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Hyperuricemia as a risk factor for cerebral hemorrhage in young and middle-aged hypertensive patients at high altitude

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Abstract

Background: The purpose of this research was to investigate the effect of uric acid on hypertensive intracerebral hemorrhage (HICH) in young and middle-aged hypertensive patients at high altitude. *Methods:* High-altitude and low-altitude HICH patients were analyzed retrospectively, and the influence of uric acid on hemorrhage was analyzed by the correlations between age and uric acid, between age and hemoglobin, and between uric acid and hemoglobin. The individuals in the high- and low-altitude groups were assigned to a young/middle-aged group and an elderly group, and the correlation between age and uric acid was analyzed. The risk factors for HICH were analyzed by logistic regression analysis. ROC curve analysis was used to investigate the relationship between risk factors and cerebral hemorrhage. *Results:* Age was negatively correlated with uric acid concentration in patients with HICH at high altitudes but not in patients with HICH at low altitudes. In addition, age was negatively correlated with hemoglobin in patients with HICH at high altitudes but not in patients with HICH at low altitudes. Uric acid was negatively correlated with age in young and middle-aged adults at high altitudes but not in elderly individuals. Diastolic pressure, uric acid and sex were risk factors for HICH in young and middle-aged adults at high altitudes. ROC curve showed that uric acid and diastolic pressure had diagnostic significance.
Conclusions: High levels of uric acid is correlated with increased risk of cerebral hemorrhage in young and middle-aged adults with hypertension in high altitude.

Keywords: Hypertensive, cerebral hemorrhage, high altitude, low altitude, uric acid.

INTRODUCTION

Due to special climatic conditions at high altitudes, metabolic abnormalities lead to increased uric acid levels, and hyperuricemia is a well-known independent risk factor for hypertension.[1] Hyperuricemia can also lead to multiple organ damage.[2-4] In addition, uric acid is closely related to hemoglobin.[5] In recent years, it has been found that uric acid levels in young and middle-aged people at high altitudes increased, accompanied by elevated hemoglobin. Other studies have shown that in young and middle-aged patients, hypertensive intracerebral hemorrhage (HICH) is often accompanied by an increase in blood uric acid level. However, whether there is a certain relationship between uric acid and

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cerebral hemorrhage is still unclear; therefore, we compared patients with HICH at different altitudes and analyzed its risk factors to provide guidance for the prevention of HICH at high and low altitudes.

METHODS

Patient selection

This study was approved by our local ethics committee [People's Hospital of Hekou County (Ethical number: HK202201), First People's Hospital of Honghe City (Ethical number: HY2022LLSC-82)]. These case data were obtained retrospectively. For the high-altitude group, from March 2015 to April 2021, 403 patients with HICH were identified by computed tomography (CT) (GE Lightspeed 64, USA), and related laboratory investigations and assays were performed at high altitude (Gejiu City, Honghe City). The selection criteria were as follows: 1. history of hypertension; 2. altitude 1500 m-2000 m; 3. duration of high-altitude residence ≥ 5 years; and 4. complete clinical data. For the low-altitude group, from January 2015 to August 2021, 218 patients with HICH were identified by computed tomography (CT) (GE Lightspeed 64, USA), and related laboratory investigations and assays were performed at low altitude (Hekou County). The selection criteria were as follows: 1. history of hypertension; 2. altitude 50-200 m; 3. duration of low-altitude residence ≥ 5 years; and 4. complete clinical data. Patients were excluded for the following reasons: 1. vascular malformations, aneurysmal cerebral hemorrhage, tumor hemorrhage, disturbance of consciousness, or hematoma breaking into the lateral ventricle; 2. allergic constitution, asthma, hyperthyroidism, and others; and 3. incomplete medical records. The relevant data of the patients, including sex, age, nationality, underlying disease, medication history, uric acid concentration in blood, hemoglobin concentration, coagulation function, blood pressure, urico-lowering therapy (history of gout), smoking history, and drinking history, were collected and recorded in detail on admission. The patients were divided into an elderly group, >50 years old, and a young and middle-aged group, ≤50 years old, stratified by high and low altitudes (Figure 1). All data were independently and blindly reviewed by two senior neurosurgeons.

Data collection

The patient blood parameters were determined by a Sysmex XN1000 for routine blood detection and coagulation function (Japan). Blood biochemical examination was performed by using a Canon-Toshiba TBA FX8 (Japan) instrument. The patients were divided into a young and middle-aged group and an elderly group, and the uric acid and hemoglobin data in all groups were collected for further analysis.

