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Association between Plasma Osmolality and Case Fatality within 1 Year after Severe Acute Ischemic Stroke

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Purpose: Plasma osmolality, a marker of dehydration, is associated with cardiovascular mortality. We aimed to investigate whether elevated plasma osmolality is associated with case fatality within 1 year after severe acute ischemic stroke.

Materials and Methods: We included severe ischemic stroke patients (defined as National Institutes of Health Stroke Scale ≥15 score) within 24 hours from symptom onset admitted to the Department of Neurology, West China Hospital between January 2017 and June 2019. Admission plasma osmolality was calculated using the equation 1.86*(sodium+potassium)+1.15*glucose+urea+14. Elevated plasma osmolality was defined as plasma osmolality >296 mOsm/kg, indicating a state of dehydration. Study outcomes included 3-month and 1-year case fatalities. Multivariable logistic regression was performed to determine independent associations between plasma osmolality and case fatalities at different time points.

Results: A total of 265 patients with severe acute ischemic stroke were included. The mean age was 71.2±13.1 years, with 51.3% being males. Among the included patients, case fatalities were recorded for 31.7% (84/265) at 3 months and 39.6% (105/265) at 1 year. Elevated plasma osmolality (dehydration) was associated with 3-month case fatality [odds ratio (OR) 1.98, 95% confidence interval (CI) 1.07–3.66, p=0.029], but not 1-year case fatality (OR 1.51, 95% CI 0.84–2.72, p=0.165), after full adjustment for confounding factors.

Conclusion: Elevated plasma osmolality was independently associated with 3-month case fatality, but not 1-year case fatality, for severe acute ischemic stroke.

Key Words: Plasma osmolality, dehydration, severe acute ischemic stroke, case fatality.

INTRODUCTION

Stroke is the second leading cause of death worldwide.[1] In China, the age-standardized mortality of stroke has remained over 100 cases per 100000 people in the recent decades.[2] Acute ischemic stroke with an initially severe neurologic deficit has been found to account for 36.4% of all ischemic strokes.[3] Severe anterior circulation ischemia is often associated with a large middle cerebral artery (MCA) territory infarction on later neuroimaging, causing a high risk of developing life-threatening brain edema and trans-tentorial herniation on patients.[4] Meanwhile, patients frequently have impaired consciousness on presentation due to severe posterior circulation ischemia,[5] which may increase the complexity of initial diagnosis. Due to the detrimental progression, severe acute ischemic stroke both of the anterior and posterior circulation carries high case fatalities in the short and long term.[6,7] Given the large burden of stroke mortality and disability, various radiologic, clinical, and biochemical parameters have been researched as predictors of case fatality after stroke.[8,9] Under this circumstance, identifying new factors with which to predict the prognosis for this group of patients is of paramount importance for clinicians to optimize management.

Plasma osmolality, reflecting the volume of extracellular flu-

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id, serves as an indicator of dehydration.[10] A recent study has shown that older patients (≥65 years old) presenting with acute ischemic stroke have high plasma osmolality levels, which represents a fluid depleted state.[11] Inadequate hydration accompanied by increased blood viscosity and decreased collateral circulation exacerbates brain hypo-perfusion after ischemia.[12,13] Elevated plasma osmolality has been shown to be a predictor of mortality in cardiovascular diseases, including myocardial infarction and heart failure,[14,15] but the association between plasma hyperosmolality and case fatality in severe acute ischemic stroke has not been well established. Therefore, the purpose of this study was to investigate the relationship between plasma osmolality and case fatalities at 3 months and 1 year after stroke among patients with severe acute ischemic stroke.

MATERIALS AND METHODS

Study population

We consecutively enrolled patients with ischemic stroke from January 2017 to June 2019 admitted to the Department of Neurology, West China Hospital, Sichuan University. The diagnosis of ischemic stroke was based on clinical characteristics and confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). Severe ischemic stroke was defined as severe neurological deficits with a National Institutes of Health Stroke Scale (NIHSS) score of 15 or above on admission.[3,16] The inclusion criteria were 1) age ≥18 years, 2) onset to admission time within 24 hours (h), and 3) meeting the clinical criteria of severe ischemic stroke. Patients were excluded if they 1) received osmotic agents like mannitol prior to the first blood draw, 2) presented with other severe complications or comorbidities, such as a malignant tumor and hepatic or renal failure, 3) lacked follow-up neuroimaging data, or 4) had missing follow-up information. The data of eligible patients were extracted from the Chengdu Stroke Registry Database, as described in a previous study.[17] The study was approved by The Biomedical Research Ethics Committee of West China Hospital, Sichuan University [Reference No. 2020 (174)], and informed consent was obtained from the participants or their next of kin.

