BMC Neurology

RESEARCH

Open Access

Hyponatremia is associated with malignant brain edema after mechanical thrombectomy in acute ischemic stroke

Ao Qian[1], Longyi Zheng[2], Jia Duan[1], Lun Li[1], Wenli Xing[1] and Shuang Tang[1*]

Abstract

Background Hyponatremia (< 135 mmol/L) is the most common electrolyte disturbance in patients with stroke. However, few studies have reported the relationship between hyponatremia at admission and outcomes in patients with acute ischemic stroke (AIS) treated with mechanical thrombectomy (MT). This study is aimed to explore the association between hyponatremia and clinical outcomes following MT.

Methods A retrospective study was conducted at our center. The primary outcome was postoperative malignant brain edema (MBE). The secondary outcomes included mortality and adverse function at the 90-day follow-up, which were defined as modified Rankin scale scores of 6 and > 2, respectively. Patients were classified into hyponatremia and nonhyponatremia groups based on their serum sodium concentration at admission before drug use. The occurrence of MBE was evaluated via computed tomography after MT, and 90-day outcomes were obtained through in-person interviews at the clinic or via telephone. Multivariate analysis was performed to investigate the associations among postoperative MBE, 90-day mortality, adverse function and hyponatremia.

Results A total of 342 patients were enrolled into the study, of whom 52 (15.2%) had hyponatremia, 86 (25.1%) developed postoperative MBE, 93 (27.2%) died within 90 days after MT, and 201 (58.8%) had adverse functions at the 90-day follow-up. Multivariate analysis revealed that hyponatremia was significantly associated with postoperative MBE (odds ratio [OR] 3.91, 95% confidence interval [CI] 1.66 – 9.23, $p = 0.002$), 90-day mortality (OR 5.49, 95% CI 2.48 – 12.14, $p < 0.001$), and 90-day adverse function (OR 3.25, 95% CI 1.29 – 8.12, $p = 0.012$). In addition, mediation analysis revealed that postoperative MBE may partially account for the 90-day mortality/adverse function of patients with hyponatremia (regression coefficients changed by 18.6% and 23.9%, respectively).

Conclusion Hyponatremia is an independent predictor of postoperative MBE, 90-day mortality, and adverse function. Correction of hyponatremia may reduce the postoperative MBE to improve the prognosis of patients.

Keywords Hyponatremia, Acute ischemic stroke, Mechanical thrombectomy, Malignant brain edema, Mortality, Adverse function

Introduction

Acute ischemic stroke (AIS) is characterized by a high risk of morbidity and mortality, imposing substantial economic burdens on patients and society [1]. Persistent arterial occlusion leads to oxygen depletion in ischemic cerebral tissue, which may irreversibly convert the penumbra into a core infarct [2]. Thus, emergent reperfusion therapy is the basis of treatment for AIS, especially

*Correspondence:
Shuang Tang
327897603@qq.com
[1] Neurological Disorder Center, Department of Cerebrovascular Disease, Suining Central Hospital, Sichuan 629000, China
[2] Department of Radiology, School of Medicine, Xiang'an Hospital of Xiamen University, Xiamen University, Xiamen 361101, China

for large artery occlusion (LAO), in which rapid recanalization of blocked vessels and reperfusion of affected brain tissue can not only effectively promote the survival of patients but also relieve the deterioration of neurological function. Currently, mechanical thrombectomy (MT) has become the standard therapeutic method for LAO of the anterior circulation [3]. Despite the efficacy of MT, postoperative complications certainly hinder the achievement of favorable prognoses. Malignant brain edema (MBE) is a catastrophic complication that can result in rapid neurological deterioration and cerebral herniation [2, 4]. Furthermore, even when aggressive therapy, such as enhanced osmotic or decompressive craniectomy, is applied for MBE, a high risk of neurological dysfunction is still inevitable [5]. Therefore, it is vital to identify risk factors for MBE to reduce associated mortality and disability.

Hyponatremia is the most common electrolyte disorder in stroke patients and may exacerbate seizures or cerebral edema in the acute phase of stroke [6]. Many studies have revealed that hyponatremia is a risk factor for unfavorable outcomes in patients with intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) [7–10]. Recently, several studies have reported that hyponatremia in patients with AIS is consistently related to increased mortality and disability [11–14]. However, the relationship between hyponatremia and MBE in AIS patients after MT has not been confirmed. Therefore, we conducted a retrospective study and set a primary objective to explore the relationship between admission hyponatremia and postoperative MBE in patients treated with MT. Our secondary purpose was to identify the value of hyponatremia for predicting mortality and functional outcomes at the 90-day follow-up.

Methods

Study design and data collection

This study was approved by our institutional ethics committee (KYLLKS20240174). Patients treated with MT at Suining Central Hospital from January 2021 to June 2024 were screened. The inclusion criteria were as follows: (1) LAO in the terminal internal carotid artery (ICA) or (M1 or M2) middle cerebral artery (MCA); (2) age greater than 18 years; (3) symptoms at admission $\leq$ 24 h. The exclusion criteria were as follows: (1) patients with LAO in the posterior circulation; (2) patients without data on serum sodium at admission and clinical outcomes at follow-up; (3) patients with decompensated or progressive comorbidities before AIS onset; (4) patients with a history of stroke with obvious residual dysfunction before AIS onset (modified Rankin scale [mRS] score > 1). Data, including demographics, neurological function assessed by the National Institute of Health Stroke Scale (NIHSS), intravenous thrombolysis, previous medical history, time from onset to recanalization, laboratory parameters, imaging findings, vascular patency evaluated by the modified Thrombolysis in Cerebral Infarction (mTICI) score, etiology of the AIS, and outcomes, were reviewed. The medical history was determined by reports of patients or family members, medical records, and the presence of relative drug use. Smokers were those who had smoked at least one cigarette per day for at least one year [15]. Alcoholism was defined as drinking at least 80 g of liquor per day [16]. The etiology of AIS in our study was classified as large-artery atherosclerosis (LAA), cardioembolic, and undermined or other thrombi based on the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria [17].

Noncontrast head computed tomography (CT) was used for all stroke patients admitted to our hospital to rule out ICH, and CT angiography was used to determine the existence and location of the LAO simultaneously. The presence of the hyperdense middle cerebral artery sign (HMCAS) was defined as a high-density signal in the MCA trace [18]. The standard Alberta Stroke Program Early CT Score (ASPECTS) was used to determine stroke burden [19]. Blood samples for hematologic tests, including peripheral blood cells, hsCRP, hepatorenal function, electrolytes, coagulation indicators, glucose, triglyceride, and cholesterol, were collected within 30 min after admission before drug use. In addition, the serum sodium level at 24 h after MT was also measured. Intravenous thrombolysis with alteplase was used for patients within 4.5 h after AIS onset after exclusion of contraindications. CT perfusion (CTP) was performed at 6–24 h after symptom onset to evaluate the difference between the penumbra and core volume [20]. The collateral score was evaluated by digital subtraction angiography at the beginning of the procedure and categorized as follows: grade 0 (filling less than one-third of the occluded territory), grade 1 (collaterals are less than two-thirds of the occluded region), and grade 2 (collateralization fills more than two-thirds of the occluded territory) [4]. Successful recanalization was considered an mTICI $\geq$ 2b [21]. The time from onset to recanalization was defined as the time from symptom appearance or last known normal to reperfusion or abortion of the surgery if recanalization was not achieved [3].

