

High Uric Acid Level Predicts Early Neurological Deterioration in Intracerebral Hemorrhage

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Objective: Increased level of serum uric acid (UA) is often considered a risk factor for ischemic stroke. However, there are limited data on the association between UA and intracerebral hemorrhage (ICH). This study aimed to examine the connection between UA and early neurological deterioration (END) in patients with ICH.

Methods: This is a prospective observational study. Patients with ICH were enrolled from January 2017 to December 2020. END was diagnosed as the Canadian Stroke Scale (CSS) score decreased ≥ 1 points between admission and 48 hours. UA was measured at admission. Multivariable logistic regression analysis was performed to explore the relationship between serum UA and END.

Results: Of the 498 enrolled patients, 132 (26.5%) were developed with END. Patients with END had a significantly higher level of serum UA (332 vs 270 $\mu\text{mol/L}$, $P < 0.001$). Univariate logistic regression analysis indicated that patients with the highest quartile of UA level had an OR of 3.256 (95% CI: 1.849–5.734, $P < 0.001$) for END compared with those with the lowest quartile of UA level. After adjusting for major confounders, the highest UA quartile remained as an independent predictor for END (OR = 2.282, 95% CI: 1.112–4.685, $P = 0.013$).

Conclusion: Higher serum UA level was independently associated with END in patients with ICH; therefore, intervention to lower UA level may be worth considering.

Keywords: early neurological deterioration, intracerebral hemorrhage, uric acid

Introduction

Intracerebral hemorrhage (ICH) accounts for 10–30% of all strokes and is the leading cause of stroke-related death and disability.^{1,2} There is compelling evidence from preclinical and clinical research that ICH outcome is strongly affected by a multitude of variables associated with metabolism,^{3,4} inflammation^{5,6} and drug actions.⁷ All these factors may act at the site of cerebral damage and/or at systemic level, and hence, influence neurovascular recovery, secondary-induced damage and systemic complications. The early stage of ICH is extremely unstable, and about 20% of patients are prone to occur early neurological deterioration (END) within two days of onset,⁸ which is associated with poor prognosis.⁹ Accordingly, it is important to identify risk factors of END to improve clinical outcomes.

Uric acid (UA) is the final product of purine metabolism in the body. It has been proven that hyperuricemia is related to gout, chronic kidney disease, hypertension, diabetes, coronary heart disease and ischemic stroke.^{10–16} In addition, hyperuricemia potentially leads to poor outcome, increased symptomatic ICH and mortality in ischemic stroke.^{17–19}

Based on the neurologically damaging effect of hyperuricemia, we speculate that it may play a part in END in patients with ICH. However, the association between UA and END in patients with ICH has not been assessed to date. Therefore, this study aimed to explore the relationship between serum UA levels and END in patients with ICH.

Materials and Methods

Study Population

Patients with ICH were enrolled consecutively from the First Affiliated Hospital of Anhui University of Science and Technology from January 2017 to December 2020 in this prospective observational study. Patients were included if they: (1) were diagnosed with ICH verified by CT scans within 24 h from symptom onset; (2) aged ≥ 18 years; (3) Glasgow Coma Scale (GCS) score ≥ 9 . The patients were excluded if they: (1) had secondary hemorrhage as a result of tumor, trauma, vascular malformation, aneurysm, hemorrhagic transformation of cerebral infarct and blood coagulation abnormalities; (2) did not re-examine brain CT within 48 hours; (3) underwent intracranial hematoma removal or cerebrospinal fluid drainage within 48 hours; (4) had severe heart, renal or liver diseases. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the First Affiliated Hospital of Anhui University of Science and Technology. All participants signed an informed consent form.