Data collection

Demographic information and vascular risk factors were documented on admission, including information on age, sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, previous stroke (previous hemorrhagic and/or ischemic stroke), smoking, and alcohol consumption. Several aspects that reflected the severity of stroke, such as a NIHSS score, impaired consciousness, and large MCA infarction, were also assessed and recorded. The NIHSS score was evaluated on admission and at discharge in the neurology ward by a trained neurological physician according to an international scale.[18] An impaired consciousness was defined as the presence of stupor or coma on admission. Large MCA infarction was defined as the presence of hypo-density covering at least 1/3 of the MCA territory within 6 h or at least 1/2 of the MCA territory beyond 6 h with or without involvement of other arterial territories.[19,20] All patients had a baseline brain CT performed on admission to exclude intracranial hemorrhage. A follow-up CT or MRI was performed within 7 days after admission or if any neurological deterioration occurred. We also collected potentially dehydration-related clinical characteristics, such as vomiting, dysphagia, and incontinence. The etiology of stroke was classified by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[21] In-hospital treatments analyzed in our study included reperfusion therapy, osmotic therapy, and decompressive craniectomy. Stroke-related infectious complications, including stroke-associated pneumonia and urinary tract infection, were also recorded.[22] The estimated glomerular filtration rate (eGFR) was calculated using the equation $eGFR=186*SCr^{-1.154}*Age^{-0.203}*0.742$ [if female]$*1.233$ (if Chinese).[23]

Blood sample collection and assessment of plasma osmolality

Peripheral-venous blood samples were obtained on admission from the first blood draw prior to any medical intervention. Corresponding biochemical indices were analyzed via an automatic biochemical analyzer in the Department of Laboratory Medicine, West China Hospital. Plasma osmolality was determined by four biochemical components, including plasma sodium (Na^+), potassium (K^+), glucose, and urea. Plasma osmolality was calculated based on the Khajuria, et al.[24] formula: plasma osmolality$=1.86*(Na^+ + K^+)+1.15*$glucose$+$urea$+14$, which provides the best fit between measured and calculated osmolality.[25] In the formula mentioned above, all the units for the plasma constituents are millimoles per liter (mmol/L), and osmolality was expressed as milliosmoles per kilogram (mOsm/kg). Since the cutoff point of 296 mOsm/kg based on the A Khajuria equation was reported to have the best diagnostic capability in screening for dehydration status,[26] elevated plasma osmolality was defined as plasma osmolality >296 mOsm/kg, which was consistent with a state of dehydration.

Outcome definitions and assessment

The primary endpoint was 3-month case fatality, and the secondary endpoint was 1-year case fatality. Case fatalities were defined as the proportion of overall death (regardless of cause) occurring within 3 months and 1 year after stroke onset, respectively.[8] All included patients were followed up prospectively by our research team during the first year after stroke via telephone interviews. A structured follow-up form was designed to conduct the follow up. If a patient died, we recorded the date of death or month of death if the specific date of death was not available. Modified Rankin Score (mRS) was evaluated and recorded at 3 months and 1 year after stroke onset.

Statistical analysis

We used descriptive statistics to show baseline characteristics. Continuous variables are expressed as a mean±standard deviation or median (interquartile range) as appropriate. Categorical variables are presented as a frequency and percentage. We conducted Student's t test or Mann-Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, when appropriate. To evaluate the effect of plasma osmolality on stroke case fatalities, univariable and multivariable logistic regression models were designed. For controlling confounding factors, both the significant variables in the univariable model and clinically significant variables were included in the multivariable models. To evaluate the robustness of the primary finding, we conducted stratified logistic regression analysis. The differences between subgroups were tested by interaction analysis using a likelihood ratio test. When appropriate, the results are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA), and figures were drawn by the GraphPad Prism 7 (GraphPad Software Inc, LaJolla, CA, USA). A two side $p<0.05$ was statistically significant.

