Journal of Intensive Medicine 2 (2022) 274–281

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Original Article

Increase in chloride from baseline is independently associated with mortality in intracerebral hemorrhage patients admitted to intensive care unit: A retrospective study

Dawei Zhou, Tong Li*, Dong Zhao, Qing Lin, Dijia Wang, Chao Wang, Rongli Zhang

Department of Critical Care Medicine, Beijing Tongren Hospital, Capital Medical University, No.1 Dongjiaominxiang Street, Dongcheng District, Beijing 100730, China

ARTICLE INFO

Keywords:
Intracerebral hemorrhage
Hyperchloremia
Normal saline
Serum chloride
Mortality

ABSTRACT

Background: Hyperchloremia is associated with increased mortality in critically ill patients. The objective of this study was to investigate the association between increased chloride levels and mortality outcomes in intracerebral hemorrhage (ICH) patients admitted to the intensive care unit (ICU).

Methods: We performed a retrospective study of all patients diagnosed with ICH and included in the Medical Information Mart for Intensive Care (MIMIC-III) from 2001 to 2012. Inclusion criteria were the first diagnosis of ICH, ICU length of stay (LOS) over 72 h, and not receiving hypertonic saline treatment. Serum chloride perturbation within 72 h of admission was evaluated as a predictor of outcomes. The increase in chloride from baseline was dichotomized based on an increase in chloride in 72 h (≤5 mmol/L or >5 mmol/L). The primary outcome was 90-day mortality.

Results: A total of 376 patients (54.5% male, median age 70 years, interquartile range:58–79 years) were included. The overall 90-day mortality was 32.2% (n=121), in-hospital mortality was 25.8% (n=97), and Day 2 acute kidney injury (AKI) occurred in 29.0% (n=109) of patients. The prevalence of hyperchloremia on admission, during the first 72 h, and an increase in chloride (>5 mmol/L) were 8.8%, 39.4%, and 42.8%, respectively. After adjusting for confounders, the hazard ratio of increase in chloride (>5 mmol/L) was 1.66 (95% confidence interval:1.05–2.64, P=0.031). An increase in chloride (>5 mmol/L) was associated with a higher odds ratio for 90-day mortality in both the AKI and non-AKI groups.

Conclusions: An increase in chloride from baseline is common in adult patients with ICH admitted to ICU. The increase is significantly associated with elevated mortality. These results support the significance of diligently monitoring chloride levels in these patients.

Introduction

Acute spontaneous intracerebral hemorrhage (ICH) affects approximately 2 million people globally each year. It is a life-threatening illness with a poor prognosis and few proven treatments [1–3]. Dysnatremias have received significant attention in ICH patients, [4–6] but chloride, a major strong anion in the blood, has been the focus of less research [7].

Accumulating evidence has shown a correlation between hyperchloremia and outcomes in critically ill patients with sepsis, sepsis shock, trauma, severe pancreatitis, non-cardiac surgery, and stroke [8–13]. Ditch et al. [14] showed hyperchloremia – not concomitant hypernatremia – independently predicts early mortality in critically ill patients with moderate-severe traumatic brain injury. Riha et al. [15] found higher in-hospital mortality rates in ICH patients who developed moderate hyperchloremia (chloride ≥115 mmol/L) during treatment with continuous infusion of 3% hypertonic saline. However, the relationship between hyperchloremia and outcome is unknown for ICH patients not administered hypertonic saline.

The purpose of this study was to determine the association between 90-day mortality in ICH patients admitted to the intensive care unit (ICU) and an increase in the chloride level during the first 72 h of admission. We hypothesized that a perturba-

* Corresponding author.
E-mail addresses: tricumd@126.com, tryyicu@aliyun.com (T. Li).

https://doi.org/10.1016/j.jointm.2022.04.002
Received 20 December 2021; Received in revised form 17 March 2022; Accepted 3 April 2022. Managing Editor: Jingling Bao
Available online 21 May 2022

tion in chloride homeostasis is independently associated with mortality in ICH patients admitted to ICU.

Methods

Setting

This study used data stored in the high-resolution database, the Medical Information Mart for Intensive Care (MIMIC-III, mimic.physionet.org), which comprises information about more than 58,000 patients admitted to the ICU of the Beth Israel Deaconess Medical Center from 2001 to 2012. A detailed description of MIMIC-III is available elsewhere [16]. Our analysis of MIMIC-III data was exempt from institutional review board (IRB) approval because of the retrospective design, lack of direct patient intervention, and the security schema of the database, which includes the Health Insurance Portability and Accountability Act (HIPAA) compliant de-identification. After completing a National Institutes of Health (NIH) web-based training course (Protecting Human Research Participants), the author gained approval to access the database for research purposes (certification number: 28795067).

Study population

All patients in the MIMIC-III were eligible for inclusion in the investigation. For those admitted to ICU more than once, only the first stay was taken into consideration. We selected all adult patients admitted to ICU whose first diagnosis was primary ICH (ICD-9 code: 431) with ICU length of stay (LOS) >72 h. Patients were excluded for the following reasons: (1) elective admission, (2) ICH secondary to trauma, subarachnoid hemorrhage, or brain tumor, (3) history of end-stage renal disease, (4) treated with hypertonic saline within 72 h of ICU admission, (5) only one laboratory test for chloride within 72 h, and (6) international normalized ratio (INR) above 1.4 during the first day.

