Prognostic significance of hyponatremia in acute intracerebral hemorrhage: pooled analysis of the INTERACT studies

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Abstract

Objective: To determine the association of hyponatremia with clinical and imaging outcomes in patients with acute intracerebral hemorrhage (ICH).

Design: Retrospective pooled analysis of prospectively collected data from 3243 participants of the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 1 and 2); international, multicenter, open, blinded endpoint, randomized controlled trials designed to assess the effects of early intensive blood pressure (BP) lowering in patients with acute ICH.

Setting: Clinical hospital sites in 21 countries.

Patients: Patients with predominantly mild-moderate severity of spontaneous ICH within 6 hours of onset and elevated systolic BP (SBP 150-220 mmHg) who were randomly assigned to receive intensive (target SBP <140 mmHg within 1 hour) or guideline-recommended (target SBP <180 mmHg) BP lowering therapy.

Measurements and Main Results: Baseline hyponatremia was defined as serum sodium <135 mEq/L. The primary outcome was death at 90 days; a secondary 90-day clinical outcome was functioning according to the modified Rankin Scale score (where 0 indicates no symptoms, 5 severe disability, and 6 death). Multivariable logistic regression was used to assess the association of hyponatraemia with important clinical events. Of 3002 patients with available data, 349 (12%) had hyponatremia. Hyponatraemia was associated with death (18% vs 11%; multivariable-adjusted odds ratio 1.81; 95% confidence interval 1.28 to 2.57; $p<0.001$) and larger baseline ICH volume (multivariable-adjusted $p=0.046$), but not to baseline perihematomal edema (PHE) volume nor with growth of ICH or PHE during the initial 24 hours.

Conclusions: Hyponatremia is associated with an increased mortality after acute ICH, through mechanisms that appear independent of ICH and PHE growth.

Introduction

Acute spontaneous intracerebral hemorrhage (ICH) accounts for approximately 10-25% of all strokes (1, 2), affecting several million people worldwide each year (3). ICH is a critical illness with up to one third of patients requiring mechanical ventilation and intensive care unit management (4-6). Factors predictive of poor clinical outcome include increasing age, clinical severity defined by the Glasgow Coma Scale (GCS), initial volume and extent of growth in ICH volume, intraventricular extension, and infratentorial location of ICH (7-10).

Hyponatremia is a consistent predictor of adverse outcome in general medical and critically ill patients (11-14), but also in those with acute ischemic stroke (15, 16). A possible explanatory mechanism for the association in patients with stroke is fluid shift in intracranial tissue leading to cerebral edema, seizures, and delayed cerebral ischemia (17). However, there is a paucity of data pertaining to the significance of hyponatremia specifically in patients with ICH; only one single-center retrospective study indicates hyponatremia as an independent predictor of in-hospital mortality (18). There are no data available on whether perihematomal edema (PHE) in ICH is related to hyponatremia.

The objectives of this study were to determine prognostic significance of hyponatremia according to clinical and imaging outcomes in a pooling analysis of ICH patients who participated in the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 1 and 2) studies.

Materials and Methods

Study design and participants

INTERACT1 and INTERACT2 were international, multicenter, open, blinded endpoint assessed, randomized controlled trials, the details of which are described elsewhere (19-21). Appendix 1 lists the participating sites. In brief, 3243 participants (404 from INTERACT1

and 2839 from INTERACT2) with spontaneous ICH within 6 hours of onset and elevated systolic BP (SBP, 150-220 mmHg) who were randomly assigned to receive intensive (target BP <140 mmHg within 1 hour) or guideline recommended (target SBP <180 mmHg) BP lowering therapy. Patients were excluded if they had a structural cerebral cause for the ICH, were in deep coma (defined as scores of 3-5 on the GCS), had massive ICH with poor prognosis, or if early surgery to evacuate the ICH was planned.

Written informed consent was obtained from each participant or their legal surrogate. The study protocol was approved by an appropriate ethics committee at each hospital site. The INTERACT studies are registered with ClinicalTrials.gov, numbers NCT00226096 and NCT00716079.