RESULTS

Characteristics of the study cohort

From January 2017 to June 2019, 1317 patients within 24 hours after stroke onset were screened in the study, and 319 patients presented with severe acute ischemic stroke. After excluding patients who received osmotic therapy prior to the first blood draw (n=9), patients with a malignant tumor or hepatic or renal failure (n=12), patients with incomplete neuroimaging data (n=14), and patients lacking follow-up information (n=19), we included 265 patients for final analysis. The first blood draw was collected within 0–3 h [46.0% (122/265)], 3–9 h [47.5% (126/265)], 9–12 h [2.6% (7/265)], and 12–24 h [3.8% (10/265)] from stroke onset. Among the included patients, the average age was 71.2±13.1 years, and 51.3% were male. The median NIHSS score on admission was 20 (interquartile range, 17–22). The mean plasma osmolality value was 295±6.1 mOsm/kg (range, 267–317 mOsm/kg).

Characteristics of plasma osmolality levels and case fatalities

Among the 265 subjects, 38.1% (101/265) were found to be dehydrated based on a plasma osmolality >296 mOsm/kg at admission. The characteristics of plasma osmolality levels and case fatalities are presented in Table 1. Patients with elevated plasma osmolality were older and had a higher proportion of diabetes, impaired consciousness, and vomiting. There was a tendency for higher proportions of male sex and hypertension and a higher rate of decompressive craniectomy in the hyper-

Table 1. Patient Characteristics and Outcomes Stratified according to Plasma Osmolality Levels

Variables	Plasma osmolality (mOsm/kg)		*p* value
	≤296 (n=164)	>296 (n=101)	
Demographics			
Age, yr	74 (61–80)	75 (66–84)	0.044
Male	91 (55.5)	45 (44.6)	0.084
Onset to admission time, hours	4 (3–6)	4 (3–6)	0.967
Vascular risk factors			
Hypertension	88 (53.7)	66 (65.3)	0.061
Diabetes	25 (15.2)	37 (36.6)	<0.001
Hyperlipidemia	12 (7.3)	8 (7.9)	0.857
Atrial fibrillation	93 (56.7)	58 (57.4)	0.909
Previous stroke	23 (14.0)	14 (13.9)	0.970
Smoking	52 (31.7)	23 (22.8)	0.117
Alcohol consumption	19 (11.6)	14 (13.9)	0.586
Clinical characteristics			
NIHSS on admission	19 (17–22)	20 (17–24)	0.142
Impaired consciousness	65 (39.6)	53 (52.5)	0.041
Vomiting	21 (12.8)	31 (30.7)	<0.001
Dysphagia	9 (5.5)	1 (1.0)	0.125
Incontinence	29 (17.7)	26 (25.7)	0.116
Large MCA infarction	76 (46.3)	51 (50.5)	0.511
TOAST classification			0.870
Large-artery atherosclerosis	57 (34.8)	36 (35.6)	
Small-artery occlusion	0 (0)	0 (0)	
Cardio-embolism	79 (48.2)	49 (48.5)	
Other etiology	4 (2.4)	1 (1)	
Undetermined etiology	24 (14.6)	15 (14.9)	
Treatments during hospitalization			
Reperfusion therapy			0.683
None	78 (47.6)	52 (51.5)	
Thrombolysis only	21 (12.8)	16 (15.8)	
Thrombectomy only	47 (28.7)	23 (22.8)	
Thrombolysis and thrombectomy	18 (11.0)	10 (9.9)	
Osmotic therapy	127 (77.4)	79 (78.2)	0.882
Decompressive craniectomy	10 (6.1)	1 (1.0)	0.088
Stroke-associated pneumonia	111 (67.7)	77 (76.2)	0.136
Urinary tract infection	44 (26.8)	25 (24.8)	0.708
Baseline values for osmolality			
Osmolality, mOsm/kg	291.1±4.1	300.7±4.0	<0.001
Sodium, mmol/L	137.4±2.6	140.5±2.0	<0.001
Potassium, mmol/L	3.7±0.4	3.7±0.5	0.962
Glucose, mmol/L	7.4 (6.2–8.6)	8.2 (7.0–11.9)	<0.001
Urea, mmol/L	5.6 (4.7–6.9)	7.0 (5.5–8.7)	<0.001
eGFR (mL/min/1.73 m^2)	109 (90–134)	96 (75–113)	<0.001
NIHSS at discharge*	14 (10–18)	15 (10–26)	0.284
Death in hospital	12 (7.3)	15 (14.9)	0.049
mRS at 3 months	4 (3–5)	5 (4–6)	0.002
mRS at 1 year	4 (2–6)	6 (3–6)	0.047
Case fatality			
3 months	40 (24.4)	44 (43.6)	0.001
1 year	54 (32.9)	51 (50.5)	0.005

NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; TOAST, Trial of Org 10172 in Acute Stroke Treatment classification; mRS, modified Rankin Score; eGFR, estimated Glomerular Filtration Rate.
Data are presented as mean±standard deviation, median (interquartile range) or n (%).
*Due to death in a hospital, NIHSS at discharge was available only from those alive at discharge.

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osmolality group (p=0.084, 0.061, and 0.088, respectively). Compared with patients in the non-hyperosmolality group, those in the hyperosmolality group had relatively poorer renal function evaluated by eGFR (median 109 vs. 96 mL/min/1.73 m^2, p< 0.001). Moreover, patients with elevated plasma osmolality were more likely to have greater levels of plasma sodium, glucose, and urea values (all p<0.001). Regarding the short- and long-term functional outcomes assessed by mRS at 3 months and 1 year after stroke onset, patients in the hyperosmolality group had more adverse functional outcomes (p=0.002 and 0.047, respectively). With regard to case fatalities, patients with elevated plasma osmolality had higher case fatalities both at 3 months and 1 year (all p<0.05).

Association between plasma osmolality and case fatalities

Univariable logistic regression models are shown in Table 2. NIHSS on admission, impaired consciousness, large MCA in-

Table 2. Univariable Logistic Regression Analysis for Potential Confounding Factors between Plasma Osmolality and Case Fatalities

Variables	3-month case fatality		1-year case fatality	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Demographics				
Age, yr	1.01 (0.99–1.04)	0.174	1.02 (1.00–1.04)	0.059
Male	0.99 (0.59–1.67)	0.977	1.01 (0.62–1.65)	0.977
Onset to admission time, hours	0.96 (0.93–1.00)	0.050	0.99 (0.96–1.02)	0.452
Vascular risk factors				
Hypertension	1.26 (0.74–2.14)	0.394	1.30 (0.78–2.14)	0.311
Diabetes	1.51 (0.83–2.73)	0.177	1.47 (0.83–2.61)	0.190
Hyperlipidemia	0.92 (0.34–2.48)	0.865	0.81 (0.31–2.10)	0.661
Atrial fibrillation	1.01 (0.60–1.70)	0.971	0.95 (0.58–1.56)	0.833
Previous stroke	0.90 (0.42–1.92)	0.782	1.35 (0.67–2.72)	0.398
Smoking	0.86 (0.48–1.53)	0.603	0.81 (0.47–1.40)	0.449
Alcohol consumption	0.79 (0.35–1.77)	0.560	0.99 (0.47–2.09)	0.977
Clinical characteristics				
NIHSS on admission	1.06 (1.01–1.12)	0.023	1.06 (1.01–1.12)	0.024
Impaired consciousness	1.71 (1.01–2.88)	0.044	1.81 (1.10–2.97)	0.020
Vomiting	1.61 (0.86–3.02)	0.135	2.27 (1.23–4.20)	0.009
Dysphagia	0.53 (0.11–2.54)	0.425	0.64 (0.16–2.54)	0.529
Incontinence	1.30 (0.70–2.43)	0.404	1.79 (0.98–3.26)	0.056
Large MCA infarction	2.87 (1.67–4.92)	<0.001	2.25 (1.36–3.72)	0.002
TOAST classification				
Large-artery atherosclerosis	Reference		Reference	
Small-artery occlusion	NA	NA	NA	NA
Cardio-embolism	0.60 (0.34–1.08)	0.086	0.62 (0.36–1.08)	0.088
Other etiology	1.16 (0.18–7.27)	0.877	0.85 (0.14–5.30)	0.858
Undetermined etiology	1.09 (0.50–2.34)	0.836	1.34 (0.63–2.83)	0.450
Treatments during hospitalization				
Reperfusion therapy				
None	Reference		Reference	
Thrombolysis only	0.58 (0.24–1.37)	0.214	0.45 (0.20–1.04)	0.060
Thrombectomy only	1.40 (0.76–2.55)	0.277	1.33 (0.74–2.38)	0.340
Thrombolysis and thrombectomy	0.57 (0.22–1.51)	0.260	0.56 (0.23–1.37)	0.206
Osmotic therapy	2.40 (1.17–4.89)	0.017	2.28 (1.19–4.35)	0.013
Decompressive craniectomy	0.47 (0.10–2.21)	0.336	0.56 (0.15–2.16)	0.398
Stroke-associated pneumonia	3.81 (1.89–7.69)	<0.001	3.80 (2.02–7.14)	<0.001
Urinary tract infection	0.70 (0.38–1.28)	0.245	0.82 (0.47–1.45)	0.503
eGFR (mL/min/1.73 m^2)	1.00 (0.99–1.00)	0.319	0.99 (0.99–1.00)	0.134
Plasma osmolality (continuous)	1.08 (1.03–1.13)	0.001	1.06 (1.02–1.11)	0.006
Plasma osmolality (>296 mOsm/kg)	2.39 (1.41–4.07)	0.001	2.08 (1.25–3.45)	0.005

OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; TOAST, Trial of Org 10172 in Acute Stroke Treatment classification; eGFR, estimated Glomerular Filtration Rate; NA, not available due to limited sample size.

farction, osmotic therapy, and stroke-associated pneumonia were significantly associated with case fatalities at 3 months and 1 year (p<0.05). Additionally, vomiting was found to be possible confounding factor associated with case fatality at 1 year.

In multivariable logistic regression adjusting for age, male sex, diabetes, NIHSS on admission, impaired consciousness, vomiting, large MCA infarction, osmotic therapy, and stroke-associated pneumonia. A plasma osmolality increase by 1 mOsm/kg was significantly associated with case fatality at 3 months (OR 1.06, 95% CI 1.01–1.12, p=0.025) (Table 3). When dividing patients into two groups according to hydration status, patients with dehydration (plasma osmolality >296 mOsm/kg) were independently associated with case fatality at 3 months (OR 1.98, 95% CI 1.07–3.66, p=0.029). Other statistically significant variables related to case fatality at 3 months in multivariable logistic regression were large MCA infarction and stroke-associated pneumonia. With regard to case fatality at 1 year, neither plasma osmolality increase by 1 mOsm/kg nor elevated plasma osmolality achieved statistical significance (OR 1.04, 95% CI 0.99–1.09, p=0.144; OR 1.51, 95% CI 0.84–2.72, p=0.165, respectively) after full adjustment for confounding factors.

Subgroup analysis

Many factors are known to influence plasma osmolality, such as older age with decreased thirst, diabetes with a poor control of plasma glucose, and osmotic therapy with osmotic diuresis. Meanwhile, large MCA infarction and impaired consciousness are also important factors related to case fatality and dehydration. Considering possible reverse causality mentioned above, we stratified patients according to age groups (<65 years or ≥65 years), diabetes, osmotic therapy, large MCA infarction, and impaired consciousness and further conducted a stratified logistic regression analysis. The model was not adjusted for the stratification variable in each stratified analysis. As shown in Fig. 1, the interactions between these potential modifiers and elevated plasma osmolality (>296 mOsm/kg) on case fatality were not significant (All p for interaction >0.05).

DISCUSSION

In this study, we found that among patients with severe acute ischemic stroke, elevated plasma osmolality (>296 mOsm/kg), as a marker of dehydration, was associated with an increased risk of case fatality at 3 months, whereas elevated plasma osmolality seemed to be unrelated to case fatality at 1 year.

