Early prediction of death in acute hypertensive intracerebral hemorrhage

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Abstract. Hypertensive intracerebral hemorrhage (HICH) has been on the decline. However, mortality at long-term follow up is on the increase. The aim of the present study was to investigate early warning signals of death in patients with acute HICH. The medical records of 128 patients with acute HICH within 6 h of onset were retrospectively analyzed. For these patients, systolic blood pressure (BP) was recorded at different time points (emergency, admission, every 6 h within 24 h and twice daily after 24 h) within 1 week. Computed tomography scanning was performed at emergency and the following 24±3 h to assess the hematoma volume. Neurological impairment was evaluated using the Glasgow Coma Scale and National Institutes of Health Stroke Scale. Outcomes were death, defined as a modified Rankin scale score 6, at 90 days. The results showed that at 90 days, 15 HICH patients succumbed (mortality of 11.7%). Of the 15 patients, 1 patient (6.7%) sucumbed within 24 h and 6 patients (40%) within 1 week. HICH mortality was closely associated with age (P<0.001) but not with gender. A significant association was detected between mortality and high BP taken at 30 min, 45 min and 6 h after admission (P=0.003), albeit not at emergency and admission (P>0.05). Death was also correlated with hematoma volume at 24 h but not with the site. Results from the multivariate binary logistic regression analysis showed that age and hematoma volume were independent risk factors of death of HICH. In conclusion, age and hematoma volume may be important early predictors of death in HICH. Proactive control and management of hematoma may reduce the mortality of HICH.

Introduction

Although the incidence of hypertensive intracerebral hemorrhage (HICH) has declined recently, the disability rate and mortality at long-term follow up thereof are on the increase (1). Previous clinical report findings showed that the mortality rate of intracerebral hemorrhage (ICH) was 34-43.9% at 90 days follow-up (2) and 47% after 1 year (3). Effective management of acute ICH, particularly its poor prognosis, requires a profound understanding of risk factors involved, including age, volume and location of hematoma, extension to intraventricular hemorrhage or not, blood sugar, blood pressure (BP), temperature and consciousness (4-6). It is important to identify early warning signals of death of HICH and take proactive interventions.

The present study aimed to examine key risk factors that provided early prediction of death, with the aim of early intervention to reduce mortality. The medical records of 128 HICH patients admitted to the Department of Xuzhou Central Hospital (Xuzhou, China) were retrospectively examined. Association of mortality and survival with age, BP, hematoma volume and neurological scores of the patients were analyzed.

Materials and methods

Patient information. A total of 128 patients, aged ≥18 years, had spontaneous ICH confirmed by computed tomography (CT) within 6 h onset and elevated systolic BP ≥150-220 mmHg. Inclusion criteria for the study were: ≥18 years of age, spontaneous HICH within 6 h confirmed by CT, and elevated systolic BP of ≥150 mmHg. Exclusion criteria for the study were: clear evidence that the HICH was secondary to a structural cerebral abnormality (e.g., arteriovenous malformation, intracranial aneurysm, or tumour) or under treatment with the use of a thrombolytic agent, or with a pre-planned decompressive neurosurgical intervention.

Analyses of clinical records
BP records. BP was recorded for each patient at the following time points: i) emergency, ii) admission, ii) once every 6 h during the first 24 h after admission, and iv) twice per day after 24 h and within 1 week.

Measurement of hematoma volume. Standard CT scanning was performed at admission, and at 24±3 h after admission. Hematoma volume was measured manually by the ABC/2 method using Philip Brilliance 64-slice CT (Philips Medical Systems, Eindhoven, The Netherlands).

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Table I. Clinical characteristics of patients who succumbed and survivors.

