

## Research Article

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# Related factors of early mortality in young adults with cerebral hemorrhage

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**Keywords:** Cerebral hemorrhage; Mortality; Related factors; Survival

**Abstract:** Background: The main causes of intracerebral hemorrhage differ between young adults and older adults. Data regarding potential targets for early intervention in young adult patients with intracerebral hemorrhage are lacking.

**Methods:** We retrospectively analysed data for 196 young adult patients with intracerebral hemorrhage who were admitted to Tianjin Huanhu Hospital and died within 30 days of admission between June 2005 and June 2015. The Kaplan–Meier method was used to calculate survival rate, and the log-rank test was used to determine survival rate significance. A Cox proportional hazards regression model was used for univariate and multivariate analyses.

**Results:** Univariate analysis revealed a statistically significant association of age, disturbance of consciousness, National Institutes of Health Stroke Scale and Glasgow Coma Scale scores, seizure occurrence, infratentorial hemorrhage, intraventricular extension, hernia, glucose level, white blood cell count, albumin level, creatinine level, uric acid level, and surgical treatment with early mortality ( $P < 0.05$ ). However, multivariate regression analysis revealed that only infratentorial hemorrhage ( $P = 0.003$ ) and intraventricular extension ( $P = 0.003$ ) were significant risk factors for early mortality.

**Conclusions:** Our results suggest that young adult patients who exhibit infratentorial hemorrhage and intraventricular extension in the early stages of intracerebral hemorrhage onset exhibit an increased risk of early mortality.

**List of acronyms:** CSF, cerebrospinal fluid; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; WBC, white blood cell

## 1 Introduction

Intracerebral hemorrhage (ICH) refers to primary nontraumatic hemorrhage of the cerebral parenchyma. The incidence rate of ICH is second only to that of cerebral ischemic stroke. Koivunen et al. reported that approximately 25 of every 100,000 individuals experience ICH each year, and the incidence rate is even higher among the Asian population [1]. The main causes of ICH differ between young adults and older adults. In the elderly, the main causes of ICH include hypertension, type 2 diabetes mellitus, hypertensive arteriopathy, cerebral amyloid angiopathy, and medication. In young adults, structural factors, systemic diseases, and other or unknown causes are substantially more prevalent [1]. However, data regarding potential targets for early intervention in young adult patients with ICH are still lacking. Therefore, we conducted the present study to analyse risk factors associated with early mortality in young adult patients with ICH, with the goal of elucidating targets for decreasing mortality and disability rates and improving clinical outcomes.

## 2 Materials and methods

### 2.1 Patients

We analysed data from a total of 196 young adult patients (mean age,  $38.51 \pm 6.36$  years; range, 16–45 years) with ICH admitted to Tianjin Huanhu Hospital who died within 30

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days of admission between June 2005 and June 2015. All patients had been confirmed to meet the diagnostic criteria for spontaneous ICH formulated at the Fourth National Cerebrovascular Disease Conference (excluding 26 cases of subarachnoid hemorrhage) [2].

All diagnoses had been confirmed via computed tomography or magnetic resonance imaging. In addition, 15 patients underwent digital subtraction angiography, magnetic resonance angiography, or computed tomography angiography. Patients who experienced pure subarachnoid hemorrhage or traumatic cerebral hemorrhage and those who died over 30 days after admission were excluded from further analysis. This study was approved by the ethics committee of Tianjin Huanhu Hospital, and the requirement for informed consent was waived due to the retrospective nature of the study design.

We compiled and analysed the following data for the included patients: sex, medical history, blood pressure at admission, glucose level, disturbance of consciousness, National Institutes of Health Stroke Scale (NIHSS) score at admission, Glasgow Coma Scale (GCS) score at admission, seizure occurrence, imaging characteristics (site of bleeding, hematoma volume, rupture of hematoma into the ventricle, and the presence of intraventricular extension), hernia (lateral shift of cerebral midline structures by  $\geq 5$  mm), fasting laboratory values (white blood cell [WBC] count, serum albumin, serum creatinine, and uric acid), and the use of surgical treatment. All laboratory values were obtained from venous blood in the early morning of the second day of admission. However, because some patients died within a very short period, certain laboratory values could not be obtained. Hemorrhage volume was calculated using the ABC/2 method [3].

