Use of Serum Creatinine and Cystatin C Improves Risk Stratification for Mannitol Therapy in Patients with Intracerebral Hemorrhage

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Abstract

Objectives: An accurate assessment of renal function is key to the hyperosmolar mannitol therapy of patients after intracerebral hemorrhage (ICH), yet a comprehensive report of this safety concern is not available. This study aims to investigate the risk stratification of patients with ICH receiving mannitol treatment using the measurements of serum creatinine, cystatin C, or both in real-world settings.

Methods: This population-based, observational, retrospective study was conducted with patients with an acute ICH admitted to a tertiary care university hospital from October 2010 to December 2018. Admission cystatin C and creatinine levels were measured in serum samples; these data were used to calculate the estimated glomerular filtration rate (eGFR). An eGFR value less than 90 mL/min/1.73 m² of body-surface area was considered abnormal. Mannitol doses were recorded by the mean dose range per day (≤ 50 , 51–100, 101–150, and >150 g/day).

Results: A total of 1,946 patients (mean age 59 years; 68.6% male) were included in the present analysis. Among patients with abnormal eGFR values calculated from serum creatinine, cystatin C, or both creatinine and cystatin C, moderate-dose (101–150 g/day) and high-dose (>150 g/day) mannitol use were associated with an increased risk of all-cause in-hospital mortality compared with a mannitol dose of ≤ 50 g/day in analyses adjusted for ICH risk factors. For patients exhibiting normal eGFR values estimated based on serum creatinine and cystatin C, high-dose mannitol administration was also independently associated with death during hospitalization. However, this association was not observed among patients with a normal eGFR derived from combined creatinine and cystatin C measurements.

Conclusions: The findings in this study provide encouraging support that eGFR use based on a combination of creatinine and cystatin C measurements for risk stratification among patients with ICH receiving hyperosmolar mannitol treatment in clinical practice.

Introduction

Mannitol is widely used as one of the first-line hyperosmolar agents in treating elevated intracranial pressure (ICP).[29, 32, 35] Nevertheless, there is a safety concern over the optimal mannitol treatment regimen in clinical practice since it may induce detrimental effects, such as hypovolemia, electrolyte disturbance, and osmotic nephrosis.[6, 7, 17, 19, 24, 31, 34] This concern is vital important among the management of patients with an intracerebral hemorrhage (ICH), for which the elevation of ICP and the utility of mannitol tend to be more common. To date, the ICH guidelines acknowledge that methods of treating elevated ICP are generally borrowed from traumatic brain injury guidelines.[9] Thus, the safety and effectiveness profile of mannitol remains a contentious area in such an ICH population.[4, 8, 20, 33] Moreover, clinicians are particularly concerned about safe doses in different scenarios with mannitol-treated patients in diverse clinical practice settings.

Herein, a key index, termed the estimated glomerular filtration rate (eGFR), was introduced to address this challenge. The eGFR is widely accepted as the clinical standard for assessing renal function.[23] Clearly,

renal function plays an important role in patients with ICH and those treated by mannitol. Knowing the mannitol administration when an individual patient demonstrates a known renal insufficiency or exhibits normal renal function can inform clinical insights. In this context, this study was designed to investigate the risk stratification of patients with ICH receiving mannitol treatment based on eGFR values using the measurements of serum creatinine, cystatin C, or a combination of creatinine and cystatin C in real-world settings.

Methods

Data Source

The data analyzed in the present study were obtained from the database of the Center of Cerebrovascular Diseases of West China Hospital, Sichuan University, Chengdu. The present study was reviewed and approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee, who waived the need for consent as de-identified data were collected. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Clinical Setting and Study Population

This population-based retrospective study included consecutive patients who were admitted to the West China Hospital of Sichuan University, a nonprofit tertiary care university hospital, from October 2010 to December 2018. Patients were enrolled in this study if they (1) were at least 18 years old, (2) had an acute first-ever diagnosis of a spontaneous ICH within 24 hours that was confirmed by brain computed tomography scans and medical records, (3) had available laboratory parameter (creatinine and cystatin C) results at the time of admission, and (4) had complete mannitol usage data during hospitalization. Patients were excluded if they had a secondary intracranial hemorrhage such as trauma, a tumor, or vascular structural abnormalities (e.g. aneurysm)[22] except for primary intraventricular hemorrhage. Patients who died within 24 hours after admission and whose mannitol usage duration was less than 2 days were also excluded.

