

Serum Uric Acid and Calcium Levels as Predictors of Hematoma Volume in Emergency Patients Experiencing Spontaneous Intracerebral Hemorrhage

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Research Article

Keywords: Serum uric acid, Serum calcium, Predictor, Hematoma volume, Intracerebral hemorrhage

Posted Date: December 14th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1045660/v1>

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Abstract

Objective: To investigate the relationship between serum uric acid and calcium levels and hematoma volume in emergency patients who experienced spontaneous intracerebral hemorrhage (SICH).

Methods: Data from 105 patients who experienced SICH and 92 with non-intracerebral hemorrhage (control group) were retrospectively analyzed. Data collected included clinical characteristics, and serum biochemical and blood coagulation indices. Hematoma volume was calculated using computed tomography (CT) imaging data.

Results: Individuals who experienced SICH exhibited higher serum uric acid levels and longer activated partial thromboplastin and thrombin times compared to those with non-intracerebral hemorrhage (all $P < 0.05$). In contrast, serum calcium levels in patients with SICH were lower than those of the control group ($P < 0.05$). Hypocalcemic patients exhibited a greater median baseline hematoma volume than normocalcemic patients.

Conclusion: High serum uric acid and low calcium levels may be predictors of larger hematoma volumes among individuals who experience SICH.

Background

As a common condition seen in the emergency department, spontaneous intracerebral hemorrhage (SICH) is a non-traumatic, intra-parenchymal hemorrhagic phenomenon and an important subtype of stroke. It has a high incidence rate worldwide, and is further characterized by high mortality and disability rates^[1]. Although the incidence of cerebral hemorrhage has decreased in the United States in recent years, it has significantly increased in developing and low-income countries, including China^[2]. Strokes that include cerebral hemorrhage brings a huge pressure on people and their families and societies^[3]. Which has resulted in extremely heavy economic burden to individuals^[4]. The primary treatment approach for intracerebral hemorrhage is surgery, which can significantly improve the prognosis of patients undergoing long-term oral antiplatelet therapy for intracerebral hemorrhage^[5]. Surgical treatment is an important treatment for cerebral hemorrhage. Early and timely surgery can improve the prognosis of patients with cerebral hemorrhage and prevent the occurrence of secondary injuries^[6]. Moreover, the prognosis of those who experience intracerebral hemorrhage is closely associated with the volume of the hemorrhage^[7].

A previous study found that the prognosis for cerebral hemorrhage and hematoma volume enlargement was correlated with blood calcium levels^[8]. However, whether there are other biochemical indicators related to cerebral hemorrhage needs further investigation. Previous studies have shown that uric acid is implicated in the occurrence of cardiovascular^[9] and cerebrovascular^[10] diseases; however, few have directly investigated the relationship between uric acid and cerebral hemorrhage. As such, whether uric acid levels can predict cerebral hemorrhage volume remains unclear.

Accordingly, in an attempt to guide treatment and improve prognosis, this study aimed to determine whether there is a correlation between serum calcium and uric acid levels and intracerebral hemorrhage volume in emergency patients who experienced SICH.

Methods

1. Patients

Patients who experienced SICH and were admitted to the emergency department of our hospital between January 2018 and January 2019, were placed in the experimental group. The inclusion criteria are as follows: 1) Severe headache, vomiting, limb movement disorder, and consciousness disorder were the main clinical manifestations, and the patient was definitively diagnosed with cerebral hemorrhage according to cranial CT examination; 2) After admission to the emergency room, the patient underwent intravenous blood collection and complete blood biochemical tests. The exclusion criteria include: 1) Traumatic cerebral hemorrhage; 2) Intracranial hemorrhage caused by hemorrhage transformation after cerebral infarction; 3) Cerebrovascular malformation and secondary cerebral hemorrhage caused by aneurysm; 4) Medicaments cause element, swollen cerebral hemorrhage caused by tumor. Basic demographic information, venous blood test results, and imaging data from head computed tomography (CT) were collected. Individuals who experienced non-cerebral hemorrhage and were admitted to the emergency room in the same time interval served as the control group.

The Ethics Committee of The Second Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu Province, China) approved the study design and all patients were older than 16 years and gave informed consent to the study. All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all patients, or their families, who participated in this study.