Outcome measures

The normal range of serum sodium at admission was 135 – 145 mmol/L in our center, and sodium concentration < 135 mmol/L was regarded as hyponatremia [7]. MBE was defined as an increase in the NIHSS score of $\geq$ 4 or consciousness evaluation part of the NIHSS score $\geq$ 1 combined with (1) parenchymal hypodensity in more than 50% of the middle cerebral artery supply

territory, accompanied by local brain edema, such as lateral ventricle compression and sulcal effacement; (2) more than 5 mm of midline shift at the septum pellucidum or pineal gland with basal cistern occlusion; or (3) brain swelling of more than one-third of the hemisphere with an obvious midline shift [4, 19, 20, 22, 23]. To confirm the presence of MBE, planned head CT scans were performed immediately after the procedure and at 24 h and 48 h after surgery. CT was also conducted whenever there was a change in neurological symptoms or a trend toward deteriorated edema in the postoperative imaging findings. For patients with MBE, imaging examinations were performed every 12–24 h to evaluate cerebral edema. The mortality and functional outcome were evaluated by qualified personnel or physicians through in-person interviews at the clinic or telephone based on the mRS score (favorable functional outcome: mRS score 0–2; adverse functional outcome: mRS score 3–6; and mortality: mRS score 6). The imaging data (CT or MRI) acquired at least 30 days after MT were also reviewed to calculate the final infarct volume using the Pullicino formula [24, 25].

Statistical analysis

The selected variables were common in clinical practice or potentially related to the outcomes according to previous studies or our experience. The categorical variables are expressed as numbers (percentages) and were compared via the chi-square test or Fisher's exact test. Continuous variables with a normal distribution are presented as the means ± SDs and were compared via the Student's t test; otherwise, they are presented as medians (interquartile ranges) and were compared using the Mann–Whitney U test. Parameters that reached statistical significance ($p < 0.05$) in the univariate analysis were included in the multivariate regression model to explore the predictive value of hyponatremia for clinical outcomes (MBE, 90-day mortality and adverse function). Moreover, the relationships between the serum sodium concentration as a continuous variable and patient outcomes were also investigated via the above multivariate regression models. Considering that the serum sodium level can be affected by glucose, a sensitivity analysis was employed to explore the associations between glucose-corrected hyponatremia and clinical outcomes [26]. Moreover, a sensitivity analysis was also performed after excluding patients with hypernatremia (> 145 mmol/L) [2]. Weighted linear regression was used to assess the multicollinearity among variables in multivariate models, defined as a variance inflation factor (VIF) ≥ 5. A planned subgroup analysis was conducted by stratifying by age (either younger than 70 years or older than 70 years), sex, intravenous thrombolysis, history of hypertension, and occluded vessel region (ICA or MCA). The interaction between hyponatremia and these stratified variables was explored via the likelihood ratio test. A Kaplan–Meier curve was generated to show the cumulative incidence of mortality within 90 days of follow-up according to the presence of hyponatremia. Restricted cubic splines (RCSs) were utilized to pinpoint any nonlinear associations between hyponatremia and outcomes. The Sobel test was applied for mediation analysis to elucidate whether MBE mediated the association between hyponatremia and 90-day mortality/adverse function. The associations between hyponatremia and core volume (measured by CTP) or final infarct volume were analyzed with univariate and multivariate linear regression analyses. The statistical analysis was performed using the SPSS 25.0 (IBM SPSS Statistics, Armonk, NY, USA) and R programs (version 4.4.1), and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Four hundred and ninety-eight patients were treated with MT between January 2021 and June 2024 in our center, and 342 patients were ultimately enrolled in this study; the mean age was 70.6 ± 12.1 years, and males constituted 53.2% ($n = 175$) of the cohort. The selection process is depicted in Fig. 1. Fifty-two patients (15.2%) presented with hyponatremia at admission. Compared with patients without hyponatremia, those with hyponatremia had higher initial NIHSS scores; baseline ASPECTS; and potassium, platelet, and serum glucose levels. Furthermore, these patients were more likely to suffer from ICA occlusion (all $p < 0.05$, Table 1). Thirteen patients (3.8%) presented with hypernatremia and 39 (11.4%) with hyponatremia based on glucose-corrected serum sodium. The rates of frequent outcomes are displayed in Table 2, revealing a significantly greater incidence of postoperative MBE, 90-day mortality and adverse function in patients with hyponatremia than in those without hyponatremia (all $p < 0.05$). However, no significant difference in hemorrhagic transformation was found between the two groups (hyponatremia vs. nonhyponatremia = 40.2% vs. 29.3%, $p = 0.112$), and further multivariate analysis was not performed.

Relationship between hyponatremia and postoperative malignant brain edema

A total of 86 (25.1%) patients developed MBE after MT. Patients with hyponatremia had a significantly higher rate of MBE than those without hyponatremia (51.9% vs. 20.3%, $p < 0.001$; Table 2). The univariate analysis revealed that sex, initial NIHSS score, baseline