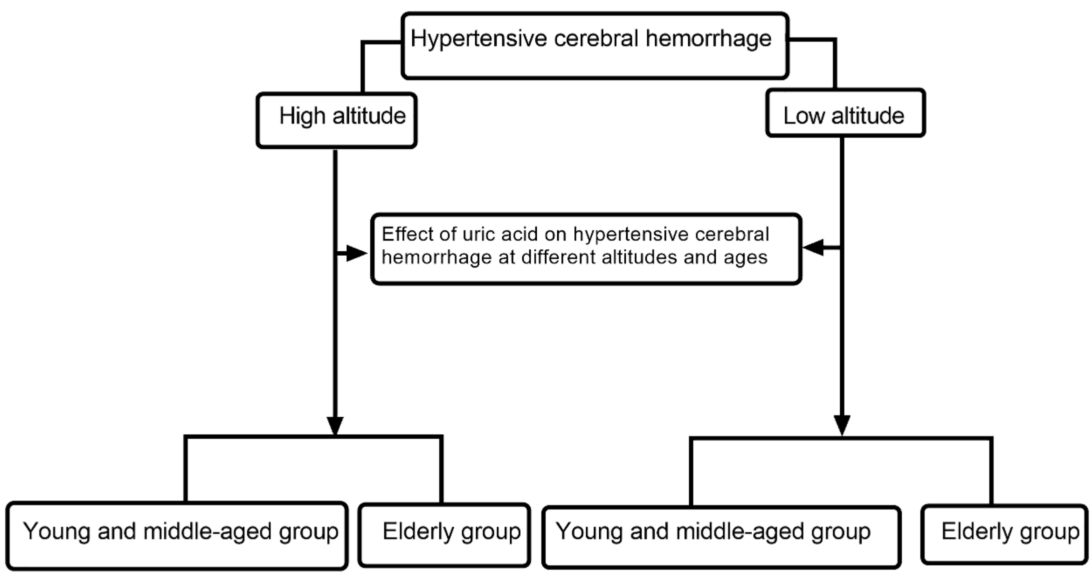

Figure 1. A flow chart for the identification process of eligible patients.

Statistical analysis

All analyses were performed using SPSS 19 (IBM Corp., Armonk, New York, USA). Normally distributed data are expressed as the mean ± standard deviation. Quantitative data were analyzed between the two groups using separate T tests, whereas categorical data were compared using chi-square tests. A scattergram with a regression line was generated to determine the association between age and hemoglobin concentration and uric acid concentration. Logistic regression analysis was performed to assess the risk factors in the young and middle-aged and elderly groups at high altitudes. Differences were considered significant at $p<0.05$. ROC curve analysis was used to investigate the diagnostic relationship between risk factors and cerebral hemorrhage. The Youden index was used to determine the optimal cut-off value as previously described.[6,7] Differences were considered significant at $p<0.05$. All data analysis was conducted by two investigators in a blinded manner.

RESULTS

Participant characteristics

For high-altitude areas, a total of 415 patients were included in the study according to the inclusion criteria. Of these, 148 met the criteria for the young and middle-aged group, and 255 met the criteria for the elderly group. For low-altitude areas, a total of 227 patients were included in the study according to the inclusion criteria. Of these, 42 were of young and middle-aged group, and 176 were of the elderly group. According to the statistical data, for patients at high altitudes, the male incidence of HICH in the young and middle-aged group was significantly higher than that in the elderly group. In addition, the incidence rate of Han nationality in the young and middle-aged group was higher than that in the elderly group. Further, the levels of uric acid and hemoglobin, systolic pressure and diastolic pressure in the young and middle-aged group were also higher than those in the elderly group. However, there were no differences in the above indicators among people at low altitudes (Table 1).

Analysis of risk factors for HICH at high altitude

To investigate the risk factors related to HICH at high altitude, logistic regression analysis was conducted according to possible risk factors. The