Procedures

Demographic and clinical characteristics including prior antihypertensive use were recorded at the time of enrolment. The severity of the stroke was assessed using the GCS and the National Institutes of Health Stroke Scale (NIHSS) (22) at baseline. Initial local laboratory parameters, including serum sodium, were taken upon the presentation of patients. The use of mannitol during the first 7 days of admission was recorded. Hyponatremia was defined according to standard criteria as sodium <135 mEq/L (23).

In the CT substudies, CT scans were performed according to standardized techniques at baseline and at 24±3 hours after the initial CT. A total of 1313 participants (346 INTERACT1, 967 INTERACT2) underwent a repeat CT scan at 24 hours using the same procedure as the baseline diagnostic CT scan. For each CT scan, uncompressed digital CT images were collected in Digital Imaging and Communications in Medicine format on a CD-ROM identified only with the patient's unique study number. For each study, ICH and PHE volumes were calculated independently by trained neurologists who were blind to clinical and

treatment data, and date and sequence of scan, using computer-assisted multi-slice planimetric and voxel threshold techniques (24).

The primary causes of death, available only for INTERACT2 participants, were divided into direct effects of the ICH, and cardiovascular and non-cardiovascular causes.

Outcomes

For these analyses, the primary clinical outcome was death at 90-days. Secondary clinical outcomes were death or major disability combined (defined by scores 3-6 on the modified Rankin Scale [mRS] [25]) and separately for major disability (mRS of 3 to 5) at 90-days. Outcomes in the CT substudies were baseline volumes of ICH and PHE, and absolute growth over 24 hours in ICH and PHE volume.

Statistical analysis

Baseline characteristics of patients in pre-defined groups were summarized as mean ± standard deviation (SD) or median (interquartile range [IQR]) for continuous variables, and as number (%) for categorical variables, with comparisons made using Wilcoxon or chi-square tests. Associations between baseline hyponatremia and clinical outcomes were made using categorical logistic regression with patients without hyponatremia as the reference. Multivariable analyses for clinical outcomes were adjusted for potential confounders which included age, sex, region of enrolment, history of diabetes mellitus, prior use of diuretic or antiplatelet agents, time from onset to randomization, baseline SBP, NIHSS score (≥14 vs <14), presence of intraventricular extension, baseline ICH volume, lobar location, and randomized treatment. ICH volume and PHE volume were log-transformed to remove skewness for all analyses. Geometrical means of these volumes were reported with 95% confidence interval (CI) obtained by back-transformation. As a significant effect of hyponatremia on mortality was observed in both crude and multivariable analyses, we

investigated further the causes of death in crude and multivariable logistic regression models, and performed Kaplan-Meier survival analysis. In the CT substudies, associations of hyponatremia and baseline volumes of ICH and PHE, and absolute growth over 24 hours in volumes of ICH and PHE were assessed by analysis of covariance, which included the same covariates as used for the clinical outcome analyses (the details of adjusting covariates are shown in Table 3). Sensitivity analyses involving an alternate definition of hyponatremia (sodium <130 mEq/L) were also conducted to assess its association with the primary trial study outcome of death and major disability. Data are reported with odds ratios (ORs) and 95% CIs. A *p* value <0.05 was regarded as indicative of statistical significance. All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

Among 3243 participants in the INTERACT pooled cohort, 3002 (93%) had information on admission sodium levels and 90-day outcomes for inclusion in these analyses (Figure 1). A total of 349 (12%) patients had hyponatremia at presentation. Table 1 shows that hyponatremic patients were more likely to have been taking a diuretic, had higher DBP, larger baseline ICH volume, more intraventricular extension and more likely to receive mannitol within 7 days, but there was no significant differences between the two groups in regard to clinical severity (ie NIHSS score), time from symptom onset to randomization, or the location of the underlying ICH. Of the 349 patients with hyponatremia at presentation, the mean sodium was 132±3 mEq/L (compared with 140±3 mEq/L for those without; $p<0.001$).