2. Collection of biochemical indicators

All patients admitted to the emergency room for treatment (i.e., experimental and control groups) immediately underwent venous blood sampling for examination. Laboratory investigations included routine blood counts and coagulation factors, renal function tests, and electrolyte levels.

3. Calculation of hematoma volume using CT imaging data

All patients underwent head CT examination within 30 min of admission. Hematoma volume was calculated using CT imaging data of the head and the multi-field formula: Hematoma volume = $ABC/2$, in which A is the maximum cross-section and diameter (mm) of the hematoma on CT, B is the maximum transverse diameter (mm) perpendicular to A, and C is the thickness of the hematoma hemorrhage layer (mm).

4. Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 19.0 (IBM Corporation Armonk, NY, USA). Categorical variables are expressed as a number (%), whereas continuous values are expressed as a mean \pm standard deviation (SD). The two-sided chi-squared test or Fisher's exact test were used to evaluate the relationship between different variables. Univariate logistic and multiple regression analysis was performed to predict hematoma volume. Differences with $P < 0.05$ were considered to be statistically significant. Data were plotted using GraphPad Prism version 6.0 (GraphPad Inc., San Diego, CA, USA).

Results

1. Demographic data of patients who experienced SICH

Requisite data from 105 patients who experienced SICH (mean age, 68 years; 75 male) were included for analysis in the present study; the hemorrhage volume in 24 patients was > 30 ml. Among the 105 patients, the baseline hematoma was located in the following regions: basal ganglion (28.6%), lobes (46.7%), epencephalon (9.5%), brainstem (6.7%), and arachnoid cavity (8.5%). In addition, 95 patients who experienced non-cerebral hemorrhage (mean age, 72 years; 69 male) were enrolled as the control group. Correlation analysis revealed that the occurrence of SICH was associated with hypertension, diabetes, and renal dysfunction ($P < 0.05$). The characteristics of all patients are summarized in Table 1.

2. Abnormal serum calcium and uric acid levels in patients who experienced SICH

In present study, data regarding 8 admission biochemical or blood coagulation parameters, including C-reactive protein (CRP), uric acid, carbamide, creatinine, calcium, activated partial thromboplastin and thrombin time (aPTT), thrombin time (TT), and prothrombin time (PT), were collected (Table 1). When compared with cases of non-cerebral hemorrhage, those who experienced SICH exhibited higher serum uric acid levels (Fig. 1b), while the results for serum calcium were the opposite, with a lower level in the SICH group (Fig. 1f). There were no other differences between the two groups (all $P > 0.05$) (Table 1, Fig. 1).

3. Serum uric acid and calcium levels predicted hematoma volume in patients who experienced SICH

A positive correlation was found between serum uric acid level and hematoma volume ($r^2 = 0.167$, $P < 0.001$; Fig. 2a), while uric acid was negatively correlated with hematoma volume ($r^2 = 0.059$, $P = 0.013$; Fig. 2b). Subsequently, the patients were divided into two groups using the upper limit of serum uric acid or lower limit of serum calcium level as the cut-off value. Results of analysis revealed that hematoma volume in the hyperuricemia group was larger than in the non-hyperuricemia group (Fig. 2c). In contrast, hematoma volume in patients with hypocalcemia was greater than that of non-hypocalcemia patients (Fig. 2d).

4. The value of combining serum calcium and uric acid levels in predicting hematoma volume

The association between serum calcium and uric acid levels was investigated and no correlation was found (Fig. 3a). Based on this, we speculated whether combining the two parameters would be a better predictor of hematoma volume. Accordingly, the patients were divided into three groups: hyperuricemia and hypocalcemia (Group 1); hyperuricemia/non-hypocalcemia or non-hyperuricemia/hypocalcemia (Group 2); and non-hyperuricemia and non-hypocalcemia (Group 3). Analysis revealed that patients in Group 1 exhibited the largest hematoma volume, while those in group 3 exhibited the smallest (Fig. 3b). These findings suggested that the combination of serum calcium and uric acid may have more utility in predicting the volume of intracerebral hemorrhage.