## 2.2 Statistical analysis

All statistical analyses were performed using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA). The threshold for statistical significance was set at a P-value of  $<0.05$ . The Kaplan–Meier method was used to calculate the survival rate, while the log-rank test was used to assess the significance of the survival rate. A Cox proportional hazards regression model was used for univariate and multivariate analyses. The survival period was defined as the period between the date of diagnosis and the date of death and was calculated in days.

## 3 Results

### 3.1 Sex and age

The study population included 168 (85.71%) men and 28 (14.29%) women, resulting in a man-to-woman ratio of 6:1. The patients were divided into three age groups: 16–25 years ( $n = 16, 8.16\%$ ), 26–35 years ( $n = 28, 14.29\%$ ), and 36–45 years ( $n = 152, 77.55\%$ ).

### 3.2 Disturbance of consciousness and seizure occurrence

Among the 196 included patients, 156 (79.59%) experienced disturbance of consciousness. The NIHSS score was 0–6 for eight patients (4.08%), 7–14 for 15 patients (7.65%), and  $>14$  for 173 patients (88.27%). The GCS score was 3–8 for 155 patients (79.08%) and 9–15 for 41 patients (20.92%). Twenty-three patients (11.73%) experienced seizures after admission.

### 3.3 Blood pressure and glucose levels at admission

The included patients were classified into three groups according to their systolic (SBP) and diastolic blood pressure (DBP) values: SBP  $< 140$  mmHg, 28 patients (14.29%);  $140 \text{ mmHg} \leq \text{BP} < 180$  mmHg, 58 patients (29.59%); SBP  $\geq 180$  mmHg, 110 patients (56.12%); DBP  $< 90$  mmHg, 52 patients (26.53%);  $90 \text{ mmHg} \leq \text{DBP} < 110$  mmHg, 71 patients (36.22%); and DBP  $\geq 110$  mmHg, 73 patients (37.24%). A total of 122 patients (62.24%) exhibited an increase in their fasting glucose levels following admission, while 55 patients (28.06%) exhibited normal glucose levels.

### 3.4 Imaging characteristics

We further classified patients according to the site of hemorrhage as follows: lobar, 24 patients (12.24%); basal ganglia, 89 patients (45.41%); thalamus, 12 patients (6.12%); and infratentorial, 47 patients (23.98%). Among these, we also noted one case of cerebellar hemorrhage (0.51%), one case involving both the cerebellum and brainstem (0.51%), 45 cases of brainstem hemorrhage (22.96%), 10 cases of ventricular hemorrhage (5.10%), and 14 cases of multiple hemorrhages (7.14%). We further classified the patients on the basis of hematoma volume as follows: 0–29

mL, 69 patients (38.12%); 30–59 mL, 54 patients (29.83%), and  $\geq 60$  mL, 58 patients (29.59%). Rupture into the ventricle was noted in 104 patients (53.06%), intraventricular extension in 120 (61.22%), and hernia in 132 (67.35%).

### 3.5 Laboratory values

A total of 163 patients (83.16%) exhibited an increased WBC count. Decreased levels of albumin, creatinine, and blood uric acid were noted in 32 (16.33%), 95 (48.47%), and 102 patients (52.04%), respectively.

### 3.6 Use of surgical treatment

Of the total 196 patients, 134 (68.37%) underwent surgery after admission and 62 (31.63%) received conservative treatment. Surgical treatment included hematoma evacuation, cerebrospinal fluid (CSF) drainage, or both.