At the 90-day outcome assessment, 64 (18%) of patients with hyponatremia had died, as compared to 289 (11%) patients without hyponatremia. Hyponatremic patients had a higher risk of death after multivariable adjustment (OR 1.81, 95% CI 1.28 to 2.57; Table 2 and Figure 2) and Kaplan-Meier curves (log-rank $p<0.001$; Figure 3). Significant associations

were also found between hyponatremia and the secondary clinical outcome of death or major disability in crude analyses (OR 1.37, 95% CI 1.09 to 1.71; Table 2) though the association was no longer significant after adjustment for covariates (OR 1.18, 95% CI 0.89 to 1.56; Table 2 and Figure 2). There was no association between hyponatremia and major disability (Table 2 and Figure 2). Among those who died, hyponatremic patients had a shorter time to death than others (median 4 versus 7 days; p=0.028; Figure 3). There were no differences regarding the causes of death between the two groups (Table 3). Similar results were found in sensitivity analyses using an alternate definition of hyponatremia (<130 mEq/L) for the outcomes of death and death and major disability in relation (Appendix 1).

Among 2791 patients with baseline ICH volume data, we found a significant association between hyponatremia and baseline ICH volume (multivariable-adjusted p=0.046) with larger volumes for those with hyponatremia. No such association was evident for baseline PHE volume (data from 1119 patients; Table 4). Among 1313 patients with repeated CT scans at 24 hours, those with admission sodium were included in evaluations of ICH volume (n=1264) and PHE volume (n= 1110) growth analyses. No significant associations were found between baseline hyponatremia and growth in ICH or PHE at 24 hours (Table 4).

Discussion

The present pooled analysis of the two large INTERACT studies, which included over 3000 patients with acute spontaneous ICH, has demonstrated an association between hyponatremia and early death. Although there was a significant relation between baseline hyponatremia and ICH volume, no associations were observed for subsequent ICH growth or for PHE volumes over 24 hours.

There are multiple studies reporting an association between hyponatremia and mortality in patients with critical illness, including acute ischemic stroke (12, 15, 16, 26). However, data

are more limited for those with acute ICH, despite the importance of this condition. While results are consistent with the previous single-center retrospective study (18), they also provide additional insights into potential mechanisms. Our analyses with a larger and broader range of patients extends previous findings by demonstrating that hyponatraemic patients present with larger ICH volumes but do not have any apparent additional expansion of the initial ICH or extention of PHE as mechanisms to explain the poor prognosis.

Two recent analyses suggest that hyponatremia is not just a marker of the severity of underlying illness, but has independent adverse effects (27) on physiological functioning on multiple organ systems (28). A population-based study of over 14,000 adults (27) has shown a 5-fold increase in mortality among subjects with hyponatremia with no significant co-morbidity as compared to matched normonatremic subjects, implying an inherent negative impact of a chronic hypotonic state beyond the underlying illness. Given our ability to record the level of sodium in subjects within several hours after the onset of symptoms (median time of symptom onset to randomization was 3 hours), it is unlikely that syndrome of inappropriate antidiuretic hormone secretion or cerebral salt wasting is an alternative explanation for our findings, as has been reported in patients with subarachnoid hemorrhage whose sodium levels only start to fall from the second to the tenth day after the onset of symptoms (29).

Although a rapid onset of hyponatremia (within 48 hours) is believed to shift water into the brain and cause cerebral edema, leading a reduced level of consciousness and possibly death from increased intracranial pressure (17, 30), we did not find any significant difference in the volume of PHE, either at baseline or over 24 hours, between patients with and without hyponatremia in our study. This may have been due to the imprecise measurements or the early time period of the assessment of PHE in INTERACT (24). The increased use of antihypertensives in our hyponatremia group suggests that pre-existing hyponatremia related to diuretic use might explain some of our findings. In chronic hyponatremia, the brain may

facilitate adaptive mechanisms to normalize osmolarity, first by compensatory displacement of water from the brain into the cerebrospinal fluid and systemic circulation, and later with the extrusion of electrolytes and concomitant loss of osmotically-driven water from neuronal tissue (31).