Discussion

As an important mineral involved in the composition of the human body, calcium plays a crucial role in the daily functions of life, including bone formation, excitatory contraction coupling of cells, maintenance of the excitability of nerve cells, activation of various enzymes, coagulation, and other aspects. Blood calcium may be implicated in the process of cerebral hemorrhage by regulating blood pressure, breaking the blood-brain barrier, promoting apoptosis, and altering the contractile function of vascular smooth muscle^[12]. Uric acid is the end product of human purine metabolism. There are two sources of uric acid in the body: endogenous and Exogenous uric acid. 2/3 of uric acid is excreted through the kidney and most of the rest through the biliary and intestinal tracts^[13]. In addition to gout, high uric acid levels have also been implicated in cardiovascular diseases, diabetes mellitus (DM), hypertension, obesity, hyperlipidemia, chronic kidney disease, and other conditions^[14]. Several studies have shown that serum calcium levels are associated with cerebral hemorrhage volume and prognosis. Excessive or inadequate serum calcium levels may lead to increased hematoma volume and stroke severity in patients who experience acute cerebral hemorrhage, and is associated with long-term survival^[12]. A retrospective study by Morotti et al. showed that hypocalcemia was associated with the volume of intracerebral hematoma and was likely to lead to secondary enlargement of the volume^[15]. However, a study by Kitamura et al. revealed that a high serum calcium level was associated with cerebral hemorrhage in patients undergoing long-term dialysis^[16]. At the same time, an investigation by Sharaf El Din et al. demonstrated that uric acid is involved in the occurrence of multiple sclerosis, renal disease, and cardiovascular disease from experimental, clinical, interventional, and epidemiological perspectives^[14]. Several studies from abroad have also shown that elevated levels of uric acid is closely associated with stroke^[17, 18], subclinical left ventricular dysfunction^[9], and hypertension^[19]. There are varying opinions regarding the role of uric acid in stroke. Some investigators, such as Iranmanesh et al., believed that uric acid was not associated with acute ischemic non-embolic stroke^[20]. Saadat et al. reported that serum uric acid level was not associated with stroke type and sex^[21]. Some investigators believe that uric acid is associated with the incidence of stroke and can be used as a prognostic factor. A study by Mapoure et al. demonstrated that hyperuricemia increased the incidence of stroke in black Africans and was a predictor of poor outcomes^[22]. However, a study by Zhang et al. found that, in young individuals who experienced acute cerebral infarction, an elevated uric acid level was an independent predictor of good prognosis^[23].

Nevertheless, few studies have directly investigated the role of uric acid in intracerebral hemorrhage. One side, Studies by Ryu et al. found that increased uric acid level was independently associated with the presence of cerebral microhemorrhage in hypertensive patients and in acute ischemic stroke patients, respectively^[17]. On the other side, Xiao N et al. found that low serum uric acid levels promote hypertensive intracerebral hemorrhage by disrupting the smooth muscle cell-elastin contractile unit and upregulating the Erk1/2-MMP axis^[24]. Our study found that those who experienced intracerebral hemorrhage exhibited higher serum uric acid and lower serum calcium levels, with statistically significant differences. Furthermore, hypocalcemic patients exhibited a higher median baseline hematoma volume than did normocalcemic patients. The results are, in part, similar to those reported by Morotti et al. However, the mechanisms of high serum uric acid and low calcium levels and how they influence hematoma volume need further research. Further studies are needed to determine whether this can be achieved by lowering uric acid levels and increasing calcium levels to reduce hematoma volume and improve the prognosis in those who experience cerebral hemorrhage. Finally, because the present study was a single-center, retrospective investigation, some selection bias may have been introduced. As such, the results need to be confirmed in larger-scale, multi-center, prospective cohorts.

Conclusions

High serum uric acid and low calcium levels may be predictors of larger hematoma volumes among patients who experience SICH.

Declarations

Ethics approval and consent to participate

The Ethics Committee of The Second Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu Province, China) approved the study design. All patients were older than 16 years and gave informed consent to the study.

Consent for publication

Not applicable.

Statement on informed consent

Written informed consent was obtained from all patients, or their families, who participated in this study.

Availability of data and materials

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Hong Ding conceived and designed the study. Xiaohui Zhang collected and analyzed the data. Xiaohui Zhang wrote the main manuscript text and prepared figures 1-3. All authors reviewed the manuscript.

Acknowledgements

Not applicable.