Clinical Data

Demographic characteristics, medical history and clinical variables were all collected from medical records. Stroke severity was assessed using the Canadian Stroke Scale (CSS) score.²⁰ The extent of consciousness was determined by the GCS score. Fasting blood samples were collected in the next morning for UA, other biochemical indicators and routine blood tests. Serum UA level was measured by uric acid oxidase reagent on a Dax analyzer (Bayer-Technicon). Hematoma expansion was defined as an increase in ICH volume on follow-up CT scans of either 6 mL or $>33\%$.⁹ END was diagnosed as the CSS score decreased ≥ 1 points between admission and 48 hours.⁸

Statistical Analysis

Continuous variables were presented as mean \pm SD or median (interquartile range). Categorical variables were presented as numbers (percentages). Independent *t* test, Mann–Whitney *U*-test, one-way ANOVA or Kruskal–Wallis *H*-test as

appropriate were employed for continuous variables. Chi-square test or Fisher's exact test was used for categorical data. Multivariate logistic regression analysis was used to explore the relationship between categorical serum UA levels and END. Model 1 was adjusted for age and sex. Model 2 was further adjusted for variables with $P < 0.1$ in univariate analysis. Results were expressed as odds ratios (ORs) with 95% confidence interval (CI). The pattern and magnitude of associations between UA and END was evaluated using a restricted cubic spline with 4 knots (at 5th, 35th, 65th, 95th) adjusted for covariates as in model 2. Results were considered as statistically significant if two-sided $P < 0.05$. The R software package version 4.0 (R Foundation, Vienna, Austria) was utilized for restricted cubic spline test, while SPSS 22.0 (IBM, New York, USA) was adopted for other statistical analyses.

Results

From January 2017 to December 2020, a total of 632 patients diagnosed with ICH were admitted to the Department of Neurology in the First Affiliated Hospital of Anhui University of Science and Technology, of them, 134 were excluded according to the exclusion criteria: secondary hemorrhage ($n = 28$), did not re-examine brain CT within 48 hours ($n = 37$), underwent intracranial hematoma removal or cerebrospinal fluid drainage within 48 hours ($n = 38$) or severe heart, renal or liver diseases ($n = 31$). Finally, 498 patients were enrolled in our analysis. Most patients were men (64.7%). The median age of the enrolled patients was 66 (54–76) years. END occurred in 132 patients (26.5%).

Table 1 illustrates the patients' demographic characteristics, clinical data and laboratory data according to the presence or absence of END. Compared with subjects without END, those with END had higher proportions of concurrent ventricular hemorrhage ($P = 0.012$) and hematoma expansion ($P = 0.005$), higher baseline hematoma volume ($P < 0.001$), baseline GCS score ($P < 0.001$) and CSS score ($P = 0.003$), higher levels of homocysteine ($P = 0.030$), creatinine ($P = 0.007$) and UA ($P < 0.001$).

Table 2 shows that the ascending quantiles of UA was associated with male sex ($P < 0.001$), hypertension ($P < 0.001$), smokers ($P = 0.033$), alcohol drinkers ($P < 0.001$), previous use of antihypertensive drugs ($P = 0.018$), higher rates of concurrent ventricular hemorrhage ($P = 0.041$) and hematoma expansion ($P = 0.030$), higher baseline hematoma ($P = 0.033$), higher systolic and diastolic blood pressure (both $P < 0.001$), higher prevalence of END ($P < 0.001$), higher levels of homocysteine ($P = 0.008$), triglycerides ($P < 0.001$), blood urea nitrogen ($P < 0.001$)