Data Collection and Definitions

Patients' hospital records were reviewed. Demographic information and clinical characteristics were retrieved including sex, age, marital status (married, divorced or separated, widowed, and never married), time from symptom onset to admission (hours), hospital stay (days), admission Glasgow Coma Scale (GCS) score, lifestyle risk factors (smoking and alcohol use), recorded comorbidities (hypertension, diabetes mellitus, and chronic kidney disease [CKD]), recorded hospital complications (intracranial or pulmonary infections), physical examinations (temperature [°C], heart rate [beats/min], respiratory rate [beats/min], systolic blood pressure [BP, mmHg], and diastolic BP [mmHg]). All patients in this study received 20% mannitol through intravenous infusion. Mannitol doses, recorded by mean dose range per day, were stratified into 4 groups: ≤ 50 , 51–100, 101–150, and >150 g/day.[18] Circulating biomarkers were obtained including sodium [mmol/L], glucose [mmol/L], hemoglobin [g/L], creatinine [μ mol/L], and

cystatin C [mg/L] tested in serum samples at the time of admission. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and previously developed equations, with measurements of serum creatinine, cystatin C, or both creatinine and cystatin C (combination), see Table S1 in the Supplementary Appendix.[11, 12, 16, 27] An eGFR ≥ 90 mL/min/1.73 m² of body-surface area [mL/min/1.73 m²] was defined as normal, accordingly, an eGFR < 90 mL/min/1.73 m² was considered as abnormal.[1] Radiology data on hematoma locations (basal ganglia, lobar, thalamus, cerebellum, brainstem), hematoma volume (mL, calculated using the formula $ABC/2$ [15]), and the presence of an intraventricular hemorrhage (IVH) or subarachnoid hemorrhage (SAH) were also collected. The primary outcome of interest was all-cause in-hospital mortality retrieved from paramedic electronic medical records.

Statistical Analysis

Descriptive statistics were presented as the mean $\pm$ standard deviation or medians (interquartile range [IQR]) for continuous variables and counts (percentages) for categorical variables. Comparisons of differences in baseline characteristics among groups were evaluated using an analysis of variance or Kruskal-Wallis test for continuous variables and the Chi-squared test or Fisher exact test (2 tailed) for categorical variables, as appropriate. Univariable and multivariable analyses were used to identify prognostic variables. Variables with $P < 0.10$ identified during univariate analysis were included in a multivariate logistic regression to determine variables independently associated with in-hospital mortality. The odds ratio [OR] and 95% confidence interval [CI] were used to assess the quantitative relationship between interest variables and in-hospital death.

First, associations between mannitol doses and in-hospital mortality were evaluated in the general-population cohorts. Second, the same analyses were conducted in populations with normal and abnormal eGFR values, respectively. To assess whether mannitol-associated mortality risk differed in patients with and without known CKD, multivariable analyses were performed in patients with and without this condition. To avoid collinearity effects, serum creatinine, cystatin C, and CKD were not entered together in multivariate models. A P value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using S-Plus software (version 6.1, Insightful) and SPSS software, (version 25.0, IBM Corp).

Results

Baseline Characteristics

This study comprised 1,946 individuals after applying the inclusion and exclusion criteria (Figure 1). The mean age of the study population was 59 years and 68.6% were men. The median duration and daily doses for patients receiving mannitol were 7 days (IQR, 4-12) and 528 ml (IQR, 375-714), respectively. Compared with patients receiving low-dose mannitol (≤ 50 g/day), those who used mannitol doses above 50 g/day were less likely to have CKD but were more likely to have low GCS scores, larger ICH

hematoma volumes, and high levels of glucose and cystatin C (all $P < 0.05$). The in-hospital mortality increased from 9.5% at a mannitol dose of ≤ 50 g/day to 20.8% at >150 g/day. The baseline characteristics of the study population according to the mannitol doses are summarized in Table 1.

