3 lists the results of the multiple regression analysis of UA levels in association with poor outcomes in ICH patients. In the unadjusted model, multivariate regression analysis showed that high UA levels were significantly associated with poor outcomes in patients with ICH (odds ratio [OR]=1.0032, 95% confidence interval [CI] 1.001–1.0054, P = 0.004). The relationship between UA levels and poor prognostic outcomes remained significant even when adjusted for potential confounders, including age, SBP in admission, BUN, CREA, hemorrhage volume, intraventricular hemorrhage, GCS scores, NIHSS scores, the statistical association remained significant (odds ratio [OR] = 1.006, 95% confidence interval...

Table 2 Association Between Each Variable and Poor Outcome

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Statistics</th>
<th>Poor Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.38 ± 15.07</td>
<td>1.03 (1.01, 1.04)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>85 (34.00%)</td>
<td>0.88 (0.52, 1.84)</td>
<td>0.637</td>
</tr>
<tr>
<td>Male</td>
<td>165 (66.00%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>183 (73.20%)</td>
<td>1.05 (0.60, 1.84)</td>
<td>0.874</td>
</tr>
<tr>
<td>No</td>
<td>67 (26.80%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (8.40%)</td>
<td>0.71 (0.29, 1.79)</td>
<td>0.472</td>
</tr>
<tr>
<td>No</td>
<td>229 (91.60%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65 (26.00%)</td>
<td>0.80 (0.45, 1.42)</td>
<td>0.445</td>
</tr>
<tr>
<td>No</td>
<td>185 (74.00%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80 (32.00%)</td>
<td>0.97 (0.57, 1.65)</td>
<td>0.896</td>
</tr>
<tr>
<td>No</td>
<td>170 (68.00%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>62 (24.80%)</td>
<td>5.66 (2.94, 10.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>188 (75.20%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Infratentorial hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtentorial</td>
<td>36 (14.40%)</td>
<td>1.08 (0.53, 2.19)</td>
<td>0.833</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>214 (85.60%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage volume</td>
<td>15.23 ± 21.51</td>
<td>1.09 (1.06, 1.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP in admission</td>
<td>162.24 ± 28.72</td>
<td>1.01 (1.01, 1.02)</td>
<td>0.002</td>
</tr>
<tr>
<td>DBP in admission</td>
<td>92.49 ± 17.74</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.161</td>
</tr>
<tr>
<td>GCS scores</td>
<td>12.78 ± 3.58</td>
<td>0.48 (0.37, 0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS scores</td>
<td>9.51 ± 6.64</td>
<td>1.40 (1.28, 1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN</td>
<td>5.64 ± 2.45</td>
<td>1.19 (1.04, 1.37)</td>
<td>0.011</td>
</tr>
<tr>
<td>CREA</td>
<td>80.13 ± 30.45</td>
<td>1.02 (1.01, 1.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>368.93 ± 120.02</td>
<td>1.00 (1.00, 1.01)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; BUN, blood urea nitrogen; CREA, Creatinine.
As can be seen in Table 4 and Figure 2, there was a significant threshold effect noted between UA level and incidence rate of short-time prognosis outcome of ICH patients. The threshold effect value was 363.9 μmol/l. In patients with a baseline UA concentration below this value, an increase in UA level was associated with a worse prognosis (OR = 0.9949, 95% CI = 0.9852–1.0048, P = 0.311). In patients with baseline UA levels higher than this value (OR = 1.0124, 95% CI = 1.0051–1.0198, P < 0.001), the incidence rate of poor outcome was steep rise.

![Figure 2](https://doi.org/10.2147/NDT.S447851)

**Figure 2** The threshold effect of uric acid levels on short-time prognosis outcome of ICH patients.
Discussion

In the present study, we explored the relationship between UA levels and the short-term prognosis of patients with ICH. This study demonstrated that the higher UA levels represent a significant and independent risk factor associated with a poor prognosis in patients with ICH. Furthermore, we found a threshold effect between UA levels and incidence rate of poor outcome, with an increase in UA levels significantly increasing the risk of poor prognosis until reaching the threshold point of 363.9 μmol/L in patients with ICH. This study not only would enhance our understanding of the relationship between uric acid and ICH outcomes but highlights the importance and necessity for monitoring and management of UA as a potential part of clinical standard-of-care protocols.