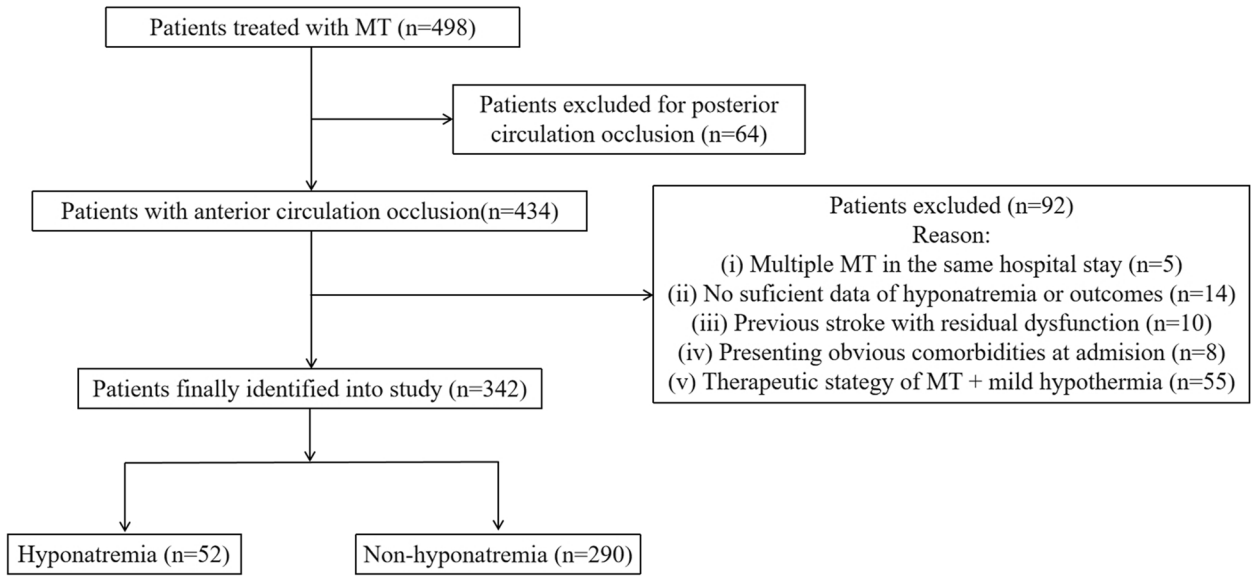

Fig. 1 Process of patient selection

ASPECTS, present HMCAS, occluded vessel region, collateral score, total calcium, lymphocytes, platelets, serum glucose, and triglycerides were potential factors associated with postoperative MBE (all $p < 0.05$, Supplementary Table S1). Considering that patients with good baseline ASPECTS rarely develop MBE, the baseline ASPECTS was dichotomized (> 8 and ≤ 8) in the multivariate regression model to predict MBE. After controlling for these confounding factors, multivariate analysis revealed that hyponatremia was significantly associated with postoperative MBE (OR 3.91, 95% CI 1.66–9.23; $p = 0.002$; Table 3). Moreover, as a continuous variable, lower serum sodium was independently associated with postoperative MBE (OR 0.90, 95% CI 0.83–0.97; $p = 0.009$). Sensitivity analysis with hyponatremia based on glucose-corrected serum sodium and a cohort excluding hypernatremia yielded similar results (OR 2.73, 95% CI 1.05–7.14, $p = 0.040$; OR 3.72, 95% CI 1.58–8.76, $p = 0.003$, respectively). No multicollinearity was found among these variables (VIF = 1.04 – 1.74). The RCS regression modeling demonstrated that the risk of MBE increased linearly with decreasing serum sodium (p for nonlinearity = 0.235, Fig. 2a). Subgroup analysis revealed a significant correlation between MBE and hyponatremia in females, patients aged both younger or older than 70 years, patients with a history of hypertension, patients who underwent intravenous thrombolysis, and patients who experienced MCA occlusion (Fig. 3a). Moreover, hyponatremia did not interact with these stratified variables (all p values for interaction > 0.05).

Relationship between hyponatremia and 90-day mortality

Ninety-three patients (27.2%) died within 90 days after MT. The details of the survivors and nonsurvivors are shown in Supplementary Table S2. Patients with hyponatremia had a more than twofold increased 90-day mortality rate compared with those without hyponatremia (57.7% vs. 21.7%, $p < 0.001$; Table 2). The Kaplan–Meier survival curve from Day 0 to Day 90 demonstrated the association between hyponatremia and a higher risk of mortality (Fig. 4). The multivariate analysis revealed that hyponatremia was significantly associated with 90-day mortality (OR 6.58, 95% CI 2.88 – 15.02, $p < 0.001$) after adjusting for sex, age, systolic pressure at admission, initial NIHSS score, present HMCAS, occluded vessel region, collateral score, successful recanalization, lymphocytes, platelets, serum glucose, and triglycerides, all of which reached significance in the univariate analysis. The multicollinearity among these variables was not apparent (VIF = 1.04 – 1.77). Furthermore, a low serum sodium concentration was a significant predictor of 90-day mortality (OR 0.89, 95% CI 0.83–0.96, $p = 0.002$; Table 3). Sensitivity analysis also revealed a significant relationship between 90-day mortality and hyponatremia with glucose-corrected serum sodium (OR 5.48, 95% CI 2.16 – 13.89, $p < 0.001$) and in the cohort excluding hypernatremia (OR 6.61, 95% CI 2.87 – 15.21, $p < 0.001$; Table 4). A linear relationship was found between reduced serum sodium and increased risk of 90-day

Table 1 Baseline characteristics between patients with and without admission hyponatremia

Variables	Hyponatremia	Non-hyponatremia	*P* value
Patients, n (%)	52 (15.2)	290 (85.8)	-
Demongraphics			
Female, n (%)	25 (48.1)	134 (46.2)	0.802
Age (years)	70.5 ± 13.5	70.6 ± 11.7	0.936
Smoker, n (%)	11 (21.2)	43 (14.8)	0.249
Alcoholism, n (%)	10 (19.2)	51 (17.6)	0.775
Medical history, n (%)			
Hypertension	29 (55.8)	136 (46.9)	0.238
Diuretics for medication	12 (23.1)	49 (16.9)	0.284
Diabetes mellitus	10 (19.2)	48 (16.6)	0.635
Coronary heart disease	5 (9.6)	38 (13.1)	0.485
Atrial fibrillation	23 (44.2)	164 (56.6)	0.100
Rheumatic heart disease	6 (11.5)	25 (8.6)	0.443
Heart failure	2 (3.8)	18 (6.2)	0.750
Prior stroke	6 (11.5)	36 (12.4)	0.859
Antiplatelet at onset	3 (5.8)	14 (4.8)	0.731
Anticoagulant at onset	6 (11.5)	29 (10.0)	0.736
Clinical and imaging characteristics			
Systolic pressure at admission (mmhg)	150.7 ± 36.9	143.1 ± 27.9	0.164
Diastolic pressure at admission (mmhg)	83.7 ± 19.7	83.8 ± 17.4	0.955
Intravenous thrombolysis, n (%)	13 (25.0)	96 (33.1)	0.248
Initial NIHSS score	17 (13–22)	14 (11–18)	**0.014**
Baseline ASPECTS	8 (7–9)	8 (8–9)	**0.014**
Present HMCAS, n (%)	16 (30.8)	108 (37.2)	0.371
Occluded vessel region, n (%)			**< 0.001**
ICA	32 (61.5)	97 (33.4)	
MCA	20 (38.5)	193 (66.6)	
TOAST classification, n (%)			0.691
LAA	17 (32.7)	85 (29.3)	
Cardioembolic	29 (55.8)	179 (61.7)	
Undetermined or others	6 (11.5)	26 (9.0)	
Collateral score, n (%)			0.247
Grade 0	16 (30.8)	61 (21.0)	
Grade 1	21 (40.4)	120 (41.4)	
Grade 2	15 (28.8)	109 (37.6)	
Time from onset to imaging (min)	276 ± 168	265 ± 126	0.596
Procedure details			
Time from onset to puncture (min)	328 ± 169	314 ± 124	0.489
Time from puncture to recanalization (min)	75 ± 47	68 ± 39	0.199
Time from onset to recanalization (min)	403 ± 173	382 ± 129	0.297
Stent implantation, n (%)	15 (28.8)	73 (25.2)	0.577
Successful Revascularization, n (%)	48 (92.3)	263 (90.7)	1.0
Laboratory findings			
Total calcium (mmol/L)	2.2 ± 0.1	2.2 ± 0.2	0.497
Potassium (mmol/L)	4.0 ± 0.5	3.8 ± 0.4	**0.042**
hsCRP (mg/L)	10.4 (2.0–18.4)	4.5 (1.4–13.1)	0.060
While blood cell, $\times 10^9$/L	10.0 ± 4.3	9.4 ± 3.1	0.295
Neutrophil, $\times 10^9$/L	8.2 ± 4.1	7.6 ± 3.2	0.198
Monocyte, $\times 10^9$/L	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.268

Table 1 (continued)