Table I Baseline Characteristics of Participants with or without END

Variables	Total (n = 498)	With END (n = 132)	Without END (n = 366)	P value
Age, years	66.0 (54.0–76.0)	65.5 (54.0–76.0)	66.0 (54.8–76.0)	0.796
Gender, Male, n (%)	322 (64.7)	92 (69.7)	230 (62.8)	0.158
Medical history, n (%)				
Hypertension	388 (77.9)	106 (80.3)	282 (77.0)	0.440
Diabetes	106 (21.3)	28 (21.2)	78 (21.3)	0.981
Hyperlipidemia	150 (30.1)	42 (31.8)	108 (29.5)	0.620
Coronary heart disease	39 (7.8)	11 (8.3)	28 (7.7)	0.802
Atrial fibrillation	16 (3.2)	2 (1.5)	14 (3.8)	0.197
Prior stroke	152 (30.5)	43 (32.6)	109 (29.8)	0.550
Smoking	127 (25.5)	37 (28.0)	90 (24.6)	0.437
Drinking	114 (22.9)	33 (25.0)	81 (22.1)	0.501
Medication history, n (%)				
Antihypertensive	221 (44.4)	66 (50.0)	155 (42.3)	0.129
Antiplatelet	105 (21.1)	34 (25.8)	71 (19.4)	0.125
Anticoagulant	3 (0.6)	0 (0.0)	3 (0.8)	0.569
Statin	88 (17.7)	29 (22.0)	59 (16.1)	0.131
Hematoma location, n (%)				
Lobe	54 (10.8)	16 (12.1)	38 (10.4)	0.582
Basal ganglia	274 (55.0)	73 (55.3)	201 (54.9)	0.939
Thalamus	114 (22.9)	34 (25.8)	80 (21.9)	0.361
Cerebellum	39 (7.8)	6 (4.5)	33 (9.0)	0.101
Brainstem	17 (3.4)	4 (3.0)	13 (3.6)	1.000
Concurrent ventricular hemorrhage, n (%)	112 (22.5)	40 (30.3)	72 (19.7)	0.012
Baseline hematoma volume, mL	12 (8–18)	15 (12–21)	11 (7–16)	<0.001
Hematoma expansion, n (%)	79 (15.9)	31 (23.5)	48 (13.1)	0.005
Clinical characteristics				
Body temperature, °C	36.6 (36.4–36.8)	36.6 (36.5–36.8)	36.5 (36.3–36.8)	0.243
Time from onset to admission, h	3.5 (2.0–6.0)	3.0 (2.0–7.8)	3.5 (2.0–6.0)	0.918
Time from onset to first CT, h	3.4 (2.3–6.4)	3.4 (2.4–7.2)	3.5 (2.3–5.5)	0.837
Baseline SBP, mmHg	165 (150–183)	170 (150–190)	164 (149–180)	0.189
Baseline DBP, mmHg	100 (88–110)	100 (90–110)	100 (86–110)	0.104
Baseline GCS score	15 (14–15)	15 (14–15)	15 (15–15)	<0.001
Baseline CSS score	7.0 (5.0–8.0)	6.5 (5.0–7.5)	7.0 (5.0–8.0)	0.003
Laboratory data				
Leukocyte, ×10 ⁹ /L	7.48 (5.92–9.34)	7.92 (6.54–9.46)	7.39 (5.69–9.30)	0.087
Neutrophil, ×10 ⁹ /L	5.45 (4.00–7.32)	5.94 (4.56–7.28)	5.34 (3.89–7.39)	0.068
Hemoglobin, g/L	129 (119–142)	131 (120–143)	129 (119–142)	0.235
C-reactive protein, mg/L	2.0 (0.9–4.0)	2.0 (1.0–4.0)	2.0 (0.9–4.9)	0.503
Plasma fibrinogen, g/L	2.80 (2.35–3.31)	2.77 (2.33–3.16)	2.82 (2.39–3.35)	0.235
Homocysteine, μmol/L	12.4 (9.0–16.5)	14.1 (10.0–18.2)	12.2 (8.8–16.0)	0.030
Total cholesterol, mmol/L	4.1 (3.5–4.9)	4.1 (3.3–5.0)	4.1 (3.5–4.8)	0.931
Triglyceride, mmol/L	1.3 (0.9–1.8)	1.3 (1.0–2.1)	1.3 (0.9–1.7)	0.134
HDL, mg/dL	1.2 (0.9–1.4)	1.2 (1.0–1.4)	1.2 (0.9–1.4)	0.965
LDL, mg/dL	2.6 (2.1–3.1)	2.6 (2.0–3.0)	2.5 (2.1–3.1)	0.920
Serum glucose, mmol/L	5.5 (4.8–6.7)	5.6 (4.8–6.9)	5.5 (4.8–6.7)	0.607
Blood urea nitrogen, mmol/L	4.8 (3.9–5.8)	4.8 (4.0–5.9)	4.8 (3.9–5.7)	0.503
Creatinine, μmol/L	88 (76–98)	91 (77–105)	86 (76–96)	0.007
UA, μmol/L	281 (224–349)	332 (245–408)	270 (220–328)	<0.001

Abbreviations: CSS, Canadian Stroke Scale; DBP, diastolic blood pressure; END, early neurological deterioration; GCS, Glasgow Coma Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; UA, uric acid.