UA is an important antioxidant molecule in the human body that effectively scavenges peroxynitrite, nitric oxide, and hydroxyl radicals, thus preventing protein nitrification and lipid peroxidation.8,11 UA concentration also affects the occurrence and development of stroke.23 Studies in animal models suggest that treatment with UA and its analogs may protect the brain from ischemic damage.24,25 This seems to be corroborated by some clinical observational studies on ischemic stroke. Research has shown that for every milligram increase in UA in patients with acute ischemic stroke, the likelihood of a good clinical outcome increases by 12%.26 Another study showed that higher serum uric acid levels were independently associated with lower hemorrhagic transformation after acute ischemic stroke.16 The protective effect of UA against acute ischemic stroke was based on the results of these observational studies.27 Although the clinical symptoms of ICH and ischemic stroke are similar, their specific mechanisms of occurrence and development are different. However, when uric acid exceeds the normal range, it can affect several systems in human body, which in turn lead to stroke. Previous studies on the association between uric acid and stroke have focused on ischemic stroke, while few studies have been conducted on hemorrhagic stroke.

The relationship between UA level and ICH has not been well studied and remains controversial. We found a significant difference in UA levels between the good prognosis and poor prognosis groups of ICH patients; the UA levels in the good prognosis group were significantly lower than those in the poor prognosis group. Further, further analysis revealed that UA level was an independent risk factor of poor prognosis in patients with ICH. Numerous studies have demonstrated that higher UA levels are associated with a higher incidence and poorer functional outcomes in atherosclerotic diseases such as acute stroke and cardiovascular disease.28,29 Previous studies also shown that elevated UA level is associated with carotid intima-media thickening,30,31 similar results were found in a study of proximal stenosis of the extracranial artery.32 These results indicate that UA level may play an important role in the pathophysiology of atherosclerosis and stroke. Studies have shown that elevated UA contributes to the progression of atherosclerosis by enhancing the production of free radicals and lipid peroxidation.33,34 High levels of UA can cause vascular endothelial dysfunction and abnormal proliferation of vascular smooth muscle cells, which may further contribute to cardiovascular and cerebrovascular diseases.35,36 Inflammatory responses resulting from high levels of UA can further increase the damage to the body through the cascading effects of factors such as C-reactive protein, and interleukin-6.37 Furthermore, high UA levels can magnify oxidative stress, which in turn further aggravates secondary damage after ICH through inflammation reaction, autophagy, and disruption of the blood–brain barrier.38,39

Here, with incidence rate of short-time prognosis outcome of ICH patients, we found that higher levels of UA were related to the incidence rate of short-time prognosis outcome of ICH patients with a threshold effect value of UA of 363.9 μmol/l. In ICH patients, when the UA levels of ICH patients were less than 363.9 μmol/l, the effect was found to plateau; when the UA levels higher than 363.9 μmol/l, the effect was associated with a worse prognosis outcome as the UA level increased. These results suggest that an increase in UA concentration from levels higher than the threshold point may have an unfavorable effect on the prognosis of patients with ICH. A previous study reported that lower UA levels (<221 μmol/l) could significantly increase the risk of poorer functional outcomes in patients with acute stroke with normoglycemic status.40 Numerous studies have suggested that UA has both pro-oxidant and antioxidant effects,11 and we presumed that pro-oxidants predominate at higher UA levels in ICH patients, further affecting their prognosis.

There are some limitations to this study. First, this was a single-center cohort study with a small sample size; thus, the statistical results may not be sufficient to represent the true population effects or detect small differences. Second, we only collected morning blood results from patients on the second day after hospitalization and did not perform multiple sample point collections. Therefore, it was not possible to assess the dynamic changes in UA levels during hospitalization and follow-up of ICH patients. Third, we adjusted for known important confounding variables in our multivariate regression analyses but did not include more
comprehensive, less common risk factors, which may have influenced our results. Finally, we found a strong correlation between UA level and prognosis in patients with ICH; however, a causal relationship could not be established, and we will confirm these results by animal experiment in the future.

Conclusion
High UA levels can increase the risk of poor clinical prognosis in patients with ICH and high UA levels are not conductive to the clinical prognosis of patients with ICH. These findings provide a new perspective on the nature of UA in the context of ICH and suggest potential therapeutic and secondary prevention strategies for patients with ICH.

Data Sharing Statement
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author, Hong Yue.

Statement of Ethics
The study was reviewed and approved by the Clinical Trial Ethics Committee of the Second People’s Hospital of Hefei City (Grant No. 2023-Scientific Research-018) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. And because this was a retrospective cohort study, the Ethics Committee authorized the exemption of patients from informed consent. The personal information and data of all patients participating in the study are kept strictly confidential. No personal information or data that could identify specific patients were disclosed in this study.

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Wenpei Wu, Zhi Geng and Aimei Wu are co-first authors for this study. The authors would like to thank all the individuals who offered help and advice on this study.

Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure
The authors report no conflicts of interest in this work.

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