Clinical variables and outcomes

Demographics (age, sex, ethnicity, including White, Asian, Black, Hispanic/Latino, or other), laboratory tests, and physical parameters were extracted from the MIMIC-III database. The laboratory parameters during the first day of ICU admission included hematocrit, hemoglobin, platelet count, white blood cell count (WBC), bicarbonate, creatinine, glucose, anion gap, potassium, prothrombin time (PT), and partial thromboplastin time (PTT). Results of all laboratory tests in the first 72 h were extracted, including for chloride and sodium. Comorbidities were also noted, including heart failure (HF), diabetes mellitus (DM), and hypertension. Furthermore, the Glasgow Coma Scale score (GCS), sequential organ failure assessment (SOFA) score, and simplified acute physiology score II (SAPS II) were calculated for each patient. Other data included the use of mannitol, mechanical ventilation, ICU LOS, and hospital LOS. We used the MIMIC Code Repository to define MIMIC-III concepts [17].

Acute kidney injury (AKI) was defined using both the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine and urine output (UO) criteria [18]. For creatinine, the value from days 0 to 2 was used. For UO, the highest UO in 0–48 hours was used. Normal saline (NS) infusion within 72 h was defined as the sum of 0.9% saline in the first 72 h after ICU admission.

The admission chloride ($[Cl]_0$) was the initial concentration obtained during the first 24 h of admission to the ICU. Peak chloride ($[Cl]_{max}$) was the highest chloride level obtained in the first 72 h of admission. Minimum chloride ($[Cl]_{min}$) was the lowest chloride level obtained in the first 72 h of admission. An increase in chloride ($\Delta[Cl]\uparrow$) was the difference between the peak and admission chloride levels ($\Delta[Cl]\uparrow = [Cl]_{max} - [Cl]_0$). A decrease in chloride ($\Delta[Cl]\downarrow$) was the difference between the admission and lowest chloride level ($\Delta[Cl]\downarrow = [Cl]_0 - [Cl]_{min}$). $\Delta[Cl]\uparrow$5+ was defined as $\Delta[Cl]\uparrow > 5$ mmol/L, and $\Delta[Cl]\uparrow$5− was defined as $\Delta[Cl]\uparrow \leq 5$ mmol/L. $\Delta[Cl]\downarrow$5+ was defined as $\Delta[Cl]\downarrow > 5$ mmol/L. A similar definition was used for sodium.

The primary endpoint of our study was 90-day mortality, defined as death observed within 90-days in the hospital or from the US government's Social Security Death Index records. Other study endpoints included hospital mortality, ICU LOS, hospital LOS, and AKI. ICU LOS was defined as the difference between the date of ICU discharge and admission, as for hospital LOS.

Statistical analysis

Continuous variables were shown as mean ± standard deviation (SD) or median and interquartile range (IQR) and compared using Student's *t*-test or Wilcoxon rank-sum test, as appropriate. Categorical variables were reported as numbers and percentages and were analyzed with the chi-square test or Fisher's exact test, as appropriate. We used the median value to impute missing data.

Receiver operating characteristic (ROC) analysis was used to evaluate the best cut-off value for $\Delta[Cl]\uparrow$. Patients were dichotomized based on their $\Delta[Cl]\uparrow$ (≤5 mmol/L, >5 mmol/L, sensitivity: 61.9%, specificity: 63.8%). Demographic, clinical, and outcome information was summarized and compared between the $\Delta[Cl]\uparrow$5+ and $\Delta[Cl]\uparrow$5− groups.

Ninety-day mortality was considered a time-to-event variable. The event was death within 90 days after ICU admission. A patient was censored if alive at 90 days. The Cox proportional hazards model was fitted to test for an association between types of chloride and mortality after adjusting for potential confounders. Confounders considered clinically relevant, or that showed a univariate relationship with the hospital mortality outcome ($P<0.10$) were entered into the Cox proportional hazards model as covariates.

Hyperchloremia in critically ill patients is usually associated with AKI. A subgroup analysis was conducted on AKI and non-AKI patients. We also conducted stratification analyses to investigate whether the effect of $\Delta[Cl]\uparrow$ differed across subgroups, including age (>60 years or ≤60 years), sex, DM, HF, hypertension, and mechanical ventilation. A logistic regression model was fitted to test the association between $\Delta[Cl]\uparrow$ and 90-day mortality after adjusting for potential confounders in subgroups.

Data extraction was performed using PostgreSQL (version 10.5, www.postgresql.org) and pgADmin PostgreSQL tools (version 4). R (version 3.5.1, www.r-project.org) was used for statistical analysis. A two-sided *P*-value of <0.05 was considered statistically significant.