Univariate analysis revealed statistically significant associations ( $P < 0.05$ ) of age ( $P = 0.000$ ), disturbance of consciousness ( $P = 0.048$ ; Fig. 1), NIHSS ( $P = 0.049$ ) and GCS ( $P = 0.005$ ) scores, seizure occurrence ( $P = 0.001$ ), infratentorial hemorrhage ( $P = 0.048$ ), intraventricular extension ( $P = 0.02$ ), hernia ( $P = 0.026$ ), glucose level ( $P = 0.014$ ; Fig. 2), WBC count ( $P = 0.023$ ), albumin level ( $P = 0.014$ ), creatinine level ( $P = 0.028$ ), uric acid level ( $P = 0.047$ ), and the use of surgical treatment ( $P = 0.024$ ) with early mortality in young adult patients with ICH. Patient sex; history of hypertension, heart disease, and/or oral

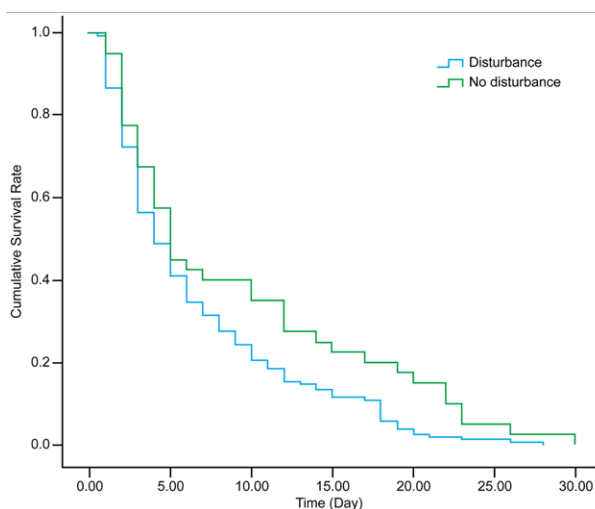
anticoagulant and antithrombotic drug use; blood pressure at admission; hematoma volume; and rupture into the ventricle were not associated with patient survival (Table 1).

### 3.7 Multivariate Cox regression analysis

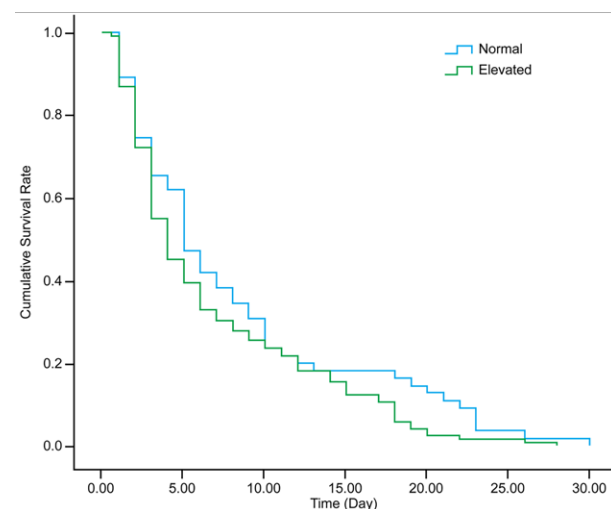
Factors that exhibited statistical significance in univariate analysis were imported into the Cox proportional hazards regression model for multivariate analysis. The results of this analysis revealed that infratentorial hemorrhage ( $P = 0.003$ ; odds ratio, 3.811) and intraventricular extension ( $P = 0.003$ ; odds ratio, 0.511) were independent risk factors for early mortality in young adult patients with ICH (Table 2).

## 4 Discussion

In the present study, we retrospectively analysed data from 196 young adult patients with ICH who had died within 30 days of hospital admission. Our results revealed a significantly higher number of male patients. The low incidence of cerebral hemorrhage in young women was related to the female gonadal hormones [4]. In addition, the frequency of unhealthy habits, such as smoking and alcohol consumption, is higher among men than among women [5]. However, no statistically significant difference was observed in the distribution of mortality rates among



**Figure 1:** The impact of consciousness disturbance on the survival rate of young adult patients with intracranial hemorrhage. Patients with consciousness disturbance following cerebral hemorrhage showed shorter survival times and a higher risk of death.



**Figure 2:** The impact of glucose level on the survival rate of young adult patients with intracranial hemorrhage. Patients with cerebral hemorrhage who showed elevated blood glucose levels tended to have shorter survival times and a higher risk of death.