Factors Associated with Mortality

The overall all-cause in-hospital mortality for the present analysis was 12.4% (242/1,946 patients) after excluding patients who died within 24 hours postadmission ($n = 136$) and those excluded who died for other reasons ($n = 112$). Univariable analysis results showed that age, marital status, admission GCS score, diabetes mellitus, pulmonary infection, temperature, heart rate, systolic blood pressure, sodium levels, glucose levels, hemoglobin levels, thalamus data, brainstem data, IVH presence, SAH presence, and hematoma volume were significant predictors of in-hospital mortality (all $P < 0.005$), as outlined in Table 2. The multivariate logistic regression analysis provided data regarding mannitol dose ($P < 0.001$), hematoma involving the brainstem (OR 2.88, 95% CI 1.75–4.75, $P < 0.001$), admission GCS score (OR 2.69, 95% CI 1.88–3.86, $P < 0.001$), hematoma involving the thalamus (OR 1.92, 95% CI 1.32–2.77, $P = 0.001$), cystatin C (OR 1.75, 95% CI 1.44–2.12, $P < 0.001$), IVH presence (OR 1.58, 95% CI 1.11–2.25, $P = 0.011$), glucose levels (OR 1.12, 95% CI 1.06–1.17, $P < 0.001$), age (OR 1.05, 95% CI 1.03–1.17, $P < 0.001$), time from symptom onset to admission (OR 0.94, 95% CI 0.90–0.98, $P = 0.005$), and serum sodium levels (OR 0.94, 95% CI 0.90–0.98, $P = 0.006$), as presented in Table 3. Results did not change significantly after excluding patients with established CKD (Table 3).

Mannitol Doses and Mortality Based on eGFR Values

The associations between mannitol doses and in-hospital mortality among ICH patients with normal and abnormal eGFR were calculated from 3 equations (Figure 2 and Table S2 in the Supplementary Appendix). Among patients with abnormal eGFR calculated from creatinine and cystatin C, mannitol doses were associated with an increased risk of all-cause in-hospital mortality (creatinine-based eGFR, OR for a mannitol dose of 101–150 g/day 2.35, 95% CI 1.21–4.53, $P = 0.011$, and OR for a mannitol dose of > 150 g/day 2.93, 95% CI 1.36–6.32, $P = 0.006$, cystatin C-based eGFR, OR for a mannitol dose of 101–150 g/day 2.33, 95% CI 1.12–4.80, $P = 0.024$, and OR for a mannitol dose of > 150 g/day 2.93, 95% CI 1.19–7.20, $P = 0.019$) in analyses adjusted for ICH risk factors. These correlations were also observed among patients with normal eGFR values calculated from creatinine and cystatin C who used mannitol doses above 150 g/day (OR for a creatinine-based eGFR 4.67, 95% CI 1.04–20.95, $P = 0.044$ and OR for a cystatin C-based eGFR 5.06, 95% CI 1.53–16.82, $P = 0.008$).

By contrast, among patients with an abnormal eGFR derived from combined creatinine and cystatin C measurements, compared with individuals using low-dose mannitol, those receiving mannitol doses of 101–150 or > 150 g/day were also independently associated with in-hospital death (OR for a mannitol dose of 101–150 g/day 2.14, 95% CI 1.08–4.23, $P = 0.029$ and OR for a mannitol dose of >150 g/day 3.03, 95% CI 1.35–6.78, $P = 0.007$) based on multivariate analysis findings. However, this association was not observed among patients with a normal eGFR derived from combination measurements (Figure 2 and Table S2 in the Supplementary Appendix).

Discussion

In this study, serum creatinine, cystatin C, and measurements combining those 2 biomarkers were utilized to calculate eGFR values that were then used to investigate the association between mannitol doses and the risk of in-hospital mortality in patients with ICH. These data demonstrate that patients with abnormal eGFR values (calculated from either serum creatinine, cystatin C, or both combined) receiving mannitol treatment at a dose of above 100 g/day were associated with an increased risk of in-hospital mortality. Moreover, among the entire study population, those exhibiting normal eGFR values calculated from serum creatinine and cystatin C alone and who received mannitol doses above 150 g/day were also independently associated with in-hospital mortality. However, this association was not observed among patients with normal eGFR values derived from combined creatinine and cystatin C measurements. These results provide novel evidence for the dose-dependent association of mannitol and adverse outcomes among those who had abnormal eGFR values.