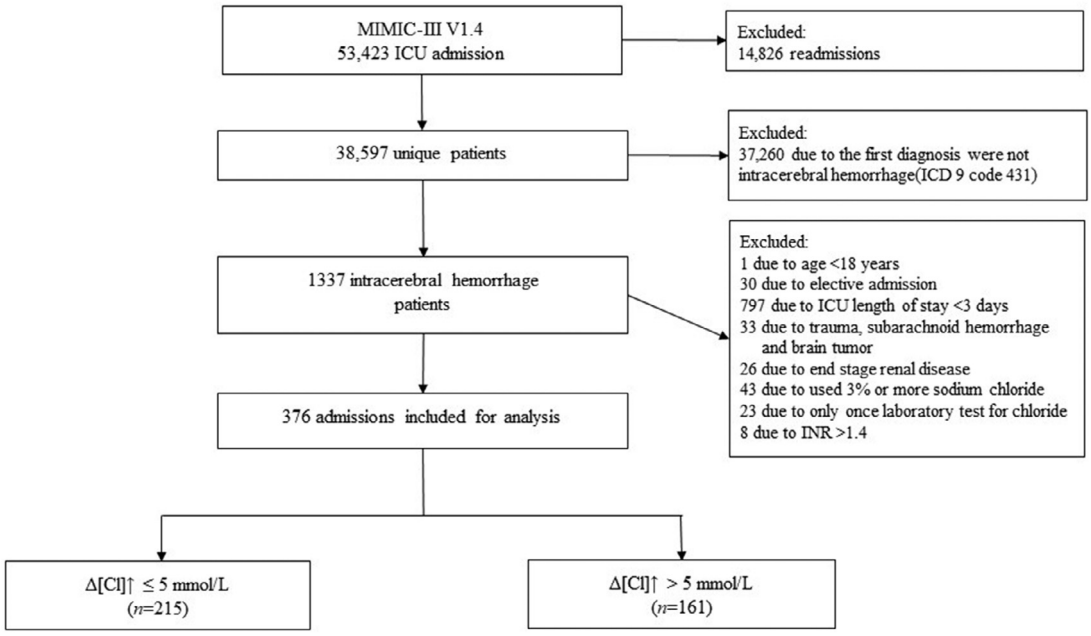

Figure 1. Flowchart of subject selection.
ICU: Intensive care unit; INR: International normalized ratio; MIMIC-III: Medical Information Mart for Intensive Care; Δ[Cl]↑: Increase in chloride.

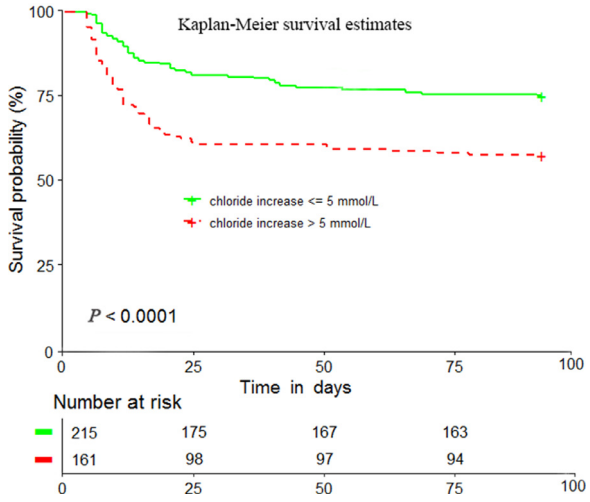

Figure 2. Kaplan–Meier survival curves by Δ[Cl]↑ category (log-rank P<0.001).

Results

A total of 1337 ICH patients were admitted to the ICU during the study period. After exclusion, the final sample included in the analysis was 376 [Figure 1]. The overall 90-day mortality was 32.2% (n=121), in-hospital mortality was 25.8% (n=97), and Day 2 AKI occurred in 29.0% of patients (n=109). Demographic and baseline characteristics of alive and expired patients are presented in Table 1. Admission chloride and sodium were not significantly different between the two groups. Table 2 shows differences in chloride and sodium between alive and expired patients. Patients with higher $[Cl]_{max}$, Δ[Cl]↑, $[Na]_{max}$, and Δ[Na]↑ had significantly higher hospital mortality, and patients with a higher percentage of Δ[Cl]↑5+, first 72 h hyperchloremia, Δ[Na]↑5+, and first 72 h hypernatremia also had higher mortality.

Classification of individuals based on Δ[Cl]↑ resulted in two phenotypes summarized in Table 3. Δ[Cl]↑5+ occurred in 42.8% (n=161) of the population. Δ[Cl]↑5+ was associated with a significantly higher percentage of past hypertension, higher admission WBC, admission glucose, admission chloride and sodium, SAPS II score, higher NS infusion within 72 h, a higher percentage of mechanical ventilation, higher ICU, hospital and 90-day mortality. Figure 2 displays the Kaplan–Meier survival curves by Δ[Cl]↑ categories, which shows that Δ[Cl]↑5− was associated with a higher probability of survival (log-rank P<0.001).

Univariate Cox regression analysis indicated Δ[Cl]↑5 + was associated with higher 90-day mortality and hazards ratio (HR) of 2.03 (95% confidence interval[CI]: 1.42–2.91, P<0.001). After adjustment for confounders including Δ[Na]↑5+, the HR of Δ[Cl]↑5+ decreased but remained statistically significant (1.66, 95% CI: 1.05–2.64, P=0.031). Unadjusted and adjusted model parameter estimates are summarized in Table 4. The combination of chloride and sodium disturbances resulted in four phenotypes: Δ[Cl]↑5− and Δ[Na]↑5−, Δ[Cl]↑5− and Δ[Na]↑5+, Δ[Cl]↑5+ and Δ[Na]↑5−, and Δ[Cl]↑5+ and Δ[Na]↑5+. After adjusting for confounders, Δ[Cl]↑5+ and Δ[Na]↑5− were shown to have higher 90-day mortality (HR=1.71,95% CI: 1.04–2.79, P=0.033) compared with Δ[Cl]↑5− and Δ[Na]↑5−.