Variables	Hyponatremia	Non-hyponatremia	*P* value
Lymphocyte, $\times 10^9$/L	1.2 ± 0.8	1.4 ± 0.8	0.286
Hemoglobin, $\times 10^9$/L	124.4 ± 19.8	125.3 ± 18.9	0.749
Platelet, $\times 10^9$/L	179.4 ± 74.5	156.9 ± 72.6	**0.042**
Serum glucose at admission (mmol/L)	9.0 ± 3.7	7.9 ± 2.9	**0.026**
PT (s)	12.1 ± 1.3	12.5 ± 2.0	0.159
TT (s)	17.1 (15.8–18.6)	17.4 (16.3–18.1)	0.983
APTT (s)	29.9 ± 5.2	31.7 ± 12.2	0.290
Fibrinogen (g/L)	3.3 ± 1.3	3.0 ± 0.9	0.122
INR	1.0 (0.9–1.1)	1.0 (1.0–1.1)	0.542
Creatinine (umol/L)	75.3 ± 20.2	74.6 ± 22.7	0.845
Albumin (g/L)	38.8 ± 4.7	39.3 ± 4.2	0.456
Cholesterol (mmol/L)	4.3 ± 1.0	4.5 ± 1.1	0.304
Triglyceride (mmol/L)	1.3 (0.9–2.1)	1.2 (0.9–1.9)	0.589
Sodium at admission (mmol/L)	131.6 ± 3.8	139.9 ± 2.9	< 0.001
Sodium at 24 h after surgery (mmol/L)	138.2 ± 4.6	139.7 ± 4.1	0.013

NIHSS National Institute of Health Stroke Scale, *ICA* internal carotid artery, *MCA* middle cerebral artery, *LAA* large-artery atherosclerosis, *CRP* C-reactive protein, *PT* prothrombin time, *TT* thrombin time, *APTT* activated partial thromboplastin time, *INR* international normalized ratio

Table 2 Frequency of frequent outcomes between patients with and without admission hyponatremia

	Hyponatremia	Non-hyponatremia	*P* value
Hemorrhagic transformation, n (%)	21 (40.4)	85 (29.3)	0.112
Postoperative MBE, n (%)	27 (51.9)	59 (20.3)	< 0.001
90-day mortality, n (%)	30 (57.7)	63 (21.7)	< 0.001
90-day adverse function (mRS > 2), n (%)	41 (78.8)	160 (55.2)	0.001

MBE malignant brain edema

Table 3 Association between admission hyponatremia/serum sodium concentration and outcomes after mechanical thrombectomy

Outcomes	Crude		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Hyponatremia				
Postoperative MBE*	4.23 (2.29–7.82)	< 0.001	3.91 (1.66–9.23)	0.002
90-day mortality^	4.91 (2.65–9.11)	< 0.001	5.49 (2.48–12.14)	< 0.001
90-day adverse function (mRS > 2)&	3.03 (1.49–6.13)	0.002	3.25 (1.29–8.12)	0.012
Serum sodium concentration				
Postoperative MBE*	0.90 (0.85–0.96)	0.001	0.90 (0.83–0.97)	0.009
90-day mortality^	0.89 (0.85–0.95)	< 0.001	0.90 (0.84–0.96)	0.003
90-day adverse function (mRS > 2)&	0.94 (0.89–0.99)	0.025	0.93 (0.86–0.99)	0.044

* Adjusted for sex, initial NIHSS score, baseline ASPECTS, present HMCAS, occluded vessel region, collateral score, total calcium, lymphocyte, platelet, serum glucose, and triglyceride

^ Adjusted for sex, age, systolic pressure at admission, initial NIHSS score, present HMCAS, occluded vessel region, collateral score, successful recanalization, lymphocyte, platelet, serum glucose, and triglyceride

& Adjusted for sex, age, hypertension, initial NIHSS score, baseline ASPECTS, present HMCAS, occluded vessel region, collateral score, time from onset to recanalization, successful recanalization, total calcium, neutrophil, lymphocyte, platelet, serum glucose, and triglyceride

MBE malignant brain edema, *mRS* modified Rankin Scale

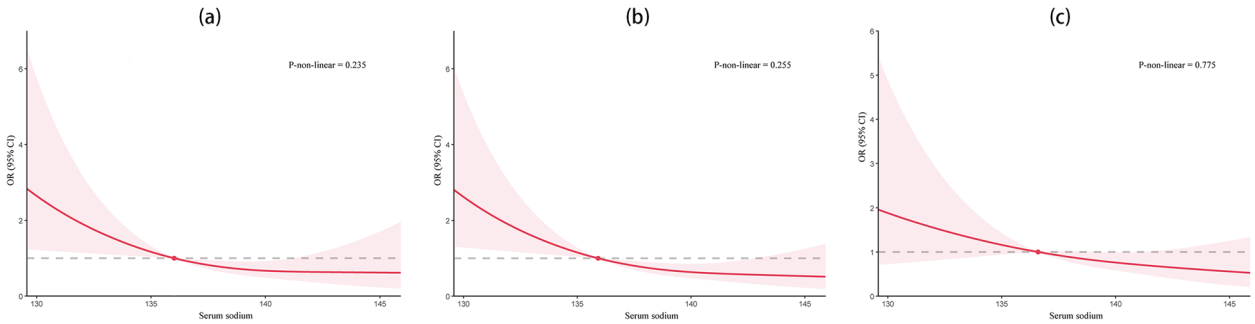

Fig. 2 Subgroup analysis revealing the associations between hyponatremia and clinical outcomes under different conditions. **a**: Malignant brain edema; **b**: 90-day mortality; **c**: 90-day adverse effects

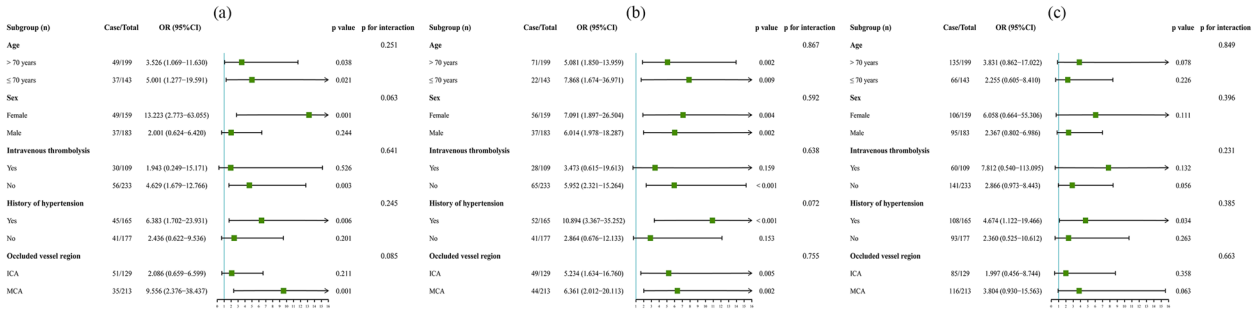

Fig. 3 Restricted cubic spline for the association between serum sodium levels and outcomes. (**a**) Malignant brain edema; (**b**) 90-day mortality; (**c**) 90-day adverse function

mortality in the RCS analysis (p for nonlinearity = 0.255, Fig. 2b). Subgroup analysis revealed an association between hyponatremia and 90-day mortality under most conditions, except for patients who underwent intravenous thrombolysis and without a history of hypertension (Fig. 3b).