The exact mechanisms related to large mannitol doses and mortality are warranted further investigation. In fact, renal insufficiency is associated with risk factors such as older age, coagulation dysfunction, vascular damage, larger hematomas, and cardiovascular events, including mortality.[2, 21, 37, 39] Patients treated with large mannitol doses experienced induced or exaggerated renal impairment that subsequently lead to increased mortality. It is well recognized that a low-dose mannitol therapy is well tolerated by patients whose renal function and electrolyte profiles are normal.[24] Nevertheless, patients administered large-dose mannitol and experiencing renal insufficiency may have different outcomes.

In part, the present findings are consistent with prior studies, but data from the hemorrhagic stroke population suggest that large doses of mannitol may have adverse outcomes (e.g., serum and urine electrolyte disturbances and osmolality or acute renal failure), including mortality in individuals[7, 10, 19, 24, 25, 30, 34] and animals.[28, 40] Earlier, in the 1980s, Whelan et al. reported a case in which acute oliguric renal failure occurred without a known predisposing factor other than the intravenous infusion of massive quantities of mannitol.[34] At the same time, Goldwasser and Fotino S described 2 patients who suffered reversible acute oliguric renal failure due to a massive mannitol infusion (400–900 g/day) administered as a treatment for intracranial hypertension.[7] These 2 studies, along with later research, showed that large doses of mannitol can be detrimental even in patients with normal renal function.[7, 19, 24, 34]

In the series of studies by Cruz et al., however, patients in the high-dose mannitol group received the agent dose approximately 1.4 g/kg and resulted in good clinical outcomes.[3-5] Furthermore, Helbok et al. found that mannitol (1 g/kg) was effective in reducing ICP and improved brain metabolism. Recently, another study focusing on patients with an acute ICH showed that mannitol seems safe but might not improve outcomes based on data from the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).[33] Given these conflicting outcome data, it is important to note that previous studies used various mannitol doses in patient treatment regimens. In the present study, a dose of mannitol above 150 g/day was considered a "high" dose, though it is considerably lower than "high" values in other published

studies.[6] Moreover, patients in the present study may receive various osmotic agents like hypertonic saline and glycerin fructose rather than mannitol alone. Nevertheless, mannitol at doses above 150 g/day are still small and we did not create another larger dosage category for analysis. In addition, it may plausible that factors such as the frequency (e.g., interval time between administrations) and duration of mannitol use, individual characteristics (e.g., body mass index, illness severity, and underlying diseases) and clinical scenarios (e.g., comorbid hypertension, diabetes mellitus, or CKD) could also influence the results.

Notably, a considerable proportion of patients presented with an abnormal eGFR after an ICH. Previous studies reported that the prevalence of eGFR values $< 60 \text{ ml/min/1.73 m}^2$ in patients with ICH ranged from 20–46%.[13, 21, 39] this figure for patients with eGFR values $< 90 \text{ ml/min/1.73 m}^2$ was 64.8%.[38] In contrast, the percentages of eGFR values $< 90 \text{ ml/min/1.73 m}^2$ in the present population are 69.2%, 43.5%, and 59.0% based on serum creatinine, cystatin C, and combined creatinine and cystatin C measurements, respectively. These data suggest that renal insufficiency is prevalent in patients with ICH. Accordingly, investigations into the safety and effectiveness of mannitol for ICH patients with normal or abnormal eGFR values offer clinical value.

In this study, the association between mannitol doses and mortality was observed among patients with either normal or abnormal eGFR values based on serum creatinine and cystatin C data. Furthermore, this association was observed among patients with abnormal eGFR values derived from combined creatinine and cystatin C measurements but not for normal eGFR values based on combined measurements. Therefore, these findings suggest that eGFR calculated with a combined creatinine and cystatin C measurement may be superior to either marker alone in discriminating patient risk when using high mannitol doses, the eGFR superiority based on combined measurements is in agreement with previous data.[12, 26] Thus, it may plausible for clinicians to use this index to safely guide mannitol administration in clinical practice.