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Tables

Table1. Demographic data of patients with intracerebral hemorrhage			
Clinical characteristics	Patients		P value
	Control (92)	ICH	
No.	92	105	
Gender			
Male	69 (75.0%)	75 (71.4%)	0.573
Female	23 (25.0%)	30 (28.6%)	
Age (y; median, 95% CI)	72 (67-80)	68 (64-71)	0.819
Past medical history (%)			
Hypertension	20 (21.7%)	44 (41.9%)	0.033
Diabetes	9 (9.8%)	31 (29.8%)	0.001
Hyperlipidemia	35 (38.0%)	50 (47.6.3%)	0.176
Renal dysfunction	6 (6.5%)	27 (25.7%)	0.001
Serum indexes (mean ± SEM)			
CRP (mg/L)	16.13 (3.51)	26.92(5.11)	0.077
Uric acid (umol/L)	303.1 (10.08)	340.4 (10.43)	0.011
Carbamide (mmol/L)	7.95 (0.92)	7.74 (0.51)	0.833
Creatinine (umol/L)	112.6 (17.00)	164.3 (24.08)	0.089
Calcium (mmol/L)	2.1 (0.02)	2.2(0.21)	0.025
APTT	31.58 (0.72)	29.73 (0.65)	0.058
TT	17.15 (2.63)	16.58 (1.69)	0.068
PT	12.97 (0.20)	12.88 (0.21)	0.762
Hematoma volume (ml)			
< 10		39 (37.2%)	
10-30		42 (40.0%)	
> 30		24 (22.8%)	
Hematoma location			
Basal ganglia		30 (28.6%)	

Lobe	49 (46.7%)
Epencephalon	10 (9.5%)
Brainstem	7 (6.7%)
Arachnoid cavity	9 (8.5%)