Strengths of this study include the large sample size and heterogeneous population with early rigorous prospective and systematic evaluations after the onset of acute ICH. We also recognize some limitations in that these analyses were post-hoc, observational and not pre-specified, raising the potential for confounding and bias, particularly in relation to use of single measures of sodium without accounting for regression to the mean. Moreover, we used a non-standardized single measurement of serum sodium, and details on each patient's volume status as well as other co-morbidities such as hypothyroidism and hypertriglyceridemia (to rule out pseudohyponatremia) were unavailable. Furthermore, selection bias from using a clinical trial population where patients with a poor prognosis due to patients with massive ICH or deep coma, or who underwent early surgery being excluded ,limits the generalizability of these data. In the absence of external validation, these findings should therefore be interpreted with caution.

In conclusion, our results indicate that early hyponatremia is associated with higher mortality in patients with acute ICH. This adverse outcome could not be explained on the basis of enhanced PHE. Further investigation of the management of hyponatremia may contribute to better outcomes in patients with acute ICH.

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Figure legends

Figure 1. Patient selection flowchart.

Figure 2. Association between hyponatremia and 90-day clinical outcome.

(A) Death; (B) Death or major disability; and (C) Major disability.

Figure 3. Kaplan-Meier survival plot.

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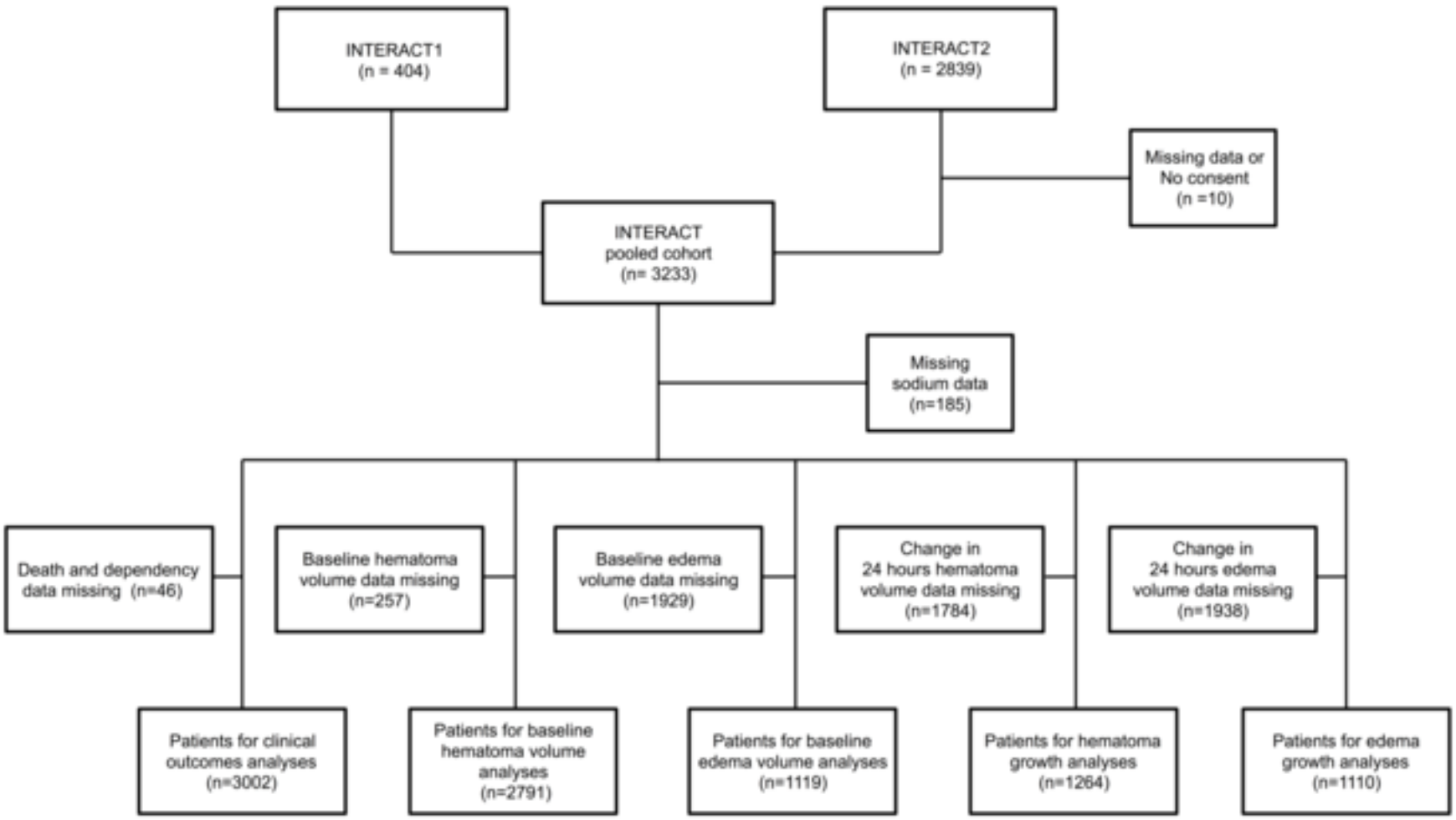