Table 1: Risk factor analysis results of the high and low altitude groups

Characteristics	High altitude				Low altitude			
	Young and middle-aged group	Old age group	t/χ^2	p	Young and middle-aged group	Old age group	$t/\chi2$	p
Age	40.66±6.46	63.23±9.23	26.16	0.000	45.57±3.25	65.34±10.10	12.51	0.000
Man	128	167	21.05	0.000	33	119	1.99	0.193
Nation								
Han	92	132			28	106		
Ethnic Minority	56	123	4.10	0.043	14	69	0.53	0.486
Drinking	51	86	0.02	0.881	8	30	0.09	0.771
Smoking	57	115	1.66	0.198	9	19	3.37	0.066
Uric acid (umol/L)	409..91±140.91	344.78±105.81	5.26	0.000	356.93±113.00	340.93±113.08	0.82	0.411
Hemoglobin (g/L)	153.14±22.41	146.57±18.65	3.16	0.002	136.12±19.41	134.48±21.86	0.45	0.941
Systolic pressure	181.13±26.83	170.84±24.16	3.96	0.000	164.90±27.01	162.52±31.69	0.45	0.269
Diastolic pressure	113.28±18.98	99.73±14.82	7.96	0.000	100.64±14.66	97.16±17.52	1.19	0.251
Urico-lowering therapy	23	38	0.03	0.863	9	28	0.733	0.392

Table 2: Results of logistic regression analysis indicating predictors of risk factors

Indicators	B	BE	Wald	*P* Value	OR (95% CI)
Uric acid	-0.003	0.001	10.257	<0.01	0.997 (0.995-0.999)
Sex	1.020	0.301	11.474	<0.01	2.774 (1.537-5.005)
Diastolic pressure	-0.54	0.10	26.190	<0.00	0.948 (0.928-0.967)
Systolic pressure	0.008	0.007	1.474	>0.05	1.008 (0.995-1.021)
Hemoglobin	0.00	0.006	0.000	>0.05	1.000 (0.988-2.336)
Nation	0.382	0.238	2.587	>0.05	1.466 (0.920-5.799)

results suggested that uric acid level, diastolic pressure and sex were risk factors for HICH at high altitude (Table 2). Since sex was not a unit of quantity, diastolic blood pressure and uric acid were used for ROC curve analysis. The ROC analysis showed that the AUC values for the uric acid and diastolic pressure were 0.643 and 0.572 for the subjects (Table 3 and Figure 2). The specificity and sensitivity of diastolic blood pressure and uric acid had diagnostic significance (Table 3 and Figure 2).

Correlation of age, uric acid and hemoglobin in each group

From analysis of the data of patients in high-altitude areas, age was negatively correlated with uric acid concentration in patients with HICH (R^2=0.06978, Y = -2.384X + 499.7, *p*=0.0001) (Figure 3 A). The younger the patients were, the higher the probability of HICH. Age was negatively correlated with hemoglobin concentration (R^2=0.03641, Y = -0.2813*X + 164.7, *p*=0.0001) (Figure 3 B). There was a positive correlation between uric acid and hemoglobin concentration (R^2=0.04275, Y = 1.266X + 179.8, *p*= 0.0001) (Figure 3 C). The higher the hemoglobin concentration, the higher the uric acid level was.

From analysis of the data of patients in the low-altitude areas, there was no correlation between age and uric acid (R^2= 0.0146, Y = -1.132X + 413.7, *p*=0.0750) (Figure 3 D) or between age and hemoglobin concentration in HICH patients (R^2= 0.0003243, Y = -0.03197X + 136.8, *p*=0.7919) (Fig. 3 E). In addition, there was no correlation between uric acid and hemoglobin concentration (R^2=0.0009139, Y= 0.005711X + 132.8, *p*=0.6579) (Figure 3 F).

Specifically, for the young and middle-aged groups, age was negatively correlated with uric acid level at high altitude (R^2= 0.04632, Y = -4.691X + 600.7, *p*= 0.0086) (Figure 4 A). There was no correlation between age and hemoglobin concentration at high altitude (R^2=0.005348, Y = -0.252*X + 163.8, *p*=0.3771) (Figure 4 B). For the elderly group, there was no correlation between age and uric acid at high altitude (R^2= 0.003087, Y = -0.6347*X + 384.9, *p*= 0.3769) (Figure 4 C). There was also no correlation between age and hemoglobin in the elderly group at high altitude (R^2= 0.01491, Y = -0.2441*X + 162.1, *p*= 0.0515) (Figure 4 D). We also found that there was no correlation between uric acid level and age (R^2=0.000958, Y = 1.075*X + 308, *p*= 0.8457) or between age and hemoglobin concentration (R^2=0.02926, Y = 1.02*X + 89.62, *p*=0.2788) in the young and middle-aged group at low altitude (Figure 5 A and B). There was also no correlation between age and uric acid level (R^2= 0.01623, Y = -1.426*X + 434.1, *p*= 0.0920) or between age and hemoglobin concentration (R^2= 0.01859, Y = -0.02231*X + 135.9, *p*= 0.8917) in the elderly group at low altitude (Figure 5 C and D).