Characteristics	Dead (n=15)	Survivors (n=113)	P-value
Age, years	75.53 (15.18)	62.79 (13.25)	0.001[a]
Male	10 (66.7%)	73 (64.7%)	0.876
Hematoma volume, ml	91.67 (24.96-133.66)	32.33 (13.78-49.67)	0.044[a]
Location			
Basal ganglia	9 (60.0%)	63 (55.8%)	0.107
Thalamus	2 (13.3%)	15 (13.3%)	0.165
Lobar	-	5 (4.4%)	-
Cerebella	1 (6.7%)	13 (11.5%)	0.341
Brain-stem	3 (20.0%)	11 (9.7%)	0.167
Intraventricular extension	-	6 (5.3%)	-
Blood pressure			
Admission	180.33 (17.17)	174.72 (16.13)	0.211
15 min	169.60 (16.92)	164.90 (17.29)	0.324
30 min	176.47 (14.46)	160.10 (20.01)	0.003[a]
45 min	166.33 (13.36)	156.01 (18.64)	0.014[a]
1 h	158.80 (15.17)	153.00 (20.20)	0.286
6 h	150.60 (18.46)	139.95 (18.50)	0.038[a]
12 h	151.21 (16.22)	141.47 (17.79)	0.053
18 h	149.69 (13.64)	142.58 (19.23)	0.198
24 h	147.31 (17.58)	143.36 (16.58)	0.421
GCS score[b]			
Admission	14 (11-14)	13 (12-14)	0.991
24 h	10 (5-13)	13 (12-15)	0.007[a]
NIHSS score[c]			
Admission	13 (7-19)	10 (4-18)	0.286
24 h	22 (9-28)	8 (4-15)	0.011[a]

[a]P<0.05. Data are no. (%), mean (standard deviation), or median (interquartile range). GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale. [b]GCS scores ranged from 3 (deep coma) to 15 (normal, alert). [c]NIHSS scores ranged from 0 (normal, no neurological deficit) to 42 (coma with quadriplegia).

Neurological deficit scoring. The neurological functions of the patients were evaluated at admission, 24 h after admission, 1 week after admission or discharge using the Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS) scoring scale.

Evaluation of neurological function recovery. The modified Rankin scale (mRS) was utilized to assess the neurological function recovery state of the patients after stroke (grading scores, 0-6). The scores used were: 0, no symptoms at all; 1, with symptoms but without obvious disabilities, able to complete all of their normal duties and day-to-day activities; 2, mild disability, failed to complete all of their normal duties and activities, but were able to handle their personal business without external assistance; 3, moderate disability, some assistance required, albeit able to walk by themselves; 4, severe disability, unable to walk without assistance or carry out daily functions; 5, complete disability, completely bedridden, suffer from gatism, and requiring continuous care and nursing; 6, death. The mRS scores were recorded at follow up on day 28 and 90.

Statistical analysis. Statistical analysis was performed using SPSS 19 software (IBM Corp., Armonk, NY, USA). Numerical data were subjected to the Kolmogorov-Smirnov normality test. Normal distribution was assessed using the t-test, and abnormal distribution was detected using the non-parametric rank sum test (Wilcoxon two-sample test). Ranked data were analyzed by the Chi-square test. Correlation and independent risk factors of death were analyzed by calculating the correlation index and logistic binary regression using Spearman's correlation.

Results

Patient characteristics. The average age of the patients included in the present study was 64.28±14.04 years. The results showed that of the 128 subjects studied, 15 patients succumbed within 90 days and the mortality of HICH was 11.7%. Of the 15 patients, 1 succumbed within 24 h, accounting for 6.7% of the total death toll, while 6 patients succumbed within 1 week, accounting for 40% of the total death toll. The remaining 8 patients succumbed between 1 week and 90 days. The average age for these patients was 64.28±14.04 years.

Table II. Correlation of hematoma volume between dead and survivors with location.

	First CT (emergence)		Second CT (following-up first CT 24±3 h)	
Characteristics	Dead	Survivors	Dead	Survivors
Hematoma volume (ml)[a]	36.93 (3.18-78.42)	27.94 (10.63-45.25)	63.63 (3.86-84.21)	31.05 (20.25-53.18)
Correlation index	0.331	0.331	0.534	0.534
P-value	0.000	0.000	0.001	0.001

[a]Data are presented as median [interquartile range (IQR)]. CT, computed tomography.