Case fatality is regarded as a quality marker of stroke management and is commonly used to document the success of stroke care.[27] A previous study reported that the 3-month and 1-year case fatalities of ischemic stroke were 18.4% and 31.6%, respectively.[28] Our study demonstrated that case fatalities for severe acute ischemic stroke were 31.7% at 3 months and 39.6% at 1 year. The case fatalities in our study were higher at different time points, compared with other studies. After excluding vari-

Table 3. Multivariable Logistic Regression Analysis between Plasma Osmolality and Case Fatalities

Variables	3-month case fatality		1-year case fatality	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Plasma osmolality (continuous)	1.06 (1.01–1.12)	0.025	1.04 (0.99–1.09)	0.144
Age	1.00 (0.98–1.03)	0.759	1.01 (0.99–1.03)	0.343
Male	0.89 (0.48–1.64)	0.699	0.95 (0.53–1.70)	0.863
Diabetes	1.17 (0.58–2.36)	0.666	1.26 (0.64–2.47)	0.500
NIHSS on admission	1.06 (0.99–1.13)	0.118	1.04 (0.98–1.11)	0.217
Impaired consciousness	1.02 (0.52–2.00)	0.961	1.16 (0.61–2.21)	0.649
Vomiting	1.23 (0.61–2.48)	0.560	2.03 (1.03–3.99)	0.041
Large MCA infarction	2.49 (1.35–4.59)	0.003	1.80 (1.01–3.19)	0.046
Osmotic therapy	1.49 (0.66–3.37)	0.342	1.55 (0.74–3.24)	0.249
Stroke-associated pneumonia	2.96 (1.38–6.35)	0.005	3.00 (1.51–5.97)	0.002
Plasma osmolality (>296 mOsm/kg)	1.98 (1.07–3.66)	0.029	1.51 (0.84–2.72)	0.165
Age	1.00 (0.98–1.03)	0.742	1.01 (0.99–1.03)	0.330
Male	0.92 (0.50–1.70)	0.790	0.98 (0.54–1.75)	0.931
Diabetes	1.26 (0.63–2.49)	0.516	1.32 (0.68–2.55)	0.412
NIHSS on admission	1.05 (0.98–1.13)	0.132	1.04 (0.98–1.11)	0.231
Impaired consciousness	1.04 (0.53–2.04)	0.904	1.18 (0.62–2.24)	0.616
Vomiting	1.13 (0.55–2.32)	0.739	1.93 (0.97–3.85)	0.062
Large MCA infarction	2.53 (1.37–4.67)	0.003	1.81 (1.02–3.21)	0.044
Osmotic therapy	1.45 (0.65–3.25)	0.369	1.54 (0.74–3.22)	0.250
Stroke-associated pneumonia	2.99 (1.40–6.40)	0.005	3.01 (1.52–5.99)	0.002

OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery.

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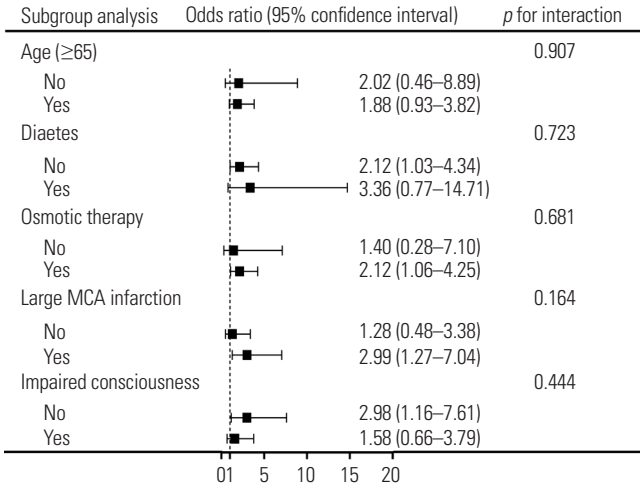

Fig. 1. Association between elevated plasma osmolality (>296 mOsm/kg) and case fatality at 3 months after stroke in stratification analyses. MCA, middle cerebral artery.

ability in study design, the differences were largely attributed to the severity of stroke, as stroke severity was a leading determinant of death. Our research subjects all had severe acute ischemic stroke, which likely explains the higher number of fatalities.