Table 3: Indices of lowest relative factors for predicting recurrence

Parameter	High altitude (n=403)	
	Uric acid	Diastolic pressure
AUC	0.572	0.643
95% CI	(0.514-0.631)	(0.586-0.700)
Sensitivity (%)	80.4%	56.8%
Specificity (%)	32.2%	68.2%
P-Value	<0.05	<0.01

The young and middle-aged group: n=148, the elderly group: n=255.

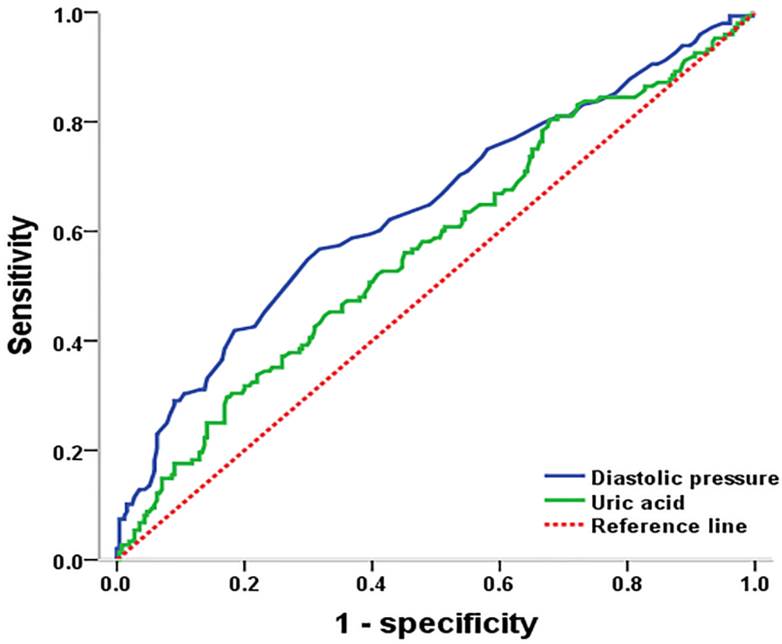

Figure 2. The ROC curve was used to measure the the uric acid and diastolic pressure for predicting the cut-off value of HICH. Specificity and sensitivity were used as measures of HICH. Analyses were performed for all subjects in the sample (n = 403, the young and middle-aged group: n=148, the elderly group: n=255). HICH was estimated using the area under the ROC curve (AUC) . The AUC values for the uric acid and diastolic pressure were 0.643 and 0.572 for the subjects. The specificity and sensitivity of diastolic blood pressure and uric acid had diagnostic significance.

DISCUSSION

In high-altitude areas, uric acid affects the incidence of HICH. According to our case analysis, hyperuricemia in young and middle-aged people at high altitude had the greatest impact on HICH, while it had no impact at low altitude. Logistic regression analysis showed that uric acid, diastolic pressure and sex were risk factors of HICH in young and middle-aged people