In this study, the dose and timing of mannitol use for patients with ICH were determined by the clinician's judgment, also, the reason and decision to prescribe mannitol in patients with renal insufficiency is unknown due to the retrospective nature of the study. In the present population, most patients with an abnormal eGFR had mild renal insufficiency and the proportion of patients with moderate-to-severe renal impairment or end-stage renal disease was quite small (17.3% for patients with eGFR values $< 60 \text{ mL/min/1.73 m}^2$, 3.5% for patients with eGFR values $< 30 \text{ mL/min/1.73 m}^2$, and 1.5% for patients with eGFR values $< 15 \text{ mL/min/1.73 m}^2$, based on eGFR values calculated from combination measurements). Hence, eGFR values were only classified as normal or abnormal rather than further categorized according to the guideline.[23] It is possible that, in an emergency situation where patients with severe hemorrhagic stroke presented with episodes of cerebral herniation, mannitol was prescribed as a fast and effective life-saving procedure. Nonetheless, the current results show that administering with mannitol larger than 100 g/day was associated with adverse outcomes among patients with abnormal eGFR values that would preclude clinicians using mannitol without an adequate trade-off or risk–benefit profile. In the

cases where mannitol use is contraindicated, other methods can be considered, for example, patients may receive osmotic hypertonic saline, which may be more effective.[14, 35] Other management approaches include elevating the head of the bed to 30°, using mild sedation, and surgical intervention. [36]

This study has several limitations and should be interpreted with caution. First, considering that acute death was more likely to be determined by illness severity, those patients who died within 24 hours were excluded. This may introduce selection bias and could result in underestimating the in-hospital mortality and detrimental mannitol effects. Second, the aim of this study was to investigate the risk of mortality based on eGFR values in patients with ICH receiving hyperosmolar mannitol treatment. Thus, the analysis focused on a safety profile rather than the effectiveness of mannitol. Also, as previously mentioned, this study did not address the issue of the mechanism for the associations observed based on the present data. Third, a single admission measurement of creatinine and cystatin C was used in this study. It is possible that dynamic laboratory parameters may provide more information on renal function. Whether the eGFR value varied between normal and abnormal ranges during the clinical course remains to be seen. Fourth, only hospital discharge outcomes were considered in the present study, long-term outcomes may deserve further investigation. Fifth, this study was limited by its retrospective and single-center design. Furthermore, mannitol seems to be much more frequently used in China than other countries.[33] These features along with the specific population studied may preclude the generalizability of the present results and their extension to other populations.

The strengths of the present study are related to its relatively large sample size and potential clinical implications. Although the present study is observational in nature, these results may be valuable because a clinical trial study regarding this topic may not yet be ethically feasible. Furthermore, the observed associations seem robust due to the relatively large sample. As clinicians consider mannitol use on an individual basis, these findings could provide clinicians with evidence to guide the decision-making process in clinical practice.

Conclusion

In conclusion, this study suggests administering moderate or high mannitol doses was independently associated with an increased risk of all-cause in-hospital mortality among patients with ICH and an abnormal eGFR. Moreover, the present results support the use of eGFR based on combined creatinine and cystatin C measurements for risk stratification among patients with ICH receiving hyperosmolar mannitol treatment in clinical practice.

Declarations

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Conflict of interest

The authors declare that there is no conflict of interest.

Availability of data and material

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Ethics approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

All participants agreed to participate in the study

Consent for publication

Written informed consent was obtained from all participants.

Authors' contributions

Conception and design: D.C, C.W, Z.JY, T.Y. Data collection: D.C, C.W, Z.JY, L.HY, C.J, W.XY. Data analysis: D.C, C.W, T.Y, L.HY. Helping with data analysis: L.HY, Z.JY, T.Y. Drafting: D.C, Z.JY, C.W, W.XY. Helping with drafting: L.HY, T.Y. Approval of final version: D.C, C.W, Z.JY, T.Y, L.HY, C.J, W.XY

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Tables

Table 1. Baseline characteristics of study population, stratified by mannitol doses.