Figures

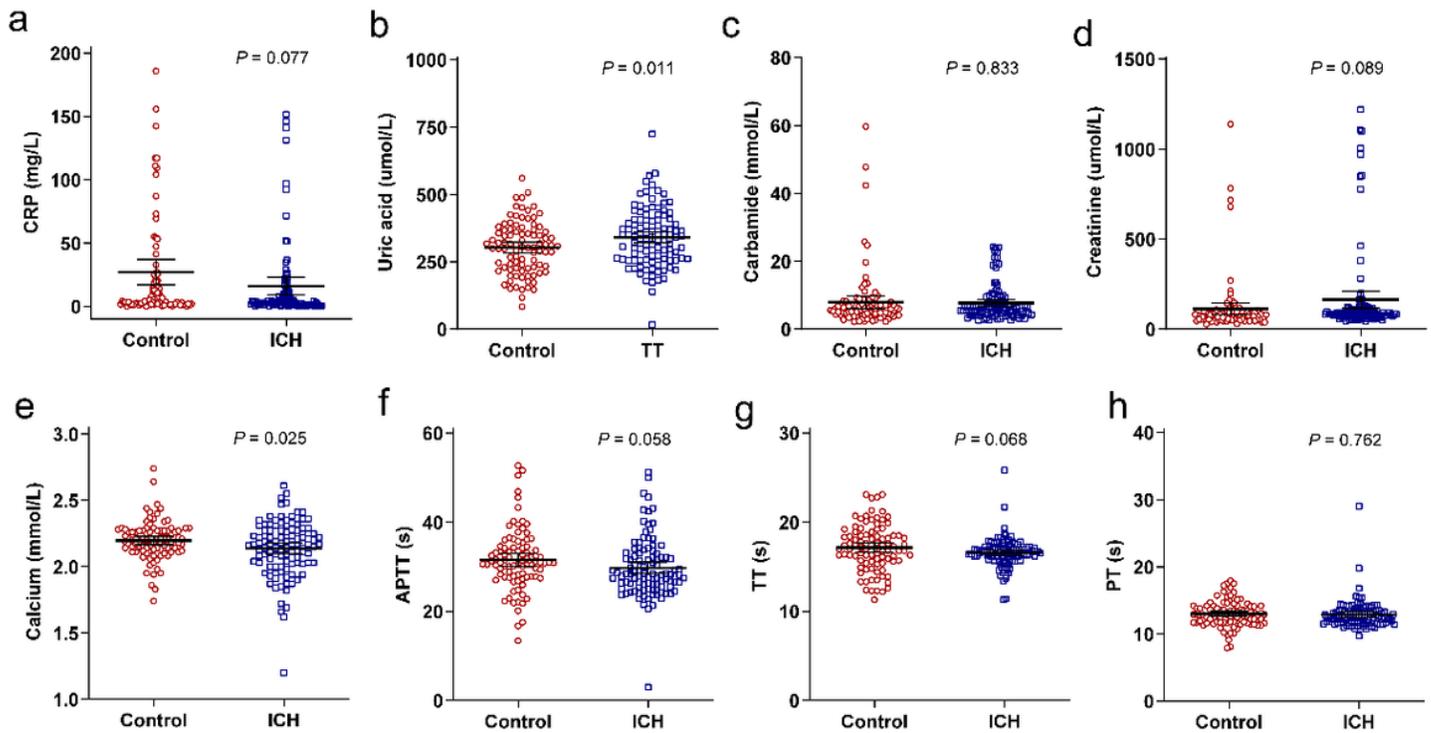


Figure 1

The admission blood indexes in cerebral hemorrhage. (a) CRP, (b) uric acid, (c) carbamide, (d) creatinine, (e) calcium, (f) APTT, (g) TT and (h) PT.