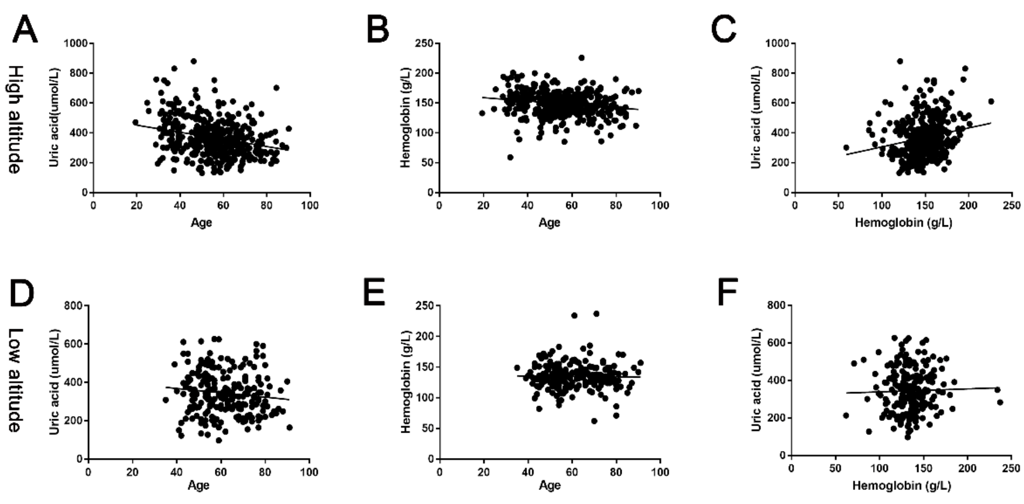

Figure 3. Scatter diagrams were depicted for the correlation between age and uric acid , hemoglobin and uric acid, and uric acid and hemoglobin at the high altitude and low altitiude patients. The correlations were linear with age and uric acid, hemoglobin and uric acid, and uric acid and hemoglobin at the high altitudes (p <0.05) (A-C). There were no linear correlation with age and uric acid, hemoglobin and uric acid, and uric acid and hemoglobin at the low altitudes (p >0.05) (D-F).

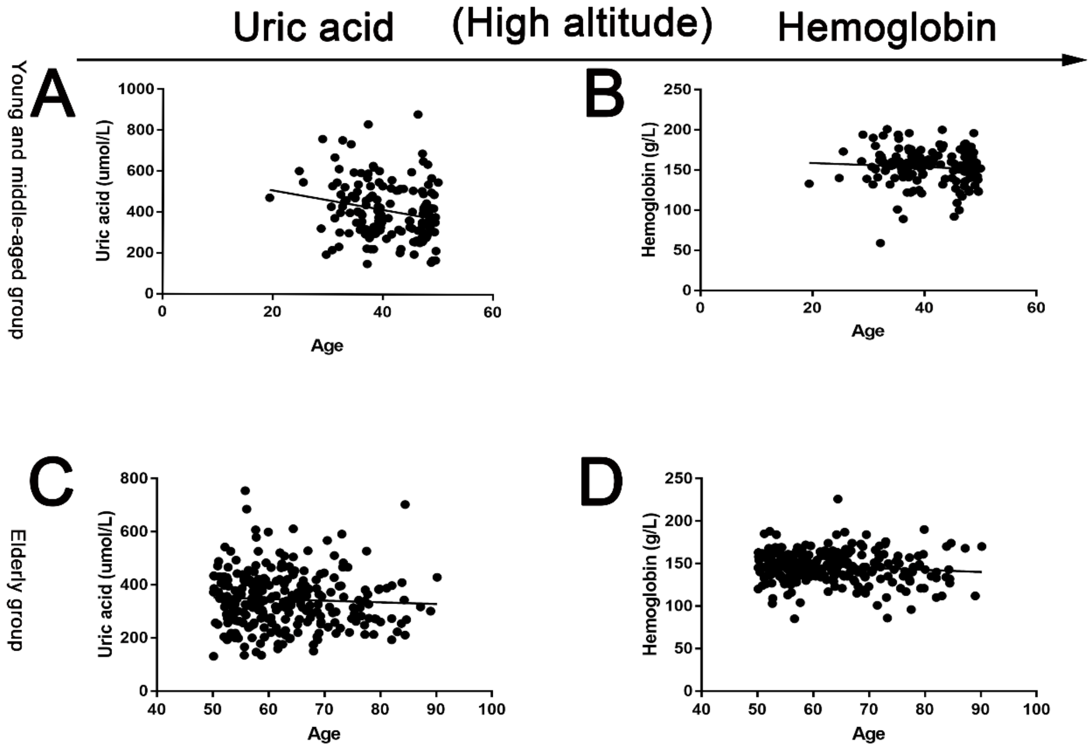

Figure 4. Scatter diagrams were depicted for the correlation between age and uric acid, as well as age and hemoglobin at high altitudes. Age is negatively correlated with uric acid for young and middle-aged group at the high altitudes (p <0.05) (A). There was no linear correlation with age and hemoglobin for young and middle-aged group at the high altitudes (p >0.05) (B). Age has no significant correlation with both uric acid and hemoglobin for elderly group at the high altitudes (p >0.05) (C-D)