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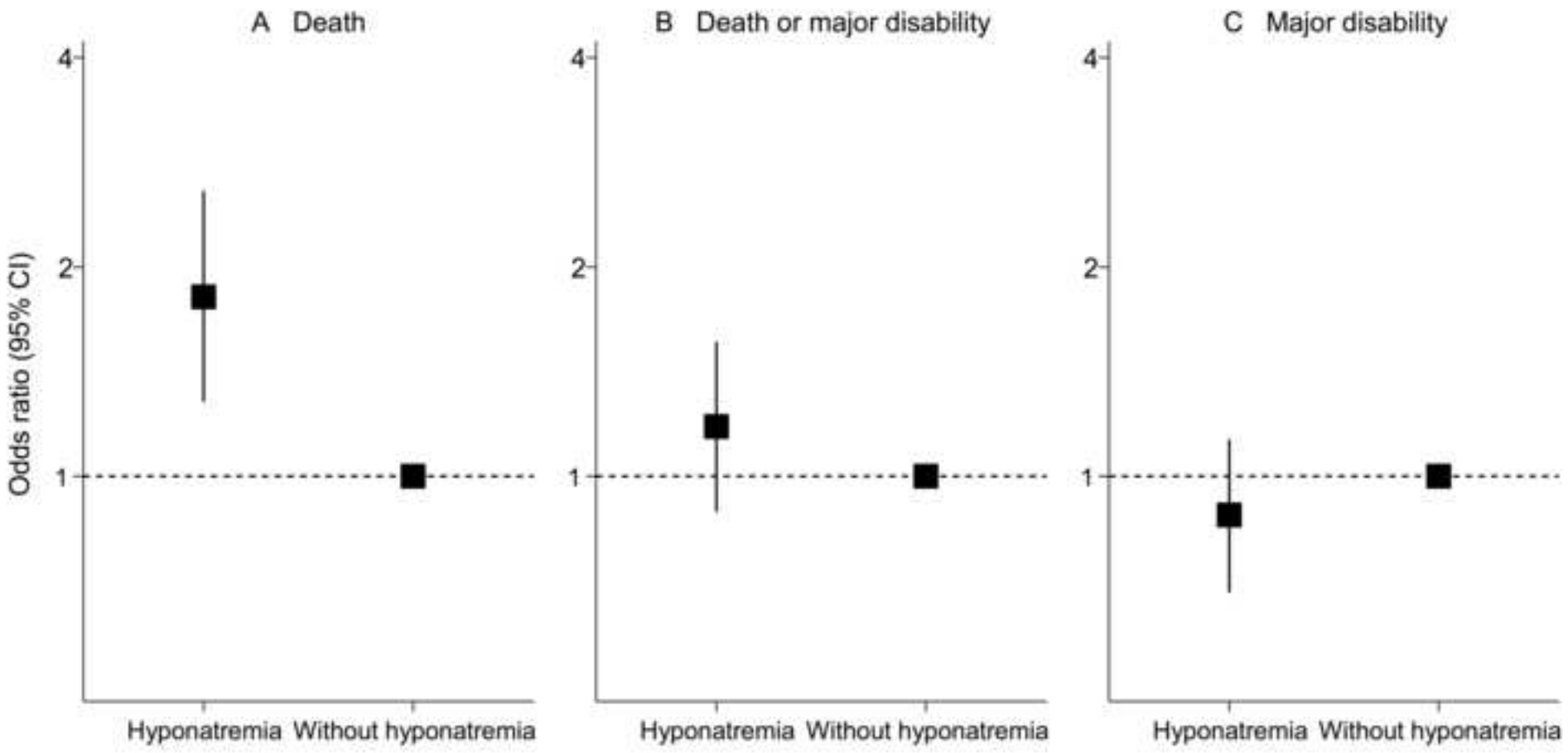