Clinicopathological characteristics and mRS scores. Clinical characteristics such as age, gender, hematoma volume and location, and BP at different time points were analyzed for patients that succumbed as well as survivors (Table I). Mortality was closely associated with age (P<0.001) although not with gender. Mortality was significantly associated with BP at 30 min, 45 min and 6 h after admission (P<0.05), although not on admission 180.33±17.17 vs. 174.72±16.13 mmHg (P=0.211). Mortality was also associated with hematoma volume but not with the location. The average age of patients who succumbed was significantly higher than that of the survivors (75.53 vs. 62.79 years, P=0.001). Higher mRS scores, signifying worse recovery of neurological functions following cerebral hemorrhage, were primarily found in senior patients aged over 64.25 years (r=0.375, P<0.001. Fig. 1). By contrast, the effect of gender on the mRS score was not significant.

Systolic BP. The systolic pressure of the HICH patients was monitored for 1 week after admission or up to death (Fig. 2). The results showed that the BP for patients who died versus those who survived during our observation period was similar at emergency (181.87±18.30 vs. 184.39±18.65 mmHg) and on admission (180.33±17.17 vs. 174.72±16.13 mmHg). However, a significant difference was observed for BP between patients who died and survivors measured at 30 min, 45 min and 6 h (Table I and Fig. 2).

GCS and NIHSS scores. The results revealed that death was associated with the hematoma volume following onset and within 24 h, but was irrelevant to the hematoma location (P>0.05) (Table II). Death occurring during 90 days was irrelevant to the NIHSS score on admission, but relevant to the neurological score within 24 h and 7 days after admission (Table III). The average GCS scores were 9.29±4.07 vs. 12.76±2.25 and 9.56±3.40 vs. 13.42±2.26 for patients who died within 24 h and 1 week, respectively. The NIHSS score for patients who died were 19.00±10.88 vs. 10.20±8.08 and 23.56±12.98 vs. 8.39±8.22 within 24 h and 1 week, respectively.

Results from the multifactor regression analysis revealed that of the risks factors examined, age and hematoma volume were independent predictors of death [age odds ratio (OR)=1.082, 95% confidence interval (CI): 1.018-1.149, p=0.011; hematoma volume OR=1.011, 95% CI: 1.000-1.023, p=0.046].
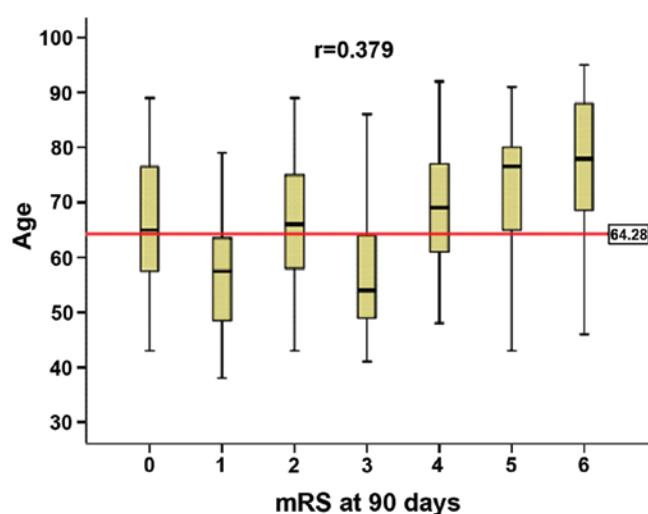

Figure 1. Association between the modified Rankin scale (mRS) scores at 90 days and the age of hypertensive intracerebral hemorrhage. Data are presented as mean, media and standard deviation. The mRS scores were calculated as 0-6 with 0 indicating no symptoms and 6 indicating mortality. Age, mean, media, standard deviation and min-max, respectively, at mRS 0 were (66.92, 65.00, 13.761, 43 and 89); mRS 1 (56.35, 57.50, 10.876, 38 and 79); mRS 2 (65.31, 66.00, 12.925, 43 and 89); mRS 3 (58.23, 54.00, 12.624, 41 and 86); mRS 4 (68.16, 69.00, 12.013, 48 and 92); mRS 5 (72.80, 76.50, 13.522, 43 and 91); and mRS 6 (75.53, 78.00, 15.175, 46 and 95); Age average was 64.28 years.