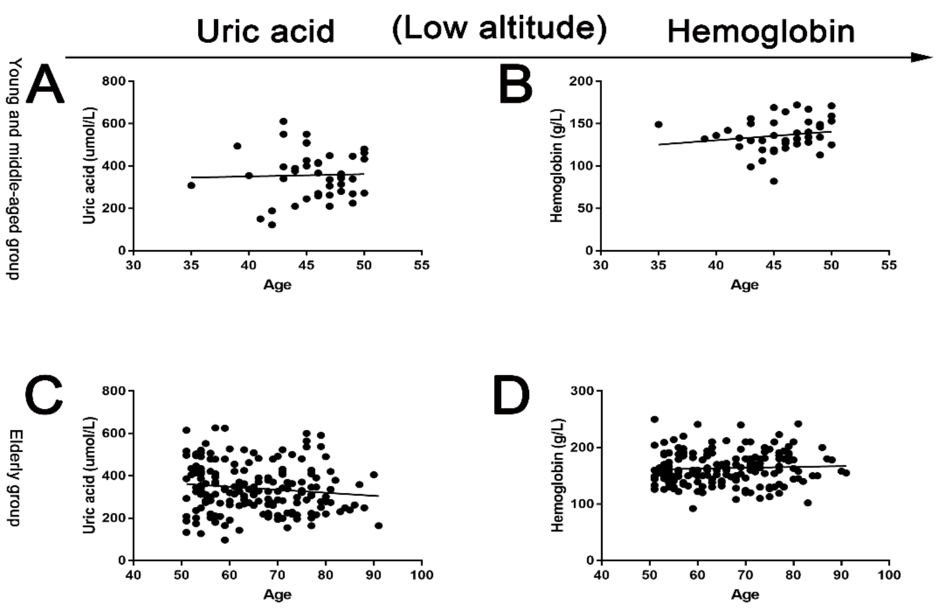

Figure 5. Scatter diagrams were depicted for the correlation between age and uric acid, as well as age and hemoglobin at low altitudes. Age has no significant correlation with both uric acid and hemoglobin for young and middle-aged group at the low altitudes (p >0.05) (A-B). Age has no significant correlation with both uric acid and hemoglobin for elderly group at the low altitudes (p >0.05) (C-D).

at high altitude. ROC curve showed that uric acid and diastolic blood pressure had diagnostic significance.

Studies have shown that high uric acid is related to an increased incidence rate of HICH.[8] Blood uric acid is a purine metabolite. Increased production or decreased excretion of human blood uric acid could lead to increased blood uric acid concentration. Hyperuricemia was defined as a serum uric acid concentration ≥ 420 μmol/L in men and ≥ 360 μmol/L in women.[9] Patients with elevated blood uric acid concentrations produce excessive urate crystals in their bodies. The oxidative stress system is activated by urate crystals, improves renin activity, and causes vasomotor dysfunction. In high-altitude areas, blood viscosity increased as hemoglobin increased, so uric acid had a more serious impact on blood vessels. A high-altitude hypoxic environment leads to a reduction in adenosine triphosphate (ATP) metabolism in the body and an increase in intracellular Ca^{2+} concentrations. Through the activation of proteinase A, the cells irreversibly catalyzed xanthine dehydrogenase to xanthine oxidase, which had enhanced activity under hypoxic conditions. In this case, xanthine oxidase could catalyze hypoxanthine to produce a large amount of uric acid. In addition, hypoxia can also increase glycolysis and lactic acid production in the body at high altitudes, which competitively inhibits the excretion of blood uric acid and causes an increase in uric acid.[3,10,11]

Our study showed that hyperuricemia increased the incidence of HICH in young and middle-aged patients with high-altitude hypertension, and uric acid concentration was negatively correlated with age in patients with HICH at high altitudes but had no correlation with age in patients with HICH at low altitudes. We also found that the hemoglobin concentration in patients with HICH was negatively correlated with age; the younger the age, the higher the hemoglobin concentration at high altitudes was. In addition, the concentration of uric acid was positively correlated with hemoglobin concentration, which was consistent with literature reports.[3] Hypertensive men with high uric acid had a higher risk of cerebral hemorrhage than women, mainly because women were protected by estrogen levels. Diastolic blood pressure increases were more pronounced in young adults at high altitude.[12] The high incidence of HICH in patients with high uric acid was mainly due to the strong vasoconstriction force caused by uric acid.[13] Regression analysis showed that uric acid, sex and systolic blood pressure were the main risk factors for HICH in young and middle-aged adults. Furthermore, the correlation was analyzed by different groupings: Uric acid concentration in the young and middle-aged group was correlated with age at high altitudes, but there were no differences in the other groups. The reason for this is not clear. We speculate that the reasons might be related to the irregular life-styel of young adults and the special geographical and climatic environment of high altitudes. Additional studies are needed to further validate this hypothesis.

This study had some limitations that need to be addressed in future studies. First, this study was a retrospective design study with a small number of cases. Second, this study was limited to patients with hypertensive intracerebral hemorrhage, posing limits to its interpretation.

DISCLOSURE

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Conflict of interest: None

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