Characteristic	≤50 g/day (n=201)	51-100 g/day (n=730)	101-150 g/day (n=775)	>150 g/day (n=240)	P value
Age	63.9±15.1	54.1±13.7	57.4±12.9	55.5±12.8	<0.001
Male sex	66 (32.8%)	238 (32.6%)	233 (30.1%)	75 (31.3%)	0.724
Marital status					0.002
Married	170 (84.6%)	675 (92.5%)	709 (91.5%)	213 (88.8%)	
Divorced or separated	4 (2.0%)	9 (1.2%)	19 (2.5%)	7 (2.9%)	
Widowed	23 (11.4%)	34 (4.7%)	28 (3.6%)	14 (5.8%)	
Never married	4 (2.0%)	12 (1.6%)	19 (2.5%)	6 (2.5%)	
Time from symptom onset to admission	5.0 (3.0-9.0)	5.0 (4.0-9.0)	6.0 (4.0- 10.0)	6.0 (4.0-8.0)	
Admission GCS score					<0.001
≤8	47 (23.4%)	194 (26.6%)	326 (42.1%)	119 (49.6%)	
>8	154 (76.6%)	536 (73.4%)	449 (57.6%)	121 (50.4%)	
Lifestyle risk factors					
Current smoking	55 (27.4%)	219 (30.0%)	253 (32.6%)	71 (29.6%)	0.434
Alcohol use	19 (9.5%)	97 (13.3%)	139 (17.9%)	28 (11.7%)	0.003
Comorbidities					
Hypertension	149 (74.1%)	571 (78.2%)	608 (78.5%)	178 (74.2%)	0.330
Diabetes mellitus	31 (15.4%)	52 (7.1%)	87 (11.2%)	28 (11.7%)	0.002
CKD	20 (10.0%)	20 (2.7%)	26 (3.4%)	6 (2.5%)	<0.001
Complications					
Intracranial infection	6 (3.0%)	8 (1.1%)	23 (3.0%)	12 (5.0%)	0.005
Pulmonary infection	48 (23.9%)	152 (20.8%)	278 (35.9%)	101 (42.1%)	<0.001
Physical examinations					
Temperature, °C	36.6 (36.5- 36.8)	36.6 (36.5- 36.8)	36.6 (36.5- 36.9)	36.7 (36.5- 37.0)	0.003
Heart rate, beats/min	80.0 (74.0- 90.0)	80.0 (72.0- 91.0)	80.0 (72.0- 92.0)	82.0 (75.0- 95.5)	0.266
Respiratory rate, beats/min	20.0 (20.0- 20.0)	20.0 (20.0- 20.0)	20.0 (20.0- 21.0)	20.0 (20.0- 21.0)	0.086

Systolic BP, mmHg	168.0 (150.0-184.0)	168.0 (149.0-187.0)	169.5 (150.0-191.5)	166.0 (142.5-192.5)	0.613
Laboratory parameters					
Sodium, mmol/L	138.9 (136.7-140.3)	139.1 (136.8-140.9)	138.5 (136.3-140.4)	138.5 (136.3-140.7)	0.005
Glucose, mmol/L	7.46 (6.09-9.29)	7.41 (6.28-8.99)	8.14 (6.82-10.32)	8.54 (7.13-11.09)	<0.001
Hemoglobin, g/L					
Male	142.0 (131.0-152.0)	143.0 (133.0-154.0)	147.0 (137.0-158.0)	145.0 (135.0-157.0)	0.002
Female	127.0 (114.0-137.5)	129.0 (121.0-138.5)	130.0 (121.0-140.0)	127.5 (118.5-135.0)	0.188
Creatinine, µmol/L					
Male	85.0 (72.0-113.0)	80.0 (69.0-95.0)	79.0 (69.0-97.0)	78.0 (67.0-92.0)	0.012
Female	62.0 (52.0-74.5)	59.0 (49.0-69.6)	61.0 (52.0-71.0)	61.0 (52.5-71.5)	0.502
Cystatin C, mg/L	0.94 (0.77-1.15)	0.86 (0.73-1.05)	0.84 (0.71-0.99)	0.80 (0.67-1.00)	<0.001
Hematoma locations ¹					
Basal ganglia	96 (47.8%)	321 (44.0%)	395 (51.0%)	116 (48.3%)	0.060
Lobar	37 (18.4%)	156 (21.4%)	186 (24.0%)	72 (30.0%)	0.015
Thalamus	42 (20.9%)	148 (20.3%)	140 (18.1%)	52 (21.7%)	0.526
Cerebellum	16 (8.0%)	60 (8.2%)	66 (8.5%)	24 (10.0%)	0.840
Brainstem	28 (13.9%)	95 (13.0%)	75 (9.7%)	21 (8.8%)	0.068
Presence of IVH	42 (20.9%)	183 (25.1%)	236 (30.5%)	69 (28.7%)	0.017
Presence of SAH	3 (1.5%)	19 (2.6%)	31 (4.0%)	12 (5.0%)	0.092
Hematoma volume, mL	8.5 (3.0-20.3)	12.4 (5.8-30.6)	30.5 (14.0-55.2)	37.7 (15.8-59.7)	<0.001
Hematoma evacuation	23 (11.4%)	150 (20.5%)	335 (43.2%)	130 (32.8%)	<0.001
Mean mannitol dose, g/day	250.0 (188.0-250.0)	375.0 (354.0-431.0)	675.0 (607.0-727.0)	800.0 (775.5-856.0)	<0.001