Relationship between hyponatremia and 90-day adverse effects

Two hundred and one patients (58.8%) had obvious disability (mRS score > 2) at the 90-day follow-up. A significantly greater incidence of adverse functional outcomes was found in patients with hyponatremia than in those without it (78.8% vs. 55.2%, $p = 0.001$; Table 2). Confounding factors, including sex; age; hypertension; initial NIHSS score; baseline ASPECTS; present HMCAS; occluded vessel region; collateral score; time from onset to recanalization; successful recanalization; and total calcium, neutrophil, lymphocyte, platelet, serum glucose, and triglyceride levels, were confirmed via univariate analysis (Supplementary Table S3). After adjustment, multivariate analysis revealed that hyponatremia and low serum sodium levels were independently associated with 90-day adverse function (OR 3.25, 95% CI 1.29–8.12, $p = 0.012$; OR 0.93, 95% CI 0.86–0.99, $p = 0.044$, respectively) (Table 3). The multicollinearity of these factors was limited (VIF = 1.06 − 1.85). Sensitivity analysis of the cohort excluding hypernatremia also revealed this association (OR 3.21, 95% CI 1.25 − 8.24, $p = 0.015$), whereas the significance of glucose-corrected hyponatremia was marginal (OR 2.03, 95% CI 0.76 − 5.44, $p = 0.157$; Table 4). A negative linear correlation was observed between the serum sodium concentration and 90-day adverse function in the RCS analysis (p for nonlinearity = 0.775, Fig. 2c). Unfortunately, subgroup analysis revealed a significant correlation only in patients with a history of hypertension (Fig. 3c).

Relationships among hyponatremia, MBE, and 90-day outcomes

On the basis of the association between hyponatremia and clinical outcomes described above, we hypothesized that postoperative MBE might be a mediator linking hyponatremia at admission to 90-day outcomes. The mediation analysis revealed a mediating effect of MBE on the effects of hyponatremia on 90-day mortality (Fig. 5a) and adverse functions (Fig. 5b), and the regression coefficients changed by 18.6% and 23.9%, respectively.

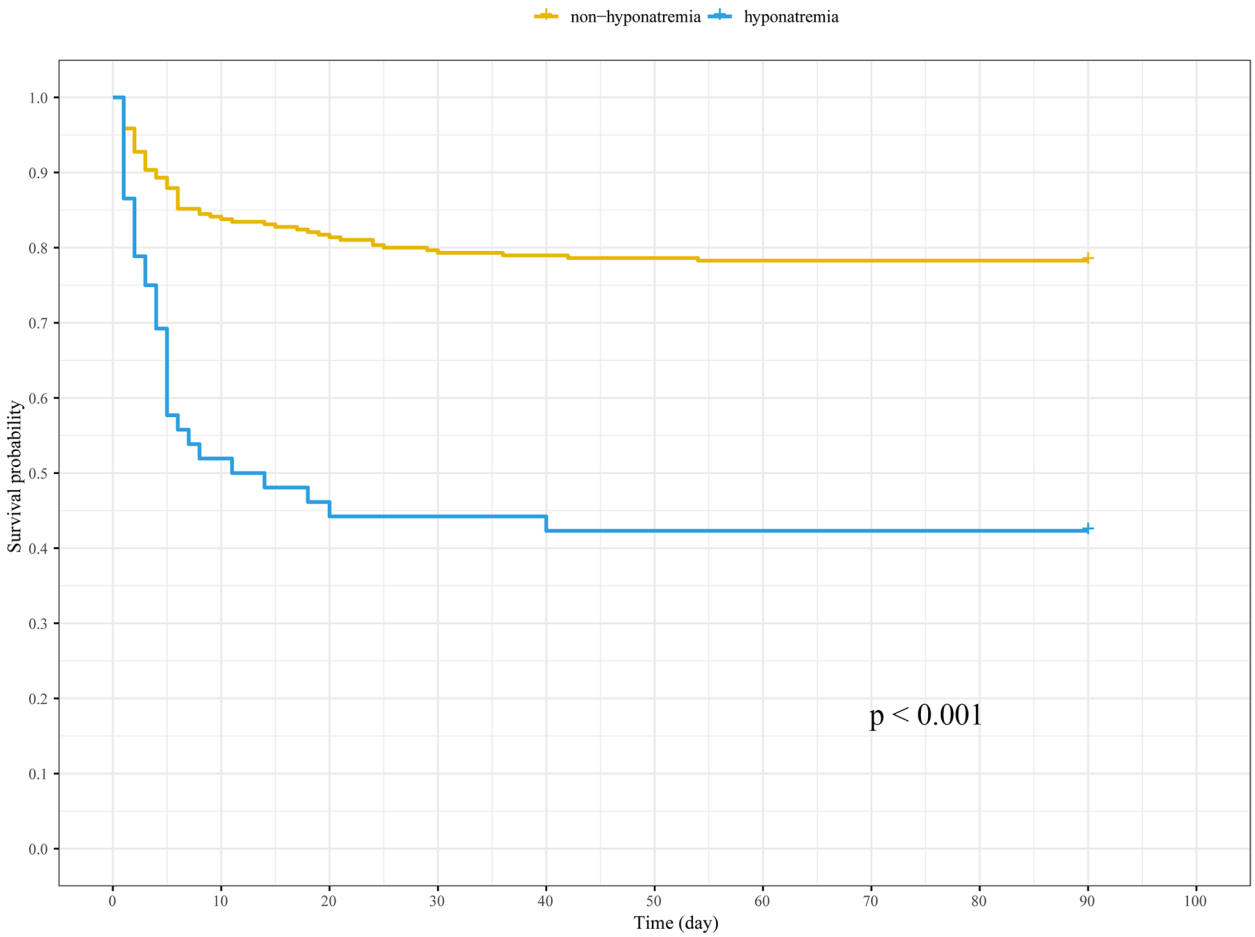

Fig. 4 The Kaplan–Meier curve indicating a greater risk of mortality in patients with hyponatremia than in those without hyponatremia

Table 4 Sensitive analysis involving glucose adjusted hyponatremia and cohort excluding hypernatremia to explore the association between admission hyponatremia and outcomes after mechanical thrombectomy

Outcomes	Crude		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Hyponatremia (glucose adjusted)				
Postoperative MBE*	3.35 (1.69–6.63)	0.001	2.73 (1.05–7.14)	0.040
90-day mortality^	3.74 (1.89–7.41)	< 0.001	4.60 (1.88–11.24)	0.001
90-day adverse function (mRS > 2)&	1.91 (0.92–3.98)	0.083	2.03 (0.76–5.44)	0.157
Cohort excluding hypernatremia				
Postoperative MBE*	4.36 (2.35–8.09)	< 0.001	3.72 (1.58–8.76)	0.003
90-day mortality^	4.93 (2.65–9.17)	< 0.001	5.46 (2.46–12.15)	< 0.001
90-day adverse function (mRS > 2)&	2.98 (1.47–6.03)	0.002	3.21 (1.25–8.24)	0.015

* Adjusted for sex, initial NIHSS score, baseline ASPECTS, present HMCAS, occluded vessel region, collateral score, total calcium, lymphocyte, platelet, serum glucose at admission, and triglyceride

^ Adjusted for sex, age, systolic pressure at admission, initial NIHSS score, present HMCAS, occluded vessel region, collateral score, successful revascularization, lymphocyte, platelet, serum glucose at admission, and triglyceride

& Adjusted for sex, age, hypertension, initial NIHSS score, baseline ASPECTS, present HMCAS, occluded vessel region, collateral score, time from onset to recanalization, successful revascularization, total calcium, neutrophil, lymphocyte, platelet, serum glucose at admission, and triglyceride