Subgroup analysis showed that AKI and non-AKI groups with Δ[Cl]↑5+ had higher odds ratios (ORs) for 90-day mortality. Other subgroup analysis results are displayed in Figure 3.

Discussion

In this analysis of a large clinical database, we found that chloride abnormalities are common among ICH patients admitted to ICU. Hyperchloremia on admission, during the first 72 h,

Table 1
Comparison of characteristics between 90-day alive and expired patients.

Variables	Total (*n*=376)	Alive (*n*=255)	Expired (*n*=121)	*P*-value
Age (years)	70 (58, 79)	66 (56, 77)	75 (63, 82)	<0.001
Sex				0.036
Male	205 (54.5)	149 (58.4)	56 (46.3)	
Female	171 (45.5)	106 (41.6)	65 (53.7)	
Ethnicity				0.016
White	260 (69.1)	174 (68.2)	86 (71.1)	
Asian	11 (2.9)	11 (4.3)	0 (0.0)	
Black	30 (8.0)	23 (9.0)	7 (5.8)	
Hispanic/Latino	17 (4.5)	14 (5.5)	3 (2.5)	
Other	58 (15.4)	33 (12.9)	25 (20.7)	
Past medical history				
DM	75 (19.9)	48 (18.8)	27 (22.3)	0.514
HF	55 (14.6)	36 (14.1)	19 (15.7)	0.803
Hypertension	246 (65.4)	164 (64.3)	82 (67.8)	0.588
Admission laboratory indicators				
Hematocrit (%)	34.06 ± 4.54	34.53 ± 4.55	33.07 ± 4.39	0.003
Hemoglobin (g/dL)	11.64 ± 1.59	11.81 ± 1.59	11.29 ± 1.54	0.003
WBC ($\times 10^9$/L)	11.5 (9.7, 14.2)	11.4 (9.6, 14.1)	12 (10.1, 14.4)	0.107
Platelet ($\times 10^9$/L)	207 (165, 247)	205 (166, 249)	211 (164, 246)	0.760
Anion gap (mmol/L)	13 (12, 15)	13 (12, 15)	14 (12, 15)	0.045
Bicarbonate (mmol/L)	24 (23, 26)	24 (23, 26)	24 (22, 26)	0.257
Creatinine (mg/dL)	0.8 (0.7, 1.1)	0.85 (0.7, 1.1)	0.8 (0.7, 1.2)	0.846
Glucose (mg/dL)	134 (119, 152)	131 (118, 147)	141 (126, 160)	0.001
Potassium (mmol/L)	3.8 (3.6, 4.0)	3.8 (3.6, 4.0)	3.8 (3.6, 3.9)	0.415
PT (s)	13.2 (12.7, 13.8)	13.1 (12.7, 13.8)	13.2 (12.7, 13.8)	0.535
PTT (s)	26.3 (24.0, 28.6)	26.4 (24.5, 29.0)	26.1 (24.0, 28.2)	0.138
Chloride (mmol/L)	104 (101, 107)	104 (102, 107)	105 (101, 108)	0.609
Sodium (mmol/L)	139 (137, 142)	139 (137, 141)	139 (137, 142)	0.477
Admission critical indicators				
GCS	14 (10, 15)	14 (10, 15)	15 (9, 15)	0.222
SOFA	3 (2, 5)	3 (2, 5)	4 (1, 6)	0.256
SAPS II	35 (28, 42)	33 (27, 40)	38 (32, 46)	<0.001
NS infusion within 72 h (mL)	4642 (2403, 6901)	4975 (2477, 7202)	4141 (2398, 5760)	0.099
Mannitol (20%)	74 (19.7)	51 (20.0)	23 (19.0)	0.312
Mechanical ventilation	283 (75.3)	177 (69.4)	106 (87.6)	<0.001
AKI	109 (29.0)	66 (25.9)	43 (35.5)	0.029
Hospital LOS (days)	13 (8, 20)	15 (10, 22)	9 (5, 14)	<0.001
ICU LOS (days)	6.9 (4.4, 12.7)	7.3 (4.2, 13.5)	6.7 (4.7, 11.0)	0.282

Data are presented as *n* (%), median (Interquartile range) and mean ± Standard deviation.
AKI: Acute kidney injury; DM: Diabetes mellitus; GCS: Glasgow Coma Scale; HF: Heart failure; ICU: Intensive care unit; LOS: Length of stay; NS: Normal saline; PT: Prothrombin time; PTT: Partial thromboplastin time; SAPS II: Simplified acute physiology score II; SOFA: Sequential organ failure assessment score; WBC: White blood cell count.

and an increase in chloride over 5 mmol/L (Δ[Cl]↑5+) comprised 8.8%, 39.4%, and 42.8% of our cohort, respectively, and was greater than corresponding serum sodium (2.9%, 20.7%, and 27.7%). Increased chloride during the first 72 h of the ICU admission (Δ[Cl]↑5+) was independently associated with increased mortality after adjusting for confounders. An increase in chloride was also associated with less favorable secondary outcomes, including the percentage of mechanical ventilation. Our results provide information to clinicians regarding the importance of closely monitoring chloride levels in ICH patients.