Table 2 Baseline Characteristics of Participants According to UA Quartiles

Variables	UA ($\mu\text{mol/L}$)				P value for Trend
	Q1 (≤ 224 , n=126)	Q2 (224–281, n=126)	Q3 (281–349, n=125)	Q4 (>349 , n=121)	
Age, years	67.0 (60.0–77.0)	70.0 (55.8–79.0)	63.0 (52.5–72.5)	64.0 (51.0–72.0)	0.001
Gender, Male, n (%)	52 (41.3)	81 (64.3)	84 (67.2)	105 (86.8)	<0.001
Medical history, n (%)					
Hypertension	82 (65.1)	106 (84.1)	96 (76.8)	104 (86.0)	<0.001
Diabetes	35 (27.8)	25 (19.8)	26 (20.8)	20 (16.5)	0.173
Hyperlipidemia	29 (23.0)	37 (29.4)	42 (33.6)	42 (34.7)	0.173
Coronary heart disease	10 (7.9)	10 (7.9)	10 (8.0)	9 (7.4)	0.998
Atrial fibrillation	4 (3.2)	6 (4.8)	2 (1.6)	4 (3.3)	0.568
Prior stroke	35 (27.8)	45 (35.7)	37 (29.6)	35 (28.9)	0.523
Smoking	22 (17.5)	32 (25.4)	32 (25.6)	41 (33.9)	0.033
Drinking	17 (13.5)	21 (16.7)	31 (24.8)	45 (37.2)	<0.001
Medication history, n (%)					
Antihypertensive	44 (34.9)	53 (42.1)	58 (46.4)	66 (54.5)	0.018
Antiplatelet	26 (20.6)	30 (23.8)	28 (22.4)	21 (17.4)	0.633
Anticoagulant	1 (0.8)	0 (0.0)	1 (0.8)	1 (0.8)	0.796
Statin	17 (13.5)	21 (16.7)	25 (20.0)	25 (20.7)	0.422
Hematoma location, n (%)					
Lobe	14 (11.1)	11 (8.7)	18 (14.4)	11 (9.1)	0.456
Basal ganglia	71 (56.3)	75 (59.5)	62 (49.6)	66 (54.5)	0.454
Thalamus	28 (22.2)	25 (19.8)	29 (23.2)	32 (26.4)	0.666
Cerebellum	9 (7.1)	14 (11.1)	9 (7.2)	7 (5.8)	0.435
Brainstem	4 (3.2)	1 (0.8)	7 (5.6)	5 (4.1)	0.200
Concurrent ventricular hemorrhage, n (%)	21 (16.7)	26 (20.6)	27 (21.6)	38 (31.4)	0.041
Baseline hematoma volume, mL	10 (7–15)	13 (8–17)	12 (8–18)	13 (10–20)	0.033
Hematoma expansion, n (%)	11 (8.7)	18 (14.3)	24 (19.2)	26 (21.5)	0.030
END, n (%)	25 (19.8)	24 (19.0)	29 (23.2)	54 (44.6)	<0.001
Clinical characteristics					
Body temperature, $^{\circ}\text{C}$	36.6 (36.4–36.8)	36.6 (36.4–36.8)	36.7 (36.4–36.8)	36.5 (36.3–36.7)	0.261
Time from onset to admission, h	3.5 (2.0–6.0)	3.0 (2.0–7.8)		3.5 (2.0–6.0)	0.487
Time from onset to first CT, h	3.0 (2.0–7.3)	4.0 (2.8–7.0)	4.0 (2.0–6.0)	3.0 (2.0–6.0)	0.705
Baseline SBP, mmHg	160 (142–175)	167 (150–185)	161 (145–180)	172 (152–192)	<0.001
Baseline DBP, mmHg	95 (80–105)	100 (85–108)	100 (90–110)	100 (94–116)	<0.001
Baseline GCS score	15 (14–15)	15 (15–15)	15 (15–15)	15 (14–15)	0.065
Baseline CSS score	6.0 (4.5–8.0)	7.0 (5.0–8.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	0.137
Laboratory data					
Leukocyte, $\times 10^9/\text{L}$	7.20 (5.62–9.16)	8.00 (5.71–9.60)	7.40 (5.90–9.22)	7.73 (6.59–9.49)	0.223
Neutrophil, $\times 10^9/\text{L}$	5.38 (3.73–7.31)	5.68 (4.05–7.76)	5.26 (3.94–7.11)	5.56 (4.16–7.05)	0.467
Hemoglobin, g/L	126 (116–142)	129 (120–142)	132 (119–142)	132 (120–142)	0.244
C-reactive protein, mg/L	2.0 (1.0–6.0)	2.0 (0.9–5.1)	1.7 (0.5–4.0)	2.0 (1.0–3.0)	0.830
Plasma fibrinogen, g/L	2.80 (2.47–3.39)	2.87 (2.42–3.33)	2.73 (2.13–3.22)	2.81 (2.39–3.29)	0.247
Homocysteine, $\mu\text{mol/L}$	11.3 (8.6–14.7)	12.1 (9.0–16.9)	12.7 (10.3–16.0)	14.4 (10.0–18.7)	0.008
Total cholesterol, mmol/L	4.0 (3.4–4.7)	4.1 (3.5–5.1)	4.1 (3.5–4.8)	4.3 (3.6–5.0)	0.237
Triglyceride, mmol/L	1.0 (0.8–1.5)	1.3 (0.9–1.8)	1.3 (1.0–2.0)	1.4 (1.0–1.9)	<0.001
HDL, mg/dL	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (1.0–1.3)	1.1 (0.9–1.4)	0.309
LDL, mg/dL	2.5 (2.0–3.0)	2.5 (2.0–3.1)	2.5 (2.0–3.0)	2.7 (2.1–3.2)	0.194
Serum glucose, mmol/L	5.5 (4.7–7.6)	5.7 (4.9–7.2)	5.4 (4.8–6.5)	5.4 (4.7–6.3)	0.213
Blood urea nitrogen, mmol/L	4.4 (3.5–5.0)	4.7 (3.8–5.5)	4.9 (3.9–6.0)	5.4 (4.6–6.9)	<0.001
Creatinine, $\mu\text{mol/L}$	77 (69–89)	86 (76–95)	88 (80–98)	97 (88–118)	<0.001