**Table 1:** Univariate analysis of factors influencing survival in 196 young adult patients with ICH

Indicator	Number of Cases	MST (Days)	Survival Rate (%)		P-Value
			10 Days	20 Days	
Sex (M/F)	168/28	5/4	25.6/10.7	7.7/3.6	0.085
Age (16–25/26–35/36–45)	16/28/152	3/4/5	12.5/35.7/26.3	0/28.6/4.6	0.000
Use of Anticoagulant and Antithrombotic Drugs (N/Y)	183/13	5/4	27.3/30.8	6.6/-	0.788
Consciousness Disturbance (N/Y)	40/156	5/4	40/24.4	15/3.8	0.048
NIHSS Score (0–6/7–14/>14)	8/15/173	6/5/4	37.5/40/26	25/13.3/5.2	0.049
GCS Score (3–8/9–15)	155/41	4/5	23.9/41.5	2.6/14.6	0.005
Systolic Blood Pressure at Admission (<140/140–180/≥180 mmHg)	28/58/110	4/4/5	35.7/25.9/26.4	10.7/5.2/6.4	0.581
Diastolic Blood Pressure at Admission (<90/90–110/≥110 mmHg)	52/71/73	4/5/5	32.7/23.9/27.4	5.8/5.6/8.2	0.335
Glucose Level at Admission (Normal/Elevated)	55/122	5/4	30.9/25.4	14.5/4.1	0.014
Hematoma Volume (0–29/30–59/≥60 mL)	69/54/58	4/5/5	18.8/29.6/24.1	4.3/9.3/3.4	0.634
Rupture into Ventricle (N/Y)	92/104	4/5	16.3/29.8	3.3/6.7	0.062
Intraventricular Extension (N/Y)	76/120	5/4	31.6/25	11.8/3.3	0.02
Hematoma Site					0.048
Lobar	24	4	25	12.5	
Basal Ganglia	89	5	28.1	7.9	
Thalamus	12	9	50	8.3	
Infratentorial	47	3	19.1	0	
Intraventricular	10	4	10	0	
Multiple Hemorrhage	14	5	35.7	7.1	
Hernia (N/Y)	64/132	3/5	25/28.8	6.3/4.5	0.026
Surgical Treatment (N/Y)	62/134	3/5	14.5/27.6	1.6/6.7	0.024
Seizure Onset (N/Y)	173/23	10/4	56.5/23.7	8.7/5.8	0.001
White Blood Cells (Elevated/Normal/Low)	163/14/2	4/5/10	26.4/28.6/-	5.5/21.4/-	0.023
Albumin (Elevated/Normal/Low)	5/140/32	4/5/3	-/27.1/25	-/7.9/6.3	0.014
Creatinine (Elevated/Normal/Low)	95/79/3	4/5/-	25.3/30.4/-	5.3/10.1/-	0.028
Uric Acid (Elevated/Normal)	102/72	4/5	27.5/26.4	5.9/9.7	0.047

ICH: intracranial hemorrhage, NIHSS: National Institutes of Health Stroke Scale, GCS: Glasgow Coma Scale, MST: median survival time.

**Table 2:** Multivariate analysis of factors influencing survival in 196 young adult patients with ICH

	B	SE	Wald	df	P	Exp (B)	95.0% CI applied in Exp (B)	
							Lower Section	Upper Section
Intraventricular Extension	-0.671	.229	8.611	1	.003	0.511	0.326	0.800
Site of Hematoma	1.338	.449	8.879	5	.003	3.811	1.581	9.186

ICH: intracranial hemorrhage, CI: confidence interval, B: Partial regression coefficient, SE: standard error of survival rate, df: degree of freedom, Exp (B): Odds ratio value, 95.0% CI applied in Exp (B): 95% confidence interval

men and women in the present study. This finding is consistent with the findings of previous studies [6,7].