Discussion

The aim of the present study was to investigate early warning signals of death in patients with acute HICH. Of the 128 patients with acute HICH included in this study, mortality was 0.8% within 24 h, 4.7% within 1 week, increasing to 11.7% in the follow up at 90 days Mortality was irrelevant to gender, but closely relevant to age. The average ages of the dead and surviving patients were 75.53±15.18 vs. 62.79±13.25 (p<0.05). This result indicated that the older the patients, the higher the mortality, which was consistent with literature reports showing patients >75 had a higher mortality (7). An increase in age leads to degeneration of the function of tissues and organs within the body, thus, compensation ability becomes exacerbated. As for the blood vessel itself, the vascular wall of elderly patients was more vulnerable to degenerative changes: their lipid became hyaline-degenerated, fibrous protein became necrotic, and segmental aortic structure was broken,

Table III. Spearman correlation between dead at 90 days and the neurological scores.

Scores time	Admission, n=128		24 h, n=127		7 days, n=122	
Neurological scores	GCS	NIHSS	GCS	NIHSS	GCS	NIHSS
Correlation index	0.058	0.112	-0.287	0.273	-0.319	0.317
P-value	0.513	0.209	0.001[a]	0.002[a]	0.000[a]	0.000[a]

[a]$P<0.01$. Death was irrelevant to the neurological score on admission ($P>0.05$), but relevant to the neurological score within 24 h and 7 days after admission ($P<0.01$). NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.
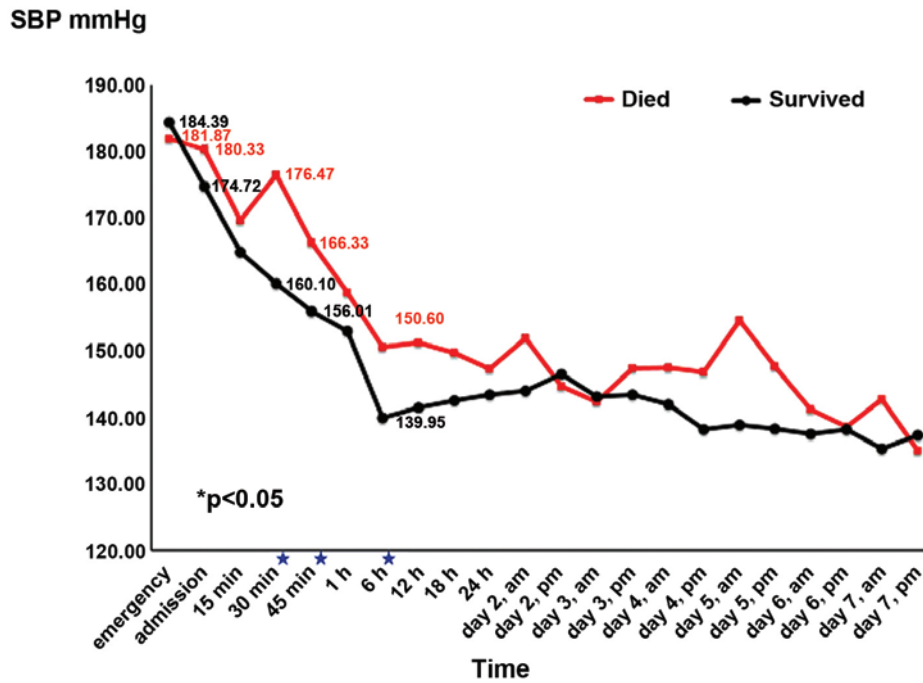

Figure 2. Comparison of systolic blood pressure (SBP) for dead and survivors within 1 week. SBP for dead and survivors at emergency (181.87±18.30 vs. 184.39±18.65 mmHg) and on admission (Table I) ($P>0.05$). At 30 min, 45 min and 6 h following admission ($P<0.05$).

in such a manner that their vascular compliance became exacerbated (5). These degenerative changes contributed to high mortality of acute HICH in senior patients.

High BP was an important factor that affected the onset and prognosis of cerebral hemorrhage. However, at which point BP should be regulated remains controversial (8-10).