MBE malignant brain edema, *mRS* modified Rankin Scale

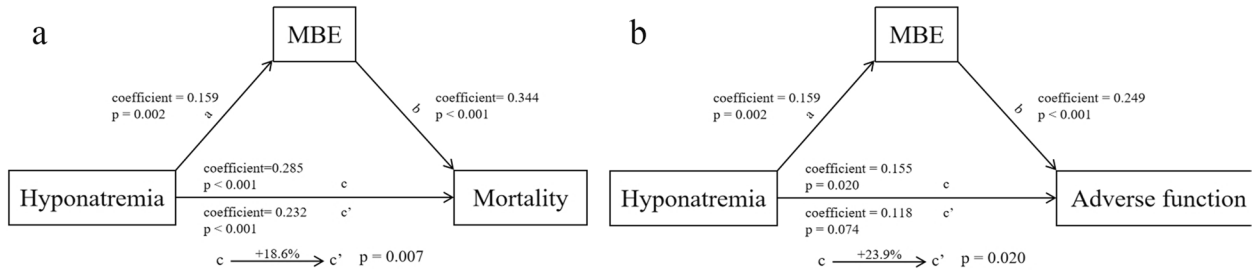

Fig. 5 Analysis of the mediating effect of postoperative malignant brain edema on the relationship between hyponatremia and 90-day mortality/adverse function. a: 90-day mortality; b: 90-day adverse effects

Relationships between hyponatremia and the core volume before mechanical thrombectomy and the final infarct volume

CTP imaging data were available for 128 patients (37.4%) in the cohort, including 18 (14.1%) with hyponatremia. The time from onset to imaging was not significantly different between patients with and without hyponatremia (428 ± 206 vs. 365 ± 136, $p = 0.097$). Patients with hyponatremia had significantly larger core volumes than those without hyponatremia (25.3 [20.7–39.7] vs. 12.3 [6.3–22.9] ml, $p < 0.001$). Significant associations were also found between a large core volume and hyponatremia, the serum sodium concentration, and hyponatremia in the cohort excluding hypernatremia (all $p < 0.05$) after adjusting for the initial NIHSS score, collateral score, total calcium level, lymphocyte count, and serum glucose level at admission (Table 5).

Information on the final infarct volume was obtained for 216 (63.2%) patients (85.5 ml IQR = 53.1 − 129.1), demonstrating that patients with hyponatremia ($n = 23$, 88.5%) had significantly larger final infarct volumes than patients without hyponatremia (124.6 [95.1 − 167.9] vs. 79.8 [48.4 − 122.8], $p < 0.001$). The multivariate linear regression analysis revealed a significant association between the final infarct volume and hyponatremia, the serum sodium concentration, glucose-corrected hyponatremia, and hyponatremia in the cohort excluding hypernatremia (all $p < 0.05$, Table 5) after adjusting for age, intravenous thrombolysis, the occluded vessel region, the initial National Institutes of Health Stroke Scale (NIHSS) score, the baseline ASPECTS, the collateral score, the time from onset to recanalization, and total calcium, hsCRP, and neutrophil, and lymphocyte levels.

Discussion

In this study, we investigated the relationship between hyponatremia and clinical outcomes in patients with LAO involving the anterior circulation treated by MT and demonstrated that hyponatremia was linked to both postoperative MBE and 90-day outcomes, even after controlling for confounding factors. Furthermore, a similar association was also found in the most sensitive analyses with glucose-corrected hyponatremia and the cohort excluding hypernatremia. Therefore, hyponatremia may serve as an independent predictor of poor prognosis in patients who undergo MT with LAO in the anterior circulation.

Hyponatremia is a readily observed electrolyte imbalance in hospitalized patients and has been recently reported to be associated with a poor prognosis in patients with AIS. In 2022, He et al. conducted a study of 963 patients with AIS who received intravenous thrombolysis therapy and reported that lower serum sodium levels were an independent risk factor for hemorrhagic transformation and poor clinical outcomes [11]. Previously, Soiza et al. published a study of 8391

Table 5 Association of hyponatremia with core infarction volume before mechanical thrombectomy, and final infarct volume

	Core infarction volume		Final infarct volume	
	Crude B (95% CI)	Adjusted B (95% CI)*	Crude B (95% CI)	Adjusted B (95% CI)^
Hyponatremia	12.22 (4.27 to 20.16)	10.38 (3.01 to 17.74)	45.22 (20.32 to 70.11)	27.00 (3.83 to 50.18)
Serum sodium concentration	−0.87 (−1.57 to −0.173)	−0.92 (−1.56 to −0.284)	- 2.82 (−4.87 to −0.769)	−2.65 (−4.47 to −0.84)
Hyponatremia (glucose adjusted)	9.03 (−0.31 to 18.37)	8.42 (−0.98 to 16.94)	44.21 (16.94 to 71.48)	27.84 (2.59 to 53.10)
Cohort excluding hypernatremia	11.73 (3.60 to 19.87)	9.12 (1.79 to 16.45)	45.61 (21.41 to 69.82)	26.70 (4.12 to 49.28)

* Adjusted for initial NIHSS score, collateral score, total calcium, lymphocyte, and serum glucose at admission

^ Adjusted for age, intravenous thrombolysis, occluded vessel region, initial NIHSS score, baseline ASPECTS, collateral score, time from onset to recanalization, total calcium, hsCRP, neutrophil, and lymphocyte

stroke patients with a 13.8% prevalence of hyponatremia at admission and suggested that hyponatremia was an independent predictor of poor outcomes after stroke in the short and long term [12]. Shima et al. performed a meta-analysis of 15 studies of 10,745 stroke cases in 2020 and revealed that patients with hyponatremia had a greater tendency toward in-hospital mortality than did those without hyponatremia [27]. However, only 2 studies have investigated the relationship between hyponatremia and outcomes in patients treated with mechanical thrombectomy/endovascular thrombectomy. Hong et al. reported that higher sodium levels at admission were an independent predictor of functional independence, early neurological recovery, and lower 3-month mRS scores in patients treated with endovascular thrombectomy [28]. In another study, in patients with reperfusion treatment for AIS, Pelouto et al. reported that hyponatremia was associated with a worse mRS score at 3 months and in-hospital mortality [2]. Moreover, consistent with our results, Pelouto et al. also failed to find an association between hyponatremia and hemorrhagic transformation. However, none of the above studies investigated the relationship between hyponatremia and MBE. In the present study, we also confirmed the associations of hyponatremia with 90-day mortality and adverse function in a relatively large cohort following MT. In addition, we first identified that hyponatremia was an independent predictor of postoperative MBE after MT.