The results of the present study indicate that the incidence of ICH tends to increase with age. This finding may be explained by the increased incidence of hypertension in older adults. In addition, a previous study reported that hypertension, smoking, and alcohol consumption were risk factors for stroke in young Chinese individuals [8]. We also report that the mortality risk in the 16–25-year age group was high. The main reason for such a high rate in this age group was the presence of congenital structural lesions such as vascular malformations. Low rates of diagnosis and poorly controlled hypertension were also noted in this group. However, Rutten-Jacobs *et al.* [6] found that the 30-day ICH mortality rate did not significantly differ by age. Therefore, multicentre studies involving larger sample sizes are required in order to confirm the findings of the present study.

Although hypertension has been found to be a primary risk factor for ICH [9,10], and it is considered a risk factor for a poor prognosis in patients with ICH [11], univariate analysis in the present study revealed no correlation between a history of hypertension and early mortality in young adults with ICH. Furthermore, we observed no significant correlation between blood pressure at admission and early mortality, which may be attributable to the fact that the conditions of some patients had become critical immediately after ICH onset, resulting in a severe decrease in blood pressure that could have masked other factors.

Numerous studies have reported a strong correlation between post-ICH elevation of glucose levels and poor prognosis. Tapia-Pérez *et al.* [12] proposed that a glucose level of >140 mg/dL within 24 hours of ICH onset might increase the risk of 30-day mortality. A study by Yi *et al.* [13] also revealed that the near-term mortality risk in patients with early high-glucose levels was 4.95 times higher than that in patients with normal glucose levels. The results of the present study are consistent with those previously reported, suggesting that glucose levels in patients with ICH should be controlled in a timely fashion.

The patient's level of consciousness can reflect the level of brain damage, and mortality was found to be four times higher in patients with disturbance of consciousness following ICH than in those who remained conscious [14]. A study by Rutten-Jacobs *et al.* [6] revealed that higher average NIHSS scores (17 vs. 10,  $P = 0.01$ ) and lower average GCS scores (3 vs. 14,  $P = 0.004$ ) were risk factors for early mortality in patients with ICH. Earlier occurrence of consciousness disturbance and more severe conditions may therefore indicate greater damage to the involved cerebral structures and a higher mortality rate.

Different causes of ICH in young adults lead to hemorrhage at different sites. The current study and previous studies suggested that deep cerebral hemorrhage is associated with a higher mortality rate compared with lobar haemorrhage [15]. In addition, the results of the present study indicate that infratentorial hemorrhage is an independent risk factor for early mortality in young adult patients with ICH, consistent with the results of previous studies [7,16]. As opposed to the results of previous studies [7,17], our univariate analysis revealed no correlation between hematoma volume and early mortality. This disparity can be explained by a hematoma volume of 0–29 mL in 47 of the 69 cases with infratentorial hemorrhage. ICH occurring either above or below the infratentorial region results in different outcomes with relatively low survival rates. Our results indicate that the site of hemorrhage exerts a greater impact on the prognosis of patients with ICH compared with hematoma volume.

Intraventricular extension is a common complication observed in patients with ICH. A recent study revealed that the 30-day mortality rate for patients with intraventricular extension was 4.7 times higher than that for patients without this complication [7]. The results of the present study also revealed that intraventricular extension was an independent risk factor for early mortality in young adult patients with ICH. Existing reports present varying conclusions regarding the impact of rupture into the ventricle at the site of hemorrhage on prognosis. A study by Jai-hi *et al.* [14] showed that a greater extent of hemorrhage rupture into the ventricle would lead to a poorer prognosis, probably because rupture influences the circulation of CSF, which increases intracranial pressure and promotes the development of hernia. However, our results indicate that hemorrhage rupture into the ventricle was not a risk factor for early mortality, likely because of the decrease in hematoma pressure shortly after rupture into the ventricle. Furthermore, timely surgery following admission allowed drainage of the hematoma and CSF, which relieved intracranial hypertension.