Baños-González *et al* reported poor prognosis for cerebral hemorrhage patients with too low or too high systolic pressure, and it was preferable to maintain the BP at 100-159 mmHg (11). If the BP for acute HICH patients with onset within 6 h was proactively under control at an early stage, particularly if the 1-h systolic pressure was within 140 mmHg, patients had a better clinical prognosis than those following the conventional depressurization standard protocol (>180 mmHg) (13). By contrast, our data showed that high systolic BP recorded, following emergent treatment (184 mmHg) and on admission (175 mmHg) (P=0.772 and P=0.375, respectively), was not significantly correlated with death for the HICH patients. It is possible that the BP in patients with acute cerebral hemorrhage increased

temporarily, however, the level of BP at this point was not influences at the 90-day prognosis of patients.

Tetri *et al* (13) reported that despite their higher BP values at admission, subjects with untreated hypertension showed improved survival and more frequently favorable outcome after BP-lowering therapy than other patients The findings may be attributed to the young age of their recruited patients and did not have cardiovascular and cerebrovascular diseases, history of anticoagulant drugs and diabetes mellitus. In this case, the level of BP following admission may not provide early warning to the prognosis of cerebral hemorrhage. Such findings were consistent with the results of our study. Our study also found that patients who died had significantly higher BP at 30, 45 and 60 min after admission than those survived (all P<0.05). The higher the BP was, the higher the mortality was (r=0.263, p=0.003). Therefore, regulation of BP within 6 h after admission was crucial. From 6 to 24 h after admission, BP was controlled at 143.21±17.76. Other studies on the safety of early active antihypertensive therapy on acute HICH also demonstrated similar findings (12,14-16). If BP was

proactively reduced at an early stage, hematoma enlargement within 24 h could be controlled, and consequently clinical prognosis could be improved.

The results of the present study have shown that mortality was closely associated with the volume of hematoma following onset and 24 h after onset, but irrelevant to the hematoma location. We performed binary logistic regression analysis on age, gender, hematoma volume on admission, level of consciousness and BP, and found that age and hematoma volume were independent risk factors of death. The larger the hematoma volume was, the higher the mortality was. This result was consistent with previous findings (17). Methods that may intervene in the enlargement of hematoma include BP adjustment, encephaledema and relieving of intracranial hypertension, surgical resection, anticoagulant therapy and hemostasis therapy (18,19). A systematic review (20) identified that ventricular drainage combined with defibrinogen therapy on patients with extension to ventricles effectively prevents hydrocephalus and improves patient quality of life. Previous findings have shown that conservative treatment by operation and medications had no difference on the short-term outcomes for young and elderly patients with cerebral hemorrhage. However, in the long term, the prognosis of operative treatment on the youth was better than those receiving conservative treatment (21).

The GCS and NIHSS scores identified on admission were not significantly correlated with death. This result indicated that the level of consciousness on admission was not predictive of death. However, mortality was relevant to the neurological score recorded at 24 h and 1 week after admission. If the GCS score was <9, the NIHSS scores were >19 and >24 within 24 h and 1 week, respectively, high mortality was observed (data not shown; GCS: 12±3, r=-0.622; NIHSS: 11±8, r=0.707). Disturbance of consciousness on admission was one of the most important factors for death of cerebral hemorrhage (3,22). However, the level of consciousness is likely to be influenced by a hematoma spot (supratentorial or subtentorial), hematoma volume, with extension to ventricles or not, and the time from onset to admission (23). In particular, hematoma occurring in the brain stem affected the ascending reticular activating system, and thus influenced the level of consciousness, resulting in somnolence and coma. Additionally, larger hematoma may cause more obvious mass effect, leading to more severe subsequent hematoma. These factors may also affect the level of patient consciousness, which may explain the reason for the consciousness level not clearly predicting death.

In conclusion, the results of the present study have shown that patient age and hematoma volume were independent risk factors of death of acute HICH, and may serve as important early warning signals for cerebral hemorrhage. Proactive control and management of hematoma may reduce the mortality of HICH.

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