Hyponatremia is commonly associated with poor prognosis in stroke patients. However, the mechanism of the relationship between hyponatremia and clinical outcomes is unclear in terms of whether hyponatremia, as a direct pathogenesis, contributes to poor prognosis or simply serves as an indicator reflecting disease severity. According to the above findings, we suggest that this association may be related to the following mechanisms. First, under the pathological conditions of AIS, hyponatremia is well known to aggravate cerebral edema by increasing the ionic gradient between the vascular compartment and interstitial fluid to provide the driving force for fluid shifts [11]. Even a small change in the percentage of the brain water content can reflect large changes in brain swelling that increase intracranial pressure and exacerbate capillary perfusion, which may lead to further ischemia [2]. Second, hyponatremia may disturb ionic transport between the internal and interstitial fluid, leading to deterioration of the AIS. For example, hyponatremia may activate the reverse mode of Na^{+}/Ca^{2+} exchange, causing an increase in the intracellular Ca2+concentration and the generation of reactive oxygen species that may reduce the recoverability of penumbral tissue [2, 29, 30]. Moreover, decreased serum sodium levels disrupt Na+/K+-ATPase activity, which can aggravate cytotoxic edema [31, 32]. Third, the increased permeability of the blood–brain barrier (BBB) contributes to the increase in serum components in the brain, leading to vasogenic cerebral edema, which serves as a vital etiology for postoperative MBE. Unfortunately, obvious ischemia secondary to LAO and mechanical injury of the vessel endothelium due to the MT procedure may aggravate dysfunction of the BBB [33]. Moreover, with breakdown of the BBB, hyponatremia can accelerate the development of vasogenic cerebral edema through disrupted ionic homeostasis [11]. Finally, the poor diagnosis of patients with hyponatremia may be the result of inappropriate sodium correction. Poststroke hyponatremia may be caused by comorbidities, medication used prior to admission, and syndromes such as inappropriate antidiuretic hormone (SIADH) or cerebral salt wasting syndrome (CSWS), but treatment for these etiologies is rather different [2, 34]. For example, SIADH is generally treated with fluid restriction, whereas CSWS is treated with sodium fluid [35]. However, on the basis of our data, we cannot identify the specific cause of hyponatremia to formulate a relevant therapeutic schedule. Furthermore, for patients with AIS caused by LAO, the early purpose of treatment is focused primarily on the reperfusion of ischemic brain tissue, and detecting the etiology of hyponatremia may be mostly neglected. In addition, we could not confirm the rapidity of the onset of hyponatremia, namely, acute or chronic hyponatremia, which is very common, with demyelination associated with rapid sodium correction [36]. Nevertheless, from a clinical perspective, we revealed that hyponatremia was significantly associated with postoperative MBE in patients treated with MT, even after controlling for confounding factors and verifying the results in a sensitivity analysis. Therefore, appropriate correction of hyponatremia may reduce the risk of MBE and improve patient prognosis.

The predictive value of hyponatremia for prognosis has been widely studied in patients with AIS; however, the potential process by which early sodium disorder affects later outcomes has not been reported. Although our study is unable to address causality, mediation analysis demonstrated that postoperative MBE may be a mediator linking hyponatremia at admission to 90-day outcomes. MBE is a catastrophic complication that leads to increased intracranial pressure, rapid deterioration of neurological function, and brain herniation [4]. In addition, the treatment efficacy of MBE is limited in that even with enhanced osmotic diuresis or decompressive craniectomy, a high risk of neurological dysfunction and mortality is still inevitable [5]. Therefore, the results of the mediation analysis indicated that restoring hyponatremia may be beneficial for reducing the risk of MBE and improving patient prognosis.

Certainly, there were also some limitations in this study. First, the retrospective, single-center design may limit the wide application of these results. Second, the etiology and duration of hyponatremia could not be identified based on our data, and further research in this area is encouraged to address this confusion. Third, potential bias may be introduced by the limited size of the cohort, which manifested as wide confidence intervals in some whole and subgroup analyses. Fourth, other potential variables that might be associated with clinical outcomes were not thoroughly explored in this study. Fifth, the results of this study were obtained based on statistical inference and merely showed a statistical correlation rather than a causal relationship, and interpretation should be combined with clinical practice.

Conclusion

Hyponatremia is a common electrolyte disturbance in AIS patients with LAO treated by MT and serves as an independent predictor of postoperative MBE and 90-day mortality and adverse function. Correction of hyponatremia may be appropriate to reduce the risk of postoperative MBE and unfavorable outcomes. Further experimental studies are essential to explore the basic mechanisms linking hyponatremia to outcomes.

Abbreviations

AIS	Acute ischemic stroke
LAO	Large artery occlusion
MT	Mechanical thrombectomy
MBE	Malignant brain edema
ICH	Intracerebral hemorrhage
SAH	Subarachnoid hemorrhage
ICA	Internal carotid artery
MCA	Middle cerebral artery
NIHSS	National Institute of Health Stroke Scale
mTICI	Modified thrombolysis in cerebral infarction
LAA	Large-artery atherosclerosis
TOAST	Trial of Org 10,172 in Acute Stroke Treatment
CT	Computed tomography
HMCAS	Hyperdense middle cerebral artery sign
ASPECTS	Alberta Stroke Program Early CT score
VIF	Variance inflation factor
RCS	Restricted cubic spline
SIADH	Syndrome of inappropriate antidiuretic hormone
CSWS	Cerebral salt wasting syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04051-5.

Supplementary Material 1

Acknowledgements

We appreciated all the medical staff in our stroke center.

Authors' contributions

Ao Qian drafted and revised the manuscript. Longyi Zheng performed statistical analysis and drafted the section of "2.3 Statistical analysis". Lun Li collected the data and made the tables. Jia Duan and Wenli Xing drew the figures. Shuang Tang conceived this study and offered the fundings.

Funding

This work was supported by the Research Project on Medical Youth Innovation in Sichuan Province (No. Q22014) and the Medical Research Project of Sichuan Province (No. S23006).

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Suining Central Hospital (KYLLKS20240174). Informed consent was obtained from the participants or their legal representatives.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 25 November 2024 Accepted: 21 January 2025
Published online: 28 January 2025

References

1. Cao W, Song Y, Bai X, et al. Systemic-inflammatory indices and clinical outcomes in patients with anterior circulation acute ischemic stroke undergoing successful endovascular thrombectomy. Heliyon. 2024;10(10):e31122. https://doi.org/10.1016/j.heliyon.2024.e31122.
2. Pelouto A, Reimer J, Hoorn EJ, et al. Hyponatremia is associated with unfavorable outcomes after reperfusion treatment in acute ischemic stroke. Eur J Neurol. 2024;31(3):e16156. https://doi.org/10.1111/ene.16156.
3. Huang X, Cai Q, Xiao L, et al. Influence of procedure time on outcome and hemorrhagic transformation in stroke patients undergoing thrombectomy. J Neurol. 2019;266(10):2560–70. https://doi.org/10.1007/s00415-019-09451-5.
4. Huang X, Yang Q, Shi X, et al. Predictors of malignant brain edema after mechanical thrombectomy for acute ischemic stroke. J Neurointerv Surg. 2019;11(10):994–8. https://doi.org/10.1136/neurintsurg-2018-014650.
5. Tracol C, Vannier S, Hurel C, et al. Predictors of malignant middle cerebral artery infarction after mechanical thrombectomy. Rev Neurol (Paris). 2020;176(7–8):619–25. https://doi.org/10.1016/j.neurol.2020.01.352.
6. Kalita J, Singh RK, Misra UK. Cerebral Salt Wasting Is the Most Common Cause of Hyponatremia in Stroke. J Stroke Cerebrovasc Dis. 2017;26(5):1026–32. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.12.011.
7. Qian A, Zheng L, He Z, et al. Predictive value of hyponatremia for short-term mortality in supratentorial spontaneous intracerebral hemorrhage: a single center study. Front Neurol. 2024;15:1301197. https://doi.org/10.3389/fneur.2024.1301197.
8. Tzoulis P, Bagkeris E, Bouloux PM. A case-control study of hyponatraemia as an independent risk factor for inpatient mortality. Clin Endocrinol (Oxf). 2014;81(3):401–7. https://doi.org/10.1111/cen.12429.
9. Maruhashi, T. and Y. Higashi, An overview of pharmacotherapy for cerebral vasospasm and delayed cerebral ischemia after subarachnoid hemorrhage. Expert Opin Pharmacother. 2021;22(12):1601–1614.https://doi.org/10.1080/14656566.2021.1912013
10. Saramma P, Menon RG, Srivastava A, et al. Hyponatremia after aneurysmal subarachnoid hemorrhage: Implications and outcomes. J Neurosci Rural Pract. 2013;4(1):24–8. https://doi.org/10.4103/0976-3147.105605.