Hospital stay, days	6.0 (4.0-10.0)	7.0 (4.0-12.0)	10.0 (5.0-18.0)	10.0 (6.0-17.0)	<0.001
In-hospital mortality	19 (9.5%)	61 (8.4%)	112 (14.5%)	50 (20.8%)	<0.001

CKD, chronic kidney disease, ICH, intracranial hemorrhage, GCS, Glasgow Coma Scale, HE, hematoma evacuation, SAH, subarachnoid hemorrhage, BP, blood pressure, IVH, intraventricular hemorrhage.

¹ Hematoma could involve more than one site.

Table 2. Univariate analysis for in-hospital mortality.

Variable	All patients (n=1946)	Survival (n=1704)	Death (n=242)	P- Value
Age	58.8±13.6	58.0±13.4	64.2±14.4	<0.001
Male sex	1334 (68.6%)	1159 (68.0%)	175 (72.3%)	0.178
Marital status				0.038
Married	1767 (90.8%)	1558 (91.4%)	209 (86.4%)	
Divorced or separated	39 (2.0%)	31 (1.8%)	8 (3.3%)	
Widowed	99 (5.1%)	79 (4.6%)	20 (8.3%)	
Never married	41 (2.1%)	36 (2.1%)	5 (2.1%)	
Time from symptom onset to admission	6.0 (4.0-9.0)	6.0 (4.0-9.0)	4.0 (3.0-7.0)	<0.001
Admission GCS score				<0.001
≤8	686 (35.3%)	517 (30.3%)	169 (69.8%)	
>8	1260 (64.7%)	1187 (69.7%)	73 (30.2%)	
Lifestyle risk factors				
Current smoking	598 (30.7%)	526 (30.9%)	72 (29.8%)	0.725
Alcohol use	283 (14.5%)	249 (14.6%)	34 (14.0%)	0.816
Comorbidities				
Hypertension	1506 (77.4%)	1324 (77.7%)	182 (75.2%)	0.386
Diabetes mellitus	198 (10.2%)	158 (9.3%)	40 (16.5%)	<0.001
Chronic kidney disease	72 (3.7%)	40 (2.3%)	32 (13.2%)	<0.001
Complications				
Intracranial infection	49 (2.5%)	40 (2.3%)	9 (3.7%)	0.203
Pulmonary infection	579 (29.8%)	479 (28.1%)	100 (41.3%)	<0.001
Physical examinations				
Temperature, °C	36.6 (36.5-36.8)	36.6 (36.5-36.8)	36.8 (36.5-37.0)	<0.001
Heart rate, beats/min	80.0 (72.0-92.0)	80.0 (72.0-90.0)	86.0 (76.0-100.0)	<0.001
Respiratory rate, beats/min	20.0 (20.0-21.0)	20.0 (20.0-21.0)	20.0 (20.0-21.5)	0.065
Systolic BP, mmHg	168.0 (149.0-189.0)	167.0 (148.0-188.0)	174.5 (152.0-203.5)	<0.001