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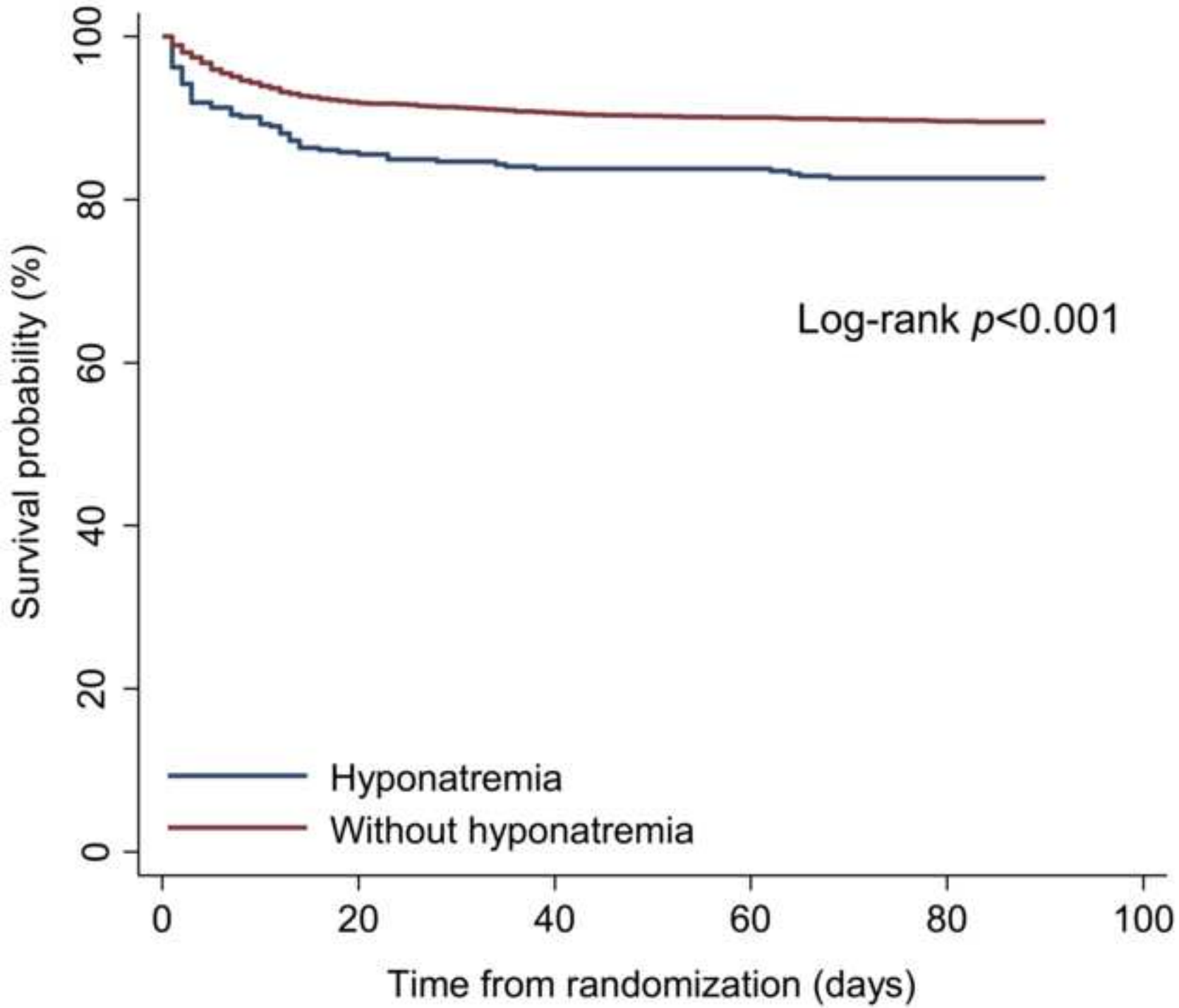