Abbreviations: CSS, Canadian Stroke Scale; DBP, diastolic blood pressure; END, early neurological deterioration; GCS, Glasgow Coma Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; UA, uric acid.

Table 3 Logistic Regression Model of UA and END

	Quartiles of UA ($\mu\text{mol/L}$)				P value
	Q1 (≤ 224 , n=126)	Q2 (224–281, n=126)	Q3 (281–349, n=125)	Q4 (>349 , n=121)	
Unadjusted model	Reference	0.951 (0.509–1.774)	1.220 (0.667–2.231)	3.256 (1.849–5.734)	<0.001
Model 1	Reference	0.951 (0.505–1.792)	1.233 (0.664–2.288)	3.303 (1.795–6.079)	<0.001
Model 2	Reference	0.823 (0.419–1.614)	1.043 (0.530–2.051)	2.282 (1.112–4.685)	0.013

Notes: Model 1: adjusted for age and sex; model 2: further adjusted for variables with P value < 0.1 in univariate analysis (concurrent ventricular hemorrhage, baseline hematoma volume, baseline GCS score, baseline CSS score, leukocyte, neutrophil, homocysteine and creatinine).

Abbreviations: CSS, Canadian Stroke Scale; END, early neurological deterioration; GCS, Glasgow Coma Scale; UA, uric acid.

and creatinine ($P < 0.001$). Also, patients with higher UA were younger ($P = 0.001$).

Table 3 exhibits the results of the binary logistic regression of END. In the unadjusted model, compared with the first quartile, patients with UA levels in the fourth quartile, were more likely to have END (OR 3.256, 95% CI 1.849–5.734, $P < 0.001$). The association remained significant after adjusting for the potential confounders (OR 2.282, 95% CI 1.112–4.685, $P = 0.013$).

Multiple-adjusted restricted cubic spline regression showed an ascending trend of UA ($P = 0.100$ for nonlinearity, as shown in Figure 1) with the risk of END.

Discussion

This study reveals a significantly increased risk of END among ICH individuals with higher serum UA levels after

adjusting for a series of potential confounders. To the best of our knowledge, this is the first study to investigate the association between UA and END in patients with ICH.