Laboratory parameters				
Sodium, mmol/L	138.8 (136.4-140.6)	138.9 (136.7-140.7)	137.9 (135.1-140.0)	<0.001
Glucose, mmol/L	7.83 (6.55-9.73)	7.65 (6.49-9.42)	9.02 (7.30-12.45)	<0.001
Hemoglobin, g/L				
Male	145.0 (134.0-155.5)	145.0 (136.0-156.0)	142.0 (125.0-154.0)	0.001
Female	129.0 (120.0-139.0)	129.0 (121.0-138.0)	129.0 (117.0-141.0)	0.322
Creatinine, μ mol/L				
Male	80.0 (69.0-96.0)	79.0 (68.5-95.0)	87.0 (71.3-111.0)	<0.001
Female	60.0 (51.0-71.0)	60.0 (51.0-70.0)	69.0 (56.0-83.0)	0.001
Cystatin C, mg/L	0.85 (0.72-1.03)	0.84 (0.71-1.01)	0.93 (0.79-1.22)	<0.001
Hematoma locations ¹				
Basal ganglia	928 (47.7%)	821 (48.2%)	107 (44.2%)	0.248
Lobar	451 (23.2%)	398 (23.4%)	53 (21.9%)	0.615
Thalamus	382 (19.6%)	296 (17.4%)	86 (35.5%)	<0.001
Cerebellum	166 (8.5%)	149 (8.7%)	17 (7.0%)	0.370
Brainstem	219 (11.3%)	171 (10.0%)	48 (19.8%)	<0.001
Presence of IVH	530 (27.2%)	426 (25.0%)	104 (43.0%)	<0.001
Presence of SAH	65 (3.3%)	49 (2.9%)	16 (6.6%)	0.002
Hematoma volume, mL	20.0 (8.2-46.5)	18.0 (7.5-42.0)	42.2 (18.9-82.9)	<0.001
Hematoma evacuation	638 (32.8%)	561 (32.9%)	77 (31.8%)	0.732
Mean mannitol dose, g/day	525.0 (375.0-711.0)	500.0 (365.0-702.5)	650.0 (473.0-750.0)	<0.001
Hospital stay, days	8.0 (5.0-15.0)	8.0 (5.0-15.0)	6.0 (3.0-11.0)	<0.001

CKD, chronic kidney disease, ICH, intracranial hemorrhage, GCS, Glasgow Coma Scale, HE, hematoma evacuation, SAH, subarachnoid hemorrhage, BP, blood pressure, IVH, intraventricular hemorrhage.

¹ Hematoma could involve more than one site.

Table 3. Multivariate logistic regression analysis for in-hospital mortality.

Variable	Model 1		Model 2	
	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Mannitol doses				
≤ 50 g	Ref.		Ref.	
51-100 g	1.42 (0.74-2.74)	0.290	1.23 (0.60-2.50)	0.571
101-150 g	2.86 (1.49-5.47)	0.002	2.71 (1.35-5.44)	0.005
> 150 g	5.47 (2.64-11.31)	<0.001	5.39 (2.50-11.62)	<0.001
Brainstem hemorrhage	2.88 (1.75-4.75)	<0.001	3.00 (1.80-5.00)	<0.001
Admission GCS score	2.69 (1.88-3.86)	<0.001	2.53 (1.73-3.70)	<0.001
Thalamus hemorrhage	1.92 (1.32-2.77)	0.001	1.66 (1.11-2.47)	0.013
Cystatin C	1.75 (1.44-2.12)	<0.001	2.63 (1.69-4.10)	<0.001
Presence of IVH	1.58 (1.11-2.25)	0.011	1.55 (1.07-2.25)	0.022
Glucose	1.12 (1.06-1.17)	<0.001	1.17 (1.09-1.25)	<0.001
Age	1.05 (1.03-1.17)	<0.001	1.04 (1.02-1.06)	<0.001
Time from symptom onset to admission	0.94 (0.90-0.98)	0.005	0.94 (0.90-0.98)	0.006
Sodium	0.94 (0.90-0.98)	0.006	0.93 (0.89-0.98)	0.003

Model 1 includes all patients, while model 2 excludes patients with known chronic kidney disease (n=72). Both models adjusted for hemoglobin, temperature, systolic BP, diabetes mellitus, presence of subarachnoid hemorrhage, and hematoma evacuation.

GCS, Glasgow Coma Scale, BP, blood pressure, IVH, intraventricular hemorrhage.

Figures

Figure 1

Flowchart of Study Population.

Figure 2

The associations between mannitol doses and in-hospital mortality among ICH patients with normal and abnormal estimated estimating glomerular filtration rate (eGFR) levels. Panel A shows the associations among patients with an eGFR less than 90 ml/min/1.73 m² and Panel B shows the same associations among patients with an eGFR equal or above 90 ml/min/1.73 m².

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