Patients with ICH accompanied by hernia are often critical. Some studies have suggested that early mortality in patients with ICH is correlated with hernia development [15]. However, our analysis indicated the opposite result, probably because of the relatively low incidence of infratentorial hemorrhage in patients without hernia; that is, only eight of the 132 patients with hernia experienced infratentorial hemorrhage. However, among the 64 patients without hernia, 39 experienced infratentorial hemorrhage. Subgroup analysis revealed that this difference was statistically significant ( $\chi^2 = 71.204$ ,  $P < 0.001$ ). Seizure is a relatively common complication of

ICH, although the mechanism of seizure onset remains unclear. One previous study indicates that seizure onset may be associated with the mass effect of the intracranial hematoma, focal ischemia, and decomposition products in the blood[18].

Seizure onset in the early stages of ICH may lead to the elevation of intracranial pressure, while overexcitement and increased metabolic demand lead to neuronal death and, consequently, increase the mortality rate. However, the conclusions of various studies on the correlation between early seizure onset and ICH mortality remain inconsistent [18]. In the present study, we found that early seizure onset was a relevant risk factor for early mortality in young adult patients with ICH. Therefore, timely clinical diagnosis and effective control and prevention of seizure onset may have significant implications for improving the prognosis and decreasing the mortality rate.

Peripheral WBC count is an indication of the immune system response and a reflection of the activation of inflammatory cascades following ICH[19]. Some studies show that activation of the peripheral immune system may aggravate post-ICH damage [20]. Blood uric acid level is closely correlated with the prognosis of patients with ICH, and a study by Zeng et al. [21] concluded that a high concentration of uric acid was a risk factor for early poor prognosis in patients with ICH. However, the relationship between uric acid level and stroke remains debatable [22], and further statistical analysis is required using larger sample sizes from multiple centres. Nevertheless, the blood uric acid level is a known independent risk factor for hypertension [23] that results in kidney damage. Previous studies [23] have shown that acute kidney injury is associated with increased hospital mortality in patients with stroke. The present study involving young adult patients with ICH found that, although acute kidney injury is related to early death, it is not an independent risk factor for early death. Further research and discussion are necessary to confirm these results. Our analysis revealed that hypoproteinaemia is associated with early mortality in young adult patients with ICH, probably because significantly low levels of serum albumin lead to poor health and decrease the level of immunity in patients. Low serum albumin levels also lead to decreases in the plasma colloid osmotic pressure, which results in accumulation of fluid in the spaces between tissues. This accumulation decreases the effective circulating blood volume, in turn leading to inadequate perfusion of vital tissues, particularly the brain tissues surrounding the hematoma, aggravation of the condition, and a poor prognosis.

It has been well-established that patients who require surgery are more critical and are more likely to exhibit

massive bleeding or early hernia and other neurological deficits, which increase the risk of death [24]. Therefore, surgical treatment is very important for patients with cerebral hemorrhage. Univariate statistical analysis in the present study showed that nonsurgical treatment was associated with a high risk of death in young adults with ICH. Han et al.[25] showed that the prognosis of patients who underwent surgery for ICH was better than that of patients who received conservative treatment. The findings of the present study are consistent with this finding. Therefore, timely surgical treatment involving hematoma evacuation and lowering of brain oedema and intracranial pressure can improve the prognosis of some patients. Additionally, younger patients exhibit better tolerance for surgery, and aggressive surgical treatment should therefore be performed for young patients with ICH.

The present study has several limitations. First, all included patients were obtained from a single centre. Second, our results may have been influenced, to some extent, by missing clinical data, because some patients died shortly after ICH onset. Third, we did not conduct a subgroup analysis for hemorrhage at different sites with regard to the hematoma volume.

## 5 Conclusion

The results of the present study, in conjunction with those of previous studies, highlight the severity of the consequences of ICH in young adult patients, which lead to high rates of disability and mortality. Affect the prognosis of young patients with ICH a lot of related factors, our results suggest that young adult patients who exhibit infratentorial hemorrhage and intraventricular extension in the early stages of ICH onset exhibit an increased risk of early mortality. Patients with ICH should seek prompt treatment to identify and control risk factors that may lead to a poor prognosis and lower the likelihood of mortality and disability.

**Conflicts of interest:** The authors have no conflicts of interest to declare.

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