Chloride is the most abundant anion in the extracellular fluid and the second main contributor to plasma tonicity. It plays an essential role in body functions, including the regulation of body fluids, electrolyte balance, acid-base status, muscular activity, osmosis, and immunomodulation. However, it has received less attention than most other ions in the critical care literature [19–21]. The association between hyperchloremia and poor outcomes in critically ill adult patients was first reported in 2011. Boniatti et al. [22] noted that hyperchloremia was associated with mortality in a prospective cohort of 175 patients. Other reports have found an association between hyperchloremia or chloride perturbations with increased in-hospital mortality [8,9,23,24].

Several investigators have shown the association between chloride abnormalities and increased mortality in neurocritical care patients. Riha et al. [15] observed higher in-hospital mortality rates in patients who developed moderate hyperchloremia (chloride ≥115 mmol/L) during treatment with continuous infusion of 3% hypertonic saline, with moderate hyperchloremia independently predicting in-hospital mortality. Rass et al. [25] found an independent association between hyperchloremia and delayed brain edema resolution. Huang et al. [13] found new-onset hyperchloremia and every 5 mmol/L increment in chloride within 72 h of ICU admission was associated with an increased odds of all-cause 30-day mortality and poor 6-month prognosis in critically ill stroke patients. The correlation between chloride and sodium is highly significant. In our study, the correlation coefficient for Δ[Na]↑ and Δ[Cl]↑ was 0.802 (95% CI : 0.76–0.84, P<0.001). Barhight et al. [23] evaluated the possible two- and three-way interactions between the increases in sodium and chloride and fluid administered in pediatric patients and found that the risks related to the in-

Table 2
Comparison of chloride and sodium between 90-day alive and expired patients.

Variables	Total (*n*=376)	Alive (*n*=255)	Expired (*n*=121)	*P*-value
Serum chloride levels (mmol/L)				
$[Cl]_0$	104 (101, 107)	104 (101, 107)	105 (101, 108)	0.609
$[Cl]_{max}$	109 (106, 113)	109 (106, 112)	110 (107, 114)	0.002
$[Cl]_{min}$	103 (100, 106)	103 (100, 05)	103 (100, 106)	0.565
Δ[Cl]↑	5 (2, 8)	4 (1, 7)	6 (3, 10)	<0.001
Δ[Cl]↓	0 (0, 2)	0 (0, 2)	0 (0, 1)	0.055
Δ[Cl]↑ 5+	161 (42.8)	93 (36.5)	68 (56.2)	<0.001
Δ[Cl]↓ 5+	22 (5.9)	15 (5.9)	7 (5.8)	1.000
Admission hyperchloremia	33 (8.8)	21 (8.2)	12 (9.9)	0.731
First 72 h hyperchloremia	148 (39.4)	88 (34.5)	60 (49.6)	0.007
Serum sodium levels (mmol/L)				
$[Na]_0$	139 (137, 142)	139 (137, 141)	139 (137, 142)	0.477
$[Na]_{max}$	142 (140, 145)	142 (140, 144)	143 (140, 147)	0.002
$[Na]_{min}$	138 (136, 140)	137 (135, 139)	138 (136, 141)	0.045
Δ[Na]↑	3 (1, 6)	2 (0, 5)	4 (2, 7)	<0.001
Δ[Na]↓	0 (0, 3)	1 (0, 3)	0 (0, 2)	0.010
Δ[Na]↑5+	104 (27.7)	58 (22.7)	46 (38.0)	0.003
Δ[Na]↓5+	27 (7.2)	19 (7.5)	8 (6.6)	0.936
Admission hypernatremia	11 (2.9)	8 (3.1)	3 (2.5)	1.000
First 72 h hypernatremia	78 (20.7)	34 (13.3)	44 (36.4)	<0.001
Chloride and sodium				0.003
Δ[Cl]↑ 5− and Δ[Na]↑ 5−	205 (54.5)	155 (60.8)	50 (41.3)	
Δ[Cl]↑ 5− and Δ[Na]↑ 5+	10 (2.7)	7 (2.7)	3 (2.5)	
Δ[Cl]↑5+ and Δ[Na]↑ 5−	67 (17.8)	42 (16.5)	25 (20.7)	
Δ[Cl]↑5+ and Δ[Na]↑5+	94 (25.0)	51 (20.0)	43 (35.5)	

Data are presented as *n* (%) and median (Interquartile range).
$[Cl]_0$: Initial chloride concentration; $[Cl]_{max}$: Maximal chloride concentration in the first 72 h; $[Cl]_{min}$: Minimum chloride concentration in the first 72 h; Δ[Cl]↑=$[Cl]_{max}$− $[Cl]_0$; Δ[Cl]↓=$[Cl]_0$− $[Cl]_{min}$; Δ[Cl]↑ 5+ : Δ[Cl]↑ > 5 mmol/L; Δ[Cl]↑ 5−: Δ[Cl]↑ ≤ 5 mmol/L; Δ[Cl]↓ 5+: Δ[Cl]↓ > 5 mmol/L; $[Na]_0$: Initial sodium concentration; $[Na]_{max}$: Maximal sodium concentration in the first 72 h; $[Na]_{min}$: Minimum sodium concentration in the first 72 h; Δ[Na]↑=$[Na]_{max}$− $[Na]_0$; Δ[Na]↓=$[Na]_0$− $[Na]_{min}$; Δ[Na]↑ 5+ : Δ[Na]↑ > 5 mmol/L; Δ[Na]↑ 5− : Δ[Na]↑≤ 5 mmol/L; Δ[Na]↓ 5+: Δ[Na]↓ > 5 mmol/L.