Table

Table 1. Patient characteristics

	Hyponatremia (n=349)	Without hyponatremia (n= 2653)	*p*
Demographics			
Age, yr	64±13	64±13	0.784
Male	213 (61)	1673 (63)	0.461
Chinese region	259 (74)	1846 (70)	0.076
Medical History			
ICH	29 (8)	226 (9)	0.904
Ischemic stroke	45 (13)	262 (10)	0.078
Acute coronary syndrome	13 (4)	78 (3)	0.417
Hypertension	261 (75)	1932 (73)	0.401
Diabetes mellitus	43 (12)	274 (10)	0.249
Medications			
Antihypertensive use	163(47)	1111(42)	0.080
Diuretics	42 (12)	221 (8)	0.021
ACE inhibitor	40 (12)	299 (11)	0.905
ARB	28 (8)	160 (6)	0.146
Antiplatelet use	31 (9)	255 (10)	0.671
Warfarin use	9 (3)	76 (3)	0.767
Clinical features			
Time from onset to randomization, h:mm	3:19 (2:16-4:25)	3:28 (2:19-4:33)	0.303
Randomized intensive BP lowering	176 (50)	1304 (49)	0.654
Systolic BP, mmHg	179±16	179±17	0.783
Diastolic BP, mmHg	103±14	101±15	0.026
Heart rate, bpm	77 (13)	78 (14)	0.805
NIHSS score	12 (7-16)	10 (6-16)	0.085
GCS score	14 (12-15)	14 (13-15)	0.174
Sodium level on admission, mEq/L	132±3	140±3	<0.001
CT findings			
Location of ICH			0.214
Lobar	41 (13)	232 (10)	
Deep	256 (80)	2020 (84)	
Brainstem	8 (3)	78 (3)	
Cerebellum	14 (4)	84 (3)	
Baseline ICH volume, mL	12.1 (6.8-22.8)	10.5 (5.4-18.8)	0.002
Baseline PHE volume, mL[a]	3.0 (1.5-7.5)	2.5 (1.1-5.8)	0.100
Presence of IVH	116 (36)	659 (27)	0.001
Treatment			
Randomized intensive BP lowering	176 (50)	1304 (49)	0.654
Mannitol within 7 days	239(68)	1663(63)	0.035

Data are given as mean (±SD), n (%), or median (interquartile range).

ICH indicates intracerebral hemorrhage; ACE, Angiotensin-converting-enzyme; ARB, Angiotensin II receptor blockers; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale, GCS,

Glasgow Coma Scale; CT, computed tomography; PHE, perihematomal edema; IVH, intraventricular extension of ICH.

[a]Based on total available 1101 patients with data on edema volume on admission: 102 in hyponatremia group, 999 in without hyponatremia group.

Table

Table 2. Association between hyponatremia and clinical outcomes

		Crude			Multivariable-adjusted[a]		
	Number of outcomes (%)	OR	95% CI	*p*	OR	95% CI	*p*
Death							
Hyponatremia	64 (18)	1.84	1.36-2.47	<0.001	1.81	1.28-2.57	<0.001[a]
Without hyponatremia	289 (11)	1.00	(Reference)		1.00	(Reference)	
Death or major disability							
Hyponatremia	207 (59)	1.37	1.09-1.71	0.007	1.18	0.89-1.56	0.249 [a]
Without hyponatremia	1370 (52)	1.00	(Reference)		1.00	(Reference)	
Major disability							
Hyponatremia	143 (41)	1.01	0.81-1.27	0.935	0.88	0.68-1.13	0.325 [a]
Without hyponatremia	1081 (41)	1.00	(Reference)		1.00	(Reference)	

OR indicates odds ratio; CI, confidence interval.