Dehydration has become a common concern after stroke. Although multiple indices could be applied to assess dehydration, such as blood urea nitrogen/creatinine ratio, urea/creatinine ratio, and plasma osmolality,[29] there is no standard approach. The prevalence of dehydration after acute stroke ranges from 4.5% to 42% according to different evaluation indices and cutoffs.[30,31] Our study showed that the incidence of dehydration (admission plasma osmolality >296 mOsm/kg) was 38.1%, which fell in the wide range mentioned above. Among various dehydration-related indices, plasma osmolality is sensitive and likely to be the best indicator for assessing dehydration state. Since the osmolality of human plasma is regulated by neuroendocrine mechanisms to a narrow range,[32] a slight elevation in plasma osmolality could reflect compromised extracellular volume.

Currently, only a few studies have evaluated associations between plasma osmolality and mortality in stroke. Bhalla, et al.[33] suggested that elevated plasma osmolality at admission results in 2.4-fold higher OR of 3-month mortality after stroke. In that work, the authors included 167 patients with acute stroke (89% ischemic stroke, 10% hemorrhagic stroke, 1% unclassified stroke). However, few studies have explored a uniform population with severe acute ischemic stroke. We demonstrated an independent association between elevated plasma osmolality and 3-month case fatality with a 1.98-fold higher OR. The result was similar with the previous study and confirmed that elevated plasma osmolality plays a role in predicting short-term case fatality in individuals with severe acute ischemic stroke. Moreover, we explored the association between admission plasma osmolality and 1-year case fatality after stroke. However, the association did not reach significance. As in another study, Ock and his colleagues[34] explored the effects of hyperglycemia and hyperosmolality on clinical outcomes among ischemic stroke patients. They also failed to find an association for hyperosmolality (with or without hyperglycemia) or hyperglycemia alone with death either at discharge or at 6 months after stroke onset. Our and Ock's studies may imply that elevated plasma osmolality more likely serves as a predictor of short-term case fatality, but not long-term case fatality, after stroke.

Several plausible mechanisms may explain how elevated plasma osmolality exerts fatal effects on stroke patients. First, hyperosmotic stress promotes the flow of water out of the cell, causing cell shrinkage.[35] This dramatic change in cell morphology could disrupt crucial intracellular components, including the nucleus and mitochondrion, which would be accompanied by energy generation failure, as well as the activation of apoptotic signaling pathways and finally cell death.[36,37] Second, elevated plasma osmolality as an inflammatory stimulus is often characterized by an upregulation of inflammatory cytokines, such as TNF, IL-1β, IL-6, and IL-8.[38] These components are strongly associated with ischemic stroke progression. Third, hyperosmolality reflects a state of inadequate hydration. Studies have shown that dehydration induces a decline in cerebral blood flow in the internal carotid and middle cerebral arteries without affecting the cerebral metabolic rate for oxygen.[39] The absolute reduction of cerebral blood flow and relative increase in cerebral oxygen metabolism can aggravate existing brain damage after brain ischemia and finally result in poor outcomes.[40]

Some limitations to this study need to be taken into consideration. First, our data were collected at a single center and analyzed retrospectively with a relatively small sample size. We first provided a clue that plasma osmolality may serve as a potential predictor for case fatality in severe acute ischemic stroke. Second, although many different calculated plasma osmolality equations could be used to assess dehydration status, there is no exclusive gold standard.[25] Nonetheless, we chose A Khajuria's equation to calculate plasma osmolality because it shows excellent concordance with measured osmolality.[24,26] In addition, calculated plasma osmolality, which integrates routine biochemical variables into a single index, is a feasible and noninvasive measure with which to reflect dehydration. Third, since plasma osmolality is dynamic, we only utilized admission plasma osmolality. Thus, we cannot draw a conclusion on whether correction of dehydration in these subjects would result in improved survival.

In conclusion, we found elevated plasma osmolality, an indicator of dehydration, to be associated with increased risk of 3-month case fatality in severe acute ischemic stroke. However, we failed to find an association between elevated plasma osmolality and risk of 1-year case fatality. Further studies are needed to explore the relationship between plasma osmolality and long-term case fatality and to investigate whether pre-

vention of dehydration could improve survival after stroke.

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AUTHOR CONTRIBUTIONS

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