Table 3
Comparison of characteristics between Δ[C*l*]↑ 5− and Δ[C*l*]↑ 5+ patients.

Variables	Total (*n*=376)	Δ[Cl]↑ 5−(*n*=215)	Δ[Cl]↑ 5 +(*n*=161)	*P*-value
Age (years)	70 (58, 79)	70 (57, 79)	69 (58, 80)	0.650
Sex				0.018
Male	205 (54.5)	129 (60.0)	76 (47.2)	
Female	171 (45.5)	86 (40.0)	85 (52.8)	
Ethnicity				0.012
White	260 (69.1)	161 (74.9)	99 (61.5)	
Asian	11 (2.9)	8 (3.7)	3 (1.9)	
Black	30 (8.0)	13 (6.0)	17 (10.6)	
Hispanic/Latino	17 (4.5)	5 (2.3)	12 (7.5)	
Other	58 (15.4)	28 (13.0)	30 (18.6)	
Past medical history				
DM	75 (19.9)	43 (20.0)	32 (19.9)	1.000
HF	55 (14.6)	39 (18.1)	16 (9.9)	0.038
Hypertension	246 (65.4)	130 (60.5)	116 (72.0)	0.026
Admission laboratory indicators				
Hematocrit (%)	34.06 ± 4.54	34.31 ± 4.70	33.73 ± 4.32	0.219
Hemoglobin (g/dL)	11.64 ± 1.59	11.74 ± 1.63	11.52 ± 1.53	0.192
WBC ($\times10^9$/L)	11.5 (9.7, 14.2)	11.1 (9.5, 13.4)	12.5 (10.0, 15.1)	0.002
Platelet ($\times10^9$/L)	207 (166, 248)	199 (165, 241)	210 (172, 257)	0.293
Anion gap (mmol/L)	13 (12, 15)	13 (12, 15)	14 (12, 15)	0.059
Bicarbonate (mmol/L)	24 (23, 26)	24 (23, 26)	24 (22, 26)	0.082
Creatinine (mg/dL)	0.8 (0.7, 1.1)	0.8 (0.7, 1.1)	0.8 (0.7, 1.1)	0.586
Glucose (mg/dL)	134 (119, 152)	130 (118, 145)	137 (123, 160)	0.003
Potassium (mmol/L)	3.8 (3.6, 4.0)	3.8 (3.6, 4.0)	3.8 (3.6, 3.9)	0.061
PT (s)	13.2 (12.7, 13.8)	13.1 (12.7, 13.7)	13.3 (12.7, 13.9)	0.112
PTT (s)	26.3 (24.3, 28.6)	26.4 (24.6, 28.5)	26.0 (23.9, 28.8)	0.471
Chloride (mmol/L)	104 (101, 107)	105 (103, 108)	102 (99, 105)	<0.001
Sodium (mmol/L)	139 (137, 142)	140 (138, 142)	138 (136, 141)	0.002
Admission critical indicators				
GCS	14 (10, 15)	14 (11, 15)	15 (9, 15)	0.830
SOFA	3 (2, 5)	3 (2, 4)	4 (2, 5)	0.091
SAPS II	35 (28, 42)	33 (27, 40)	36 (30, 44)	0.002

(*continued on next page*)

Table 3 (*continued*)

Variables	Total (*n*=376)	Δ[Cl]↑ 5−(*n*=215)	Δ[Cl]↑ 5 +(*n*=161)	*P*-value
NS infusion within 72 h (mL)	4642 (2403, 6901)	4237 (2107, 6586)	5135 (3214, 7335)	0.011
Mannitol (20%)	74 (19.7)	35 (16.3)	39 (24.2)	0.074
Mechanical ventilation	283 (75.3)	146 (67.9)	137 (85.1)	<0.001
AKI	109 (29.0)	56 (26.0)	53 (32.9)	0.181
Hospital LOS (days)	13 (8, 20)	13 (9, 20)	12 (8, 20)	0.151
ICU LOS (days)	7.0 (4.4, 12.7)	6.6 (4.3, 12.5)	7.4 (4.6, 12.9)	0.314
ICU mortality	65 (17.3)	22 (10.2)	43 (26.7)	<0.001
Hospital mortality	97 (25.8)	37 (17.2)	60 (37.3)	<0.001
90-day mortality	121 (32.2)	53 (24.7)	68 (42.2)	<0.001

Data are presented as *n* (%), median (Interquartile range) and mean ± Standard deviation.
$[Cl]_0$: Initial chloride concentration; $[Cl]_{max}$: Maximal chloride concentration in the first 72 h; Δ[Cl]↑=$[Cl]_{max}$−$[Cl]_{0,}$ Δ[Cl]↑ 5+ : Δ[Cl]↑ > 5 mmol/L; Δ[Cl]↑ 5−: Δ[Cl]↑ ≤ 5 mmol/L; AKI: Acute kidney injury; DM: Diabetes Mellitus; GCS: Glasgow Coma Scale; HF: Heart failure; ICU: Intensive care unit; LOS: Length of stay; NS: Normal saline; PT: Prothrombin time; PTT: Partial thromboplastin time; SAPS II: Simplified acute physiology score; SOFA: Sequential organ failure assessment score; WBC: White blood cell count.