[a]Adjusted for age, sex, region of enrolment, history of diabetes mellitus, prior use of diuretic or antiplatelet agents, time from onset to randomization, baseline systolic blood pressure, presence of intraventricular extension, log-transformed ICH volume, lobar location, randomized treatment, and use of mannitol.

Table

Table 3. Association between hyponatremia and causes of death

	Number of outcomes (%)	Crude			Multivariable-adjusted[a]		
		OR	95% CI	*p*	OR	95% CI	*p*
Direct ICH effect							
Hyponatremia	39 (66)	1.29	0.71- 2.34	0.400	1.15	0.60-2.22	0.666[a]
Without hyponatremia	151 (60)	1.00	(Reference)		1.00	(Reference)	
Cardiovascular causes							
Hyponatremia	5 (8)	0.92	0.33- 2.52	0.868	0.64	0.21-2.00	0.445[a]
Without hyponatremia	1 (9)	1.00	(Reference)		1.00	(Reference)	
Non-cardiovascular causes							
Hyponatremia	15 (25)	0.77	0.40- 1.47	0.428	0.93	0.46-1.90	0.838[a]
Without hyponatremia	77 (31)	1.00	(Reference)		1.00	(Reference)	

OR indicates odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage.

[a]Adjusted for age, sex, region of enrolment, history of diabetes mellitus, prior use of diuretic or antiplatelet agents, time from onset to randomization, baseline systolic blood pressure, National Institutes of Health Stroke Scale (≥14 vs <14), presence of intraventricular extension, log-transformed ICH volume, lobar location, randomized treatment and use of mannitol.

Table

Table 4. Association between hyponatremia and imaging outcomes

	Crude		Multivariable-adjusted	
	Mean (95% CI)	*p*	Mean (95% CI)	*p*
Baseline ICH volume, mL				
Hyponatremia	11.8 (10.5-13.2)	0.001	10.8 (9.8-11.9)	0.046[a]
Without hyponatremia	9.6 (9.2-10.0)		9.7 (9.4-10.1)	
Baseline PHE volume, mL				
Hyponatremia	3.4 (2.7-4.1)	0.306	2.8 (2.5-3.3)	0.324[b]
Without hyponatremia	3.0 (2.8-3.2)		3.1 (2.9-3.2)	
Absolute ICH growth, mL				
Hyponatremia	4.5 (1.8-7.3)	0.377	4.63(1.87-7.40)	0.348[c]
Without hyponatremia	3.2 (2.4-4.1)		3.25(2.38-4.11)	
Absolute PHE growth, mL				
Hyponatremia	4.1 (2.5-5.6)	0.859	3.49(2.04-4.94)	0.541[c]
Without hyponatremia	3.9 (3.4-4.4)		3.96(3.51-4.42)	

OR indicates odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage; PHE, perihematomal edema.

[a]Adjusted for age, sex, region, history of diabetes mellitus, prior use of diuretic or antiplatelet agents, time from onset to randomization, baseline systolic blood pressure, National Institutes of Health Stroke Scale (≥14 vs <14), presence of intraventricular extension, and lobar location.

[b]Adjusted for age, sex, region, history of diabetes mellitus, prior use of diuretic or antiplatelet agents, time from onset to randomization, baseline systolic blood pressure, National Institutes of Health Stroke Scale (≥14 vs <14), presence of intraventricular extension, lobar location, and log-transformed baseline ICH volume.

[c]Adjusted for age, sex, region, history of diabetes mellitus, prior use of diuretic or antiplatelet agents, time from onset to randomization, baseline systolic blood pressure, National Institutes of Health Stroke Scale (≥14 vs <14), presence of intraventricular extension, lobar location, log-transformed baseline ICH volume, randomized treatment, and use of mannitol.

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