11. He L, Guo ZN, Qu Y, et al. Hyponatremia Is Associated With Post-thrombolysis Hemorrhagic Transformation and Poor Clinical Outcome in Ischemic Stroke Patients. Front Mol Neurosci. 2022;15:879863. https://doi.org/10.3389/fnmol.2022.879863.
12. Soiza, R.L., K. Cumming, A.B. Clark, et al., Hyponatremia predicts mortality after stroke. Int J Stroke. 2015; 10 Suppl A100: 50–5.https://doi.org/10.1111/ijs.12564
13. Fofi L, Dall'armi V, Durastanti L, et al. An observational study on electrolyte disorders in the acute phase of ischemic stroke and their prognostic value. J Clin Neurosci. 2012;19(4):513–6. https://doi.org/10.1016/j.jocn.2011.07.041.
14. Rodrigues B, Staff I, Fortunato G, et al. Hyponatremia in the prognosis of acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014;23(5):850–4. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.07.011.
15. Sun Y, You S, Zhong C, et al. Neutrophil to lymphocyte ratio and the hematoma volume and stroke severity in acute intracerebral hemorrhage patients. Am J Emerg Med. 2017;35(3):429–33. https://doi.org/10.1016/j.ajem.2016.11.037.
16. Chen K, Huang W, Wang J, et al. Increased serum fibroblast growth factor 21 levels are associated with adverse clinical outcomes after intracerebral hemorrhage. Front Neurosci. 2023;17:1117057. https://doi.org/10.3389/fnins.2023.1117057.
17. Adams, H.P., Jr., B.H. Bendixen, L.J. Kappelle, et al., Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993; 24(1):35–41.https://doi.org/10.1161/01.str.24.1.35
18. Koo CK, Teasdale E, Muir KW. What constitutes a true hyperdense middle cerebral artery sign? Cerebrovasc Dis. 2000;10(6):419–23. https://doi.org/10.1159/000016101.
19. Zhang L, Li J, Yang B, et al. The risk and outcome of malignant brain edema in post-mechanical thrombectomy: acute ischemic stroke by anterior circulation occlusion. Eur J Med Res. 2023;28(1):435. https://doi.org/10.1186/s40001-023-01414-x.
20. Zeng W, Li W, Huang K, et al. Predicting futile recanalization, malignant cerebral edema, and cerebral herniation using intelligible ensemble machine learning following mechanical thrombectomy for acute ischemic stroke. Front Neurol. 2022;13:982783. https://doi.org/10.3389/fneur.2022.982783.
21. Zhang P, Chen L, Jiang Y, et al. Risk factors for and outcomes of poststroke pneumonia in patients with acute ischemic stroke treated with mechanical thrombectomy. Front Neurol. 2023;14:1023475. https://doi.org/10.3389/fneur.2023.1023475.
22. Wiącek M, Szymański M, Walewska K, et al. Blood Pressure Changes During Mechanical Thrombectomy for Acute Ischemic Stroke Are Associated With Serious Early Treatment Complications: Symptomatic Intracerebral Hemorrhage and Malignant Brain Edema. Front Neurol. 2022;13:884519. https://doi.org/10.3389/fneur.2022.884519.
23. Huang X, Xu J, Yang K, et al. Blood Pressure After Endovascular Thrombectomy and Malignant Cerebral Edema in Large Vessel Occlusion Stroke. Front Neurol. 2021;12:707275. https://doi.org/10.3389/fneur.2021.707275.
24. Gaudinski MR, Henning EC, Miracle A, et al. Establishing final infarct volume: stroke lesion evolution past 30 days is insignificant. Stroke. 2008;39(10):2765–8. https://doi.org/10.1161/strokeaha.107.512269.
25. Pullicino P, Nelson RF, Kendall BE, et al. Small deep infarcts diagnosed on computed tomography. Neurology. 1980;30(10):1090–6. https://doi.org/10.1212/wnl.30.10.1090.
26. Al-Kudsi RR, Daugirdas JT, Ing TS, et al. Extreme hyperglycemia in dialysis patients. Clin Nephrol. 1982;17(5):228–31.
27. Shima S, Niimi Y, Moteki Y, et al. Prognostic Significance of Hyponatremia in Acute Stroke: A Systematic Review and Meta-Analysis. Cerebrovasc Dis. 2020;49(5):531–9. https://doi.org/10.1159/000510751.
28. Hong, J.-B., W.K. Diprose, M.T.M. Wang, et al. Sodium Levels and Outcomes Following Endovascular Thrombectomy for Ischemic Stroke. Stroke Vasc Interv Neurol. 2022;2:e000221. https://doi.org/10.1161/SVIN.121.000221.
29. Oniki T, Teshima Y, Nishio S, et al. Hyponatraemia aggravates cardiac susceptibility to ischaemia/reperfusion injury. Int J Exp Pathol. 2019;100(5–6):350–8. https://doi.org/10.1111/iep.12338.
30. Seki S, Taniguchi M, Takeda H, et al. Inhibition by KB-r7943 of the reverse mode of the Na+/Ca2+ exchanger reduces Ca2+ overload in ischemic-reperfused rat hearts. Circ J. 2002;66(4):390–6. https://doi.org/10.1253/circj.66.390.
31. Helsper, S., F.A. Bagdasarian, X. Yuan, et al., Extended Ischemic Recovery After Implantation of Human Mesenchymal Stem Cell Aggregates Indicated by Sodium MRI at 21.1 T. Transl Stroke Res. 2022;13(4): 543–555.https://doi.org/10.1007/s12975-021-00976-4
32. Yin A, Guo H, Tao L, et al. NDRG2 Protects the Brain from Excitotoxicity by Facilitating Interstitial Glutamate Uptake. Transl Stroke Res. 2020;11(2):214–27. https://doi.org/10.1007/s12975-019-00708-9.
33. Krishnan R, Mays W, Elijovich L. Complications of Mechanical Thrombectomy in Acute Ischemic Stroke. Neurology. 2021;97(20 Suppl 2):S115-s125. https://doi.org/10.1212/wnl.0000000000012803.
34. Ehtesham M, Mohmand M, Raj K, et al. Clinical Spectrum of Hyponatremia in Patients with Stroke. Cureus. 2019;11(8):e5310. https://doi.org/10.7759/cureus.5310.
35. Gray JR, Morbitzer KA, Liu-DeRyke X, et al. Hyponatremia in Patients with Spontaneous Intracerebral Hemorrhage. J Clin Med. 2014;3(4):1322–32. https://doi.org/10.3390/jcm3041322.
36. Gankam Kengne, F., Adaptation of the Brain to Hyponatremia and Its Clinical Implications. J Clin Med. 2023;12(5).https://doi.org/10.3390/jcm12051714

Publisher's Note