Table 4
Univariate and multivariate Cox regression analysis for ICH survival according to the status of serum chloride and sodium.

Variables	Univariate Cox analysis		Multivariate Cox analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Serum chloride levels				
$[Cl]_0$	1.00 (0.96, 1.04)	0.927	0.94 (0.89, 1.00)	0.059
$[Cl]_{max}$	1.07 (1.04, 1.11)	<0.001	0.98 (0.90, 1.07)	0.684
$[Cl]_{min}$	1.01 (0.97, 1.05)	0.693	0.91 (0.86, 0.97)	0.006
Δ[Cl]↑	1.08 (1.04, 1.16)	<0.001	1.07 (1.00, 1.14)	0.049
Δ[Cl]↓	0.98 (0.91, 1.06)	0.605	1.01 (0.93, 1.10)	0.771
Δ[Cl]↑5+	2.03 (1.42, 2.91)	<0.001	1.66 (1.05, 2.64)	0.031
Δ[Cl]↓ 5+	0.64 (0.31, 1.32)	0.227	0.59 (0.26, 1.32)	0.200
Admission hyperchloremia	1.09 (0.60, 1.98)	0.780	0.84 (0.42, 1.70)	0.633
First 72 h hyperchloremia	1.69 (1.18, 2.41)	0.004	0.92 (0.57, 1.46)	0.710
Serum sodium levels				
$[Na]_0$	1.03 (0.99, 1.08)	0.178	1.08 (1.00, 1.16)	0.037
$[Na]_{max}$	1.09 (1.05, 1.13)	<0.001	1.09 (0.99, 1.19)	0.071
$[Na]_{min}$	1.05 (1.01, 1.10)	0.027	1.13 (1.05, 1.22)	0.001
Δ[Na]↑	1.08 (1.04, 1.13)	<0.001	1.00 (0.93, 1.08)	0.995
Δ[Na]↓	0.94 (0.86, 1.02)	0.131	0.93 (0.84, 1.03)	0.151
Δ[Na]↑5+	1.90 (1.32, 2.74)	<0.001	1.15 (0.72, 1.85)	0.551
Δ[Na]↓ 5+	0.83 (0.44, 1.59)	0.579	1.08 (0.52, 2.24)	0.838
Admission hypernatremia	0.82 (0.82, 2.58)	0.733	0.68 (0.19, 2.48)	0.563
First 72 h hypernatremia	2.88 (1.98, 4.17)	<0.001	2.49 (1.57, 3.96)	<0.001
Chloride and sodium combination				
Δ[Cl]↑ 5− and Δ[Na]↑ 5−	1 [reference]		1 [reference]	
Δ[Cl]↑ 5− and Δ[Na]↑5+	1.23 (0.38, 3.94)	0.728	1.35 (0.42, 4.38)	0.614
Δ[Cl]↑5+ and Δ[Na]↑ 5−	1.71 (1.06, 2.76)	0.029	1.71 (1.04, 2.79)	0.033
Δ[Cl]↑5+ and Δ[Na]↑5+	2.33 (1.55, 3.51)	<0.001	1.91 (1.25, 2. 93)	0.003

Cox proportional hazards model adjusted for age, sex, ethnicity, admission laboratory indicators (WBC, hematocrit, sodium, chloride, anion gap, glucose, PT), SAPS II, NS infusion within 72 h, AKI, mechanical ventilation.
$[Cl]_0$: Initial chloride concentration; $[Cl]_{max}$: Maximal chloride concentration in the first 72 h; $[Cl]_{min}$: Minimum chloride concentration in the first 72 h; Δ[Cl]↑=$[Cl]_{max}$− $[Cl]_{0,}$ Δ[Cl]↓=$[Cl]_0$− $[Cl]_{min}$; Δ[Cl]↑ 5+ : Δ[Cl]↑ > 5 mmol/L; Δ[Cl]↑ 5− : Δ[Cl]↑ ≤ 5 mmol/L; Δ[Cl]↓ 5+: Δ[Cl]↓> 5 mmol/L; $[Na]_0$: Initial sodium concentration; $[Na]_{maz}$: Maximal sodium concentration in the first 72 h; $[Na]_{min}$: Minimum sodium concentration in the first 72 h; Δ[Nα]↑=[$Na]_{max}$− $[Na]_{0,}$ Δ[Nα]↓=$[Na]_0$− $[Na]_{min,}$ Δ[Na]↑ 5+ : Δ[Na]↑ > 5 mmol/L; Δ[Na]↑ 5−: Δ[Na]↑≤ 5 mmol/L; Δ[Na]↓ 5+: Δ[Na]↓ > 5 mmol/L; AKI: Acute kidney injury; CI: Confidence interval; HR: Hazards ratio; ICH: Intracerebral hemorrhage; NS: Normal saline; PT: Prothrombin time; SAPS II: Simplified acute physiology score II.

crease in sodium and chloride are independent of each other and from the volume of fluid administered. In our study, we observed that chloride increases within the first 72 h were associated with higher mortality after adjusting for sodium abnormalities. The association still existed for ICH patients who only had chloride increases (>5 mmol/L) and no sodium increase (>5 mmol/L).