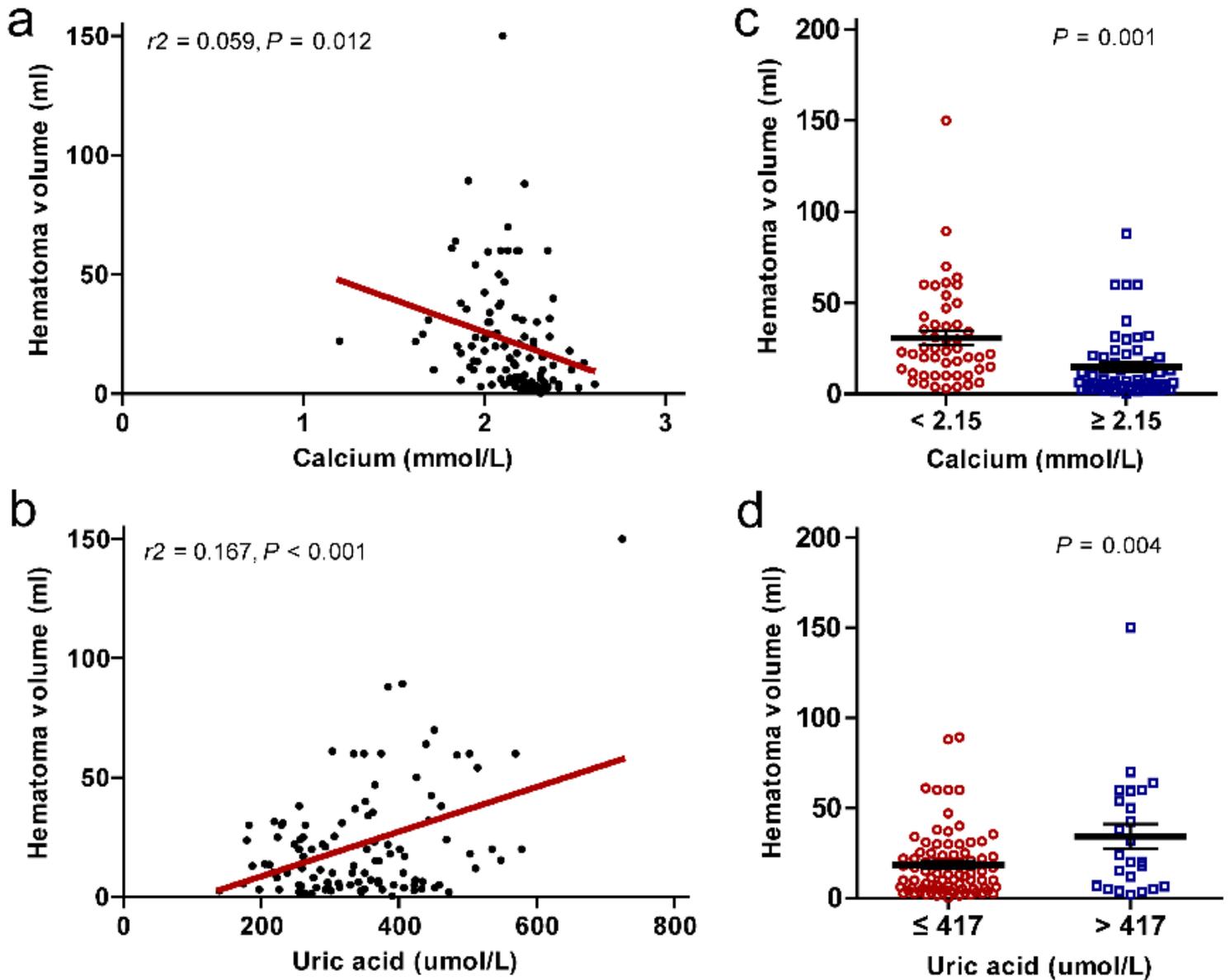


Figure 2

Association between serum uric acid and calcium levels and hematoma volume in patients who experienced spontaneous intracerebral hemorrhage. (a) Correlation analysis of serum uric acid level and hematoma volume. (b) Correlation analysis of serum calcium level and hematoma volume. (c) Patients were divided into two subgroups using the upper limit of serum uric acid level. The scatter plot shows the hematoma volume in hyperuricemia and non-hyperuricemia patients. (d) Patients were divided into two subgroups using lower limit of serum calcium. The scatter plot shows the hematoma volume in patients with hypocalcemia and the others.

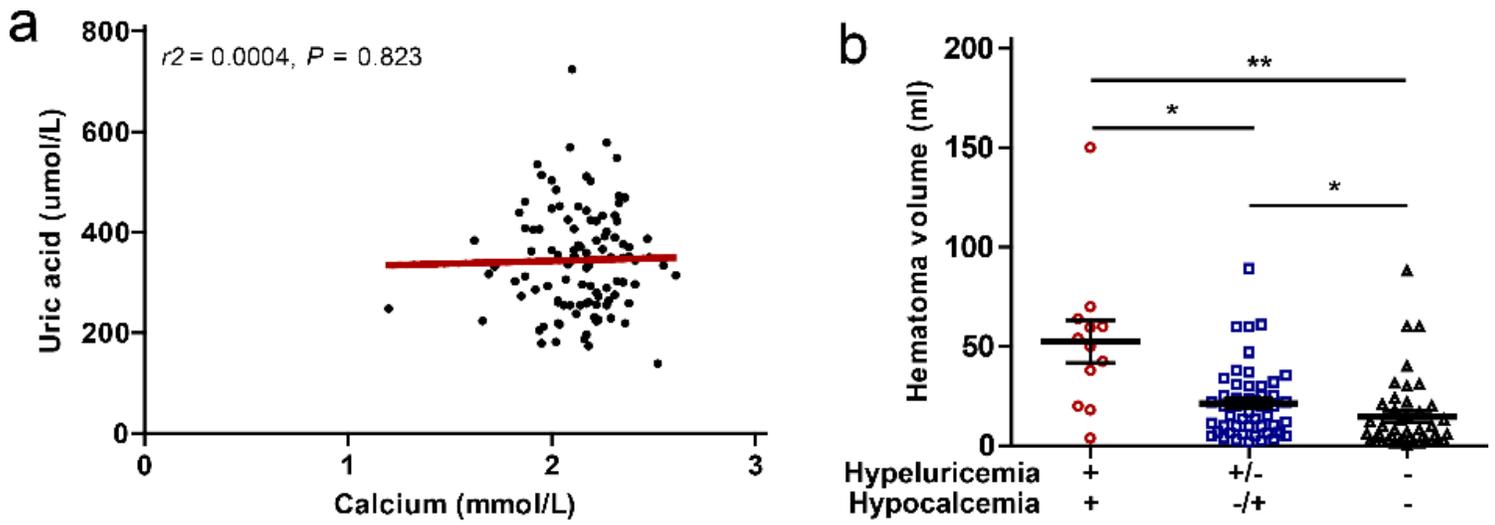


Figure 3

Combination of serum uric acid and calcium levels in predicting hematoma volume in patients who experienced spontaneous intracerebral hemorrhage. (a) Correlation analysis of serum uric acid and serum calcium levels. (b) Patients were divided into three subgroups according to the presence or absence of hypocalcemia and hyperuricemia. Scatter plot showing the hematoma volume in the above groups. *P < 0.05; **P < 0.001.