The results of previous studies on risk factors of END showed discrepancy, mainly related to the differences in diagnostic criteria and research objects. It has been reported that END was defined as a decrease in the GCS score of ≥ 3 or death within the first 72 hours,²¹ > 2 points increase in the NIHSS score within a 72-hour period,²² or a decrease in the CSS score of ≥ 1 points within 48 hours.⁸ In view of the high reliability and validity of CSS score for the assessment of neurological impairment in patients with stroke,²³ and the relatively convenient scoring procedures, END was defined as the CSS score decreased ≥ 1 points between admission and 48 hours in the current research.⁸ In this prospective study, END occurred in 26.5% of patients with ICH, slightly higher

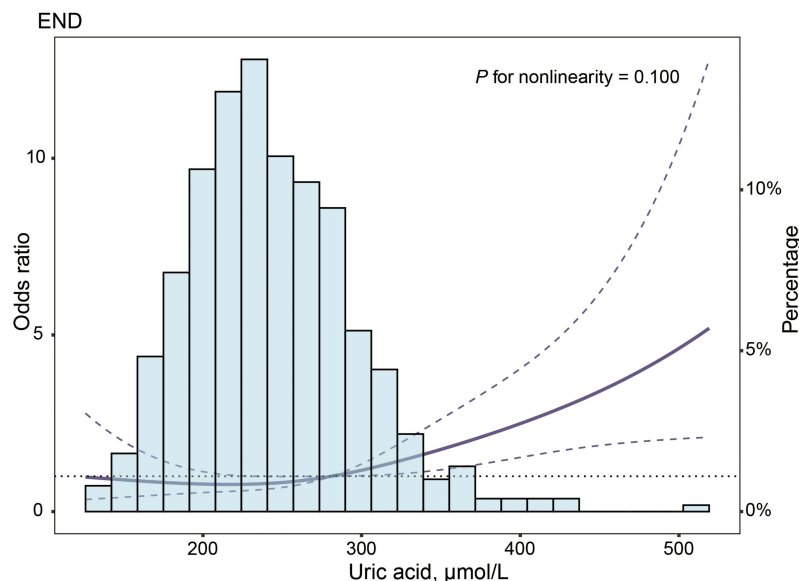


Figure 1 Association of UA with risk of END. Odds ratio and 95% CI were derived from restricted cubic spline regression, with knots placed at 5th, 35th, 65th, and 95th percentiles of UA. Odds ratio was adjusted for the same variables as in model 2 (Table 3). The solid line represented the odds ratio and the dashed lines represented the 95% confidence interval.

Abbreviations: CI, confidence interval; END, early neurological deterioration; UA, uric acid.

than the previous study, which may be due to ethnic differences in the study population.⁸

Although the exact mechanisms between UA and END in patients with ICH remained unclear, the following might explain it. First, previous studies have shown that a higher white blood cell count is predictive of END in patients with ICH, suggesting that inflammatory response may be involved in END.^{8,21} Serum UA, on the other hand, promotes the release of a range of inflammatory mediators, such as neutrophils count, C-reactive protein, interleukin-1 β (IL-1 β), IL-6, IL-18, and tumor necrosis factor- α (TNF- α),^{24,25} which may in turn lead to END. Secondly, serum UA has pro-oxidant properties by increasing the production of reactive oxygen species (ROS).²⁶ Then, the increased oxidative stress level can aggravate secondary brain injury after ICH through inflammatory response, apoptosis, autophagy and destruction of blood–brain barrier,²⁷ and eventually contribute to END. Last but not the least, individuals with higher levels of UA were more likely to have larger baseline hematoma volume, higher proportions of intraventricular hemorrhage and hematoma expansion, and all of which have been shown to be risk factors associated with END in patients with ICH.^{8,9}

Some limitations should be noted in this study. First, this was a single-center study with a relatively small sample size, thereby limiting the ability to extend the finding. Secondly, the UA level was detected only once on admission, but not dynamically monitored during the study. The pattern of dynamic change of UA could provide better prognostic information. Thirdly, recent emerging lines of evidence suggest that high blood pressure variations are important predictors of the prognosis of ICH.^{28,29} However, our study did not take this factor into account. Finally, we had little background information, such as purine consumption, history of gout and exercise habit that would affect admission serum UA concentration.

Conclusions

In conclusion, an elevated serum UA level was independently associated with END in patients with ICH. Therefore, intervention to lower UA level may be worth considering.

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Disclosure

All authors declare that there were no conflicts of interest.

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