Hyperchloremia in the ICU may occur because of disease processes or secondary to therapeutic interventions [7,19,21]. Excessive water loss – either net water loss or in excess of chloride loss – is another causative mechanism, like diuretic use and osmotic diuresis, which are common in neurocritical patients [26]. The use of 0.9% saline was common for critically ill patients and was associated with a risk of hyperchloremia, metabolic acidosis, and related complications, suggesting an increase in AKI and death risk [27,28]. In non-critically ill patients, post-admission chloride independently predicts hospital mortality [20]. Moreover, compared with saline, balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days (adjusted OR: 0.82; 95% CI: 0.70–0.95; *P*=0.01) [29]. Our study reported no association between NS infusion with 90-day mortality in ICH patients.

Several explanations have been proposed to explain the association between hyperchloremia and poor outcomes in neu-

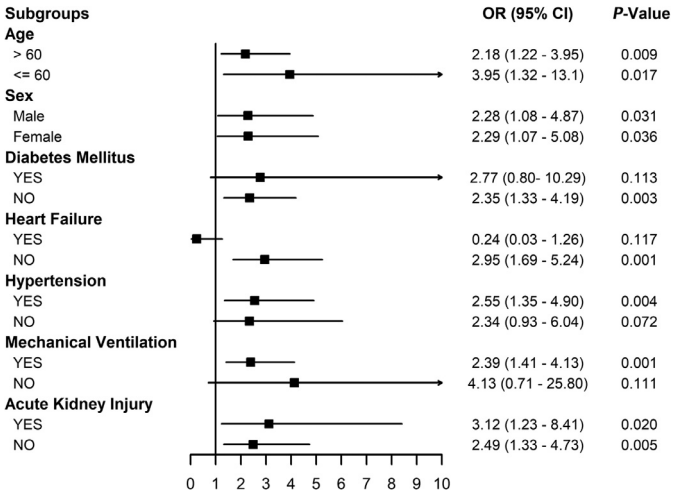

Figure 3. Adjusted odds ratio (OR) for 90-day mortality in different subgroups.

rocritical patients. In critically ill patients with subarachnoid hemorrhage, hyperchloremia was strongly associated with AKI, and AKI increased mortality [30]. In our study, AKI and non-AKI groups with Δ[Cl]↑5+ had a higher OR for 90-day mortality than those with lower chloride levels. An increased inflammatory reaction can aggravate brain injury after acute ICH [31]. Hyperchloremic metabolic acidosis may be a proinflammatory modulator and play an important role in neutrophil function [8]. Our study found that patients who had Δ[Cl]↑5+ had higher WBC counts. If the association of hyperchloremia with higher mortality is confirmed by data from randomized trials, hyperchloremia may become another indicator to guide the treatment of acute ICH. Recently, a double-blinded randomized pilot trial comparing bolus infusions of 23.4% NaCl and 16.4% NaCl/Na-acetate for treating patients with subarachnoid hemorrhage showed 16.4% NaCl/Na-acetate infusions led to lower chloride load and AKI rates than 23.4% NaCl infusions [32].

Limitations

There are several limitations to our study. First, the study was retrospective, and its *post hoc* nature should be considered when interpreting the findings. Residual confounders associated with hyperchloremia may have influenced our findings, although we attempted to account for this through several adjustments. The database included patients from 2001 to 2012, and therapy for ICH changed during this period. Second, the generalizability of the study is questionable because it was conducted at a single tertiary care hospital. We included patients admitted to the ICU, focusing on data collected during the first 72 h, further reducing the generalizability of our results. Third, there was a significant exclusion of data because we excluded patients staying less than 72 h. Fourth, for infusion, we only extracted an amount of 0.9% saline. There may be other solutions that contain chloride and sodium, which could influence findings. Fifth, we used chloride increase over 5 mmol/L as a cut-off point, although more evidence is needed to support this approach. However, we found serum chloride perturbation was common in ICH patients admitted to ICU, and chloride increase from baseline was associated with higher mortality. Although our findings support an association with perturbation in chloride from baseline and ICH patient mortality, stronger evidence is needed to establish the nature of the relationship, whether an association, an epiphenomenon, or causation.

Conclusions

An increase in chloride from baseline is common among ICH patients admitted to ICU. In our analysis, chloride increase from baseline was independently associated with 90-day mortality in ICH patients, supporting the significance of diligently monitoring chloride levels in this population. Further studies are needed to determine whether this is a causal relationship.

Ethics Statement

The MIMIC-III database used in this study was anonymized before its use (mimic.mit.edu). Due to the Health Insurance Portability and Accountability Act (HIPAA) and de-identification in this database, the Institutional Review Board (IRB) requirement was waived. All methods were carried out in accordance with relevant guidelines and regulations (declaration of Helsinki).

Funding

This study was supported by the Foundation of Beijing Tongren Hospital, Capital Medical University (No. 2021-YJJ-ZZL-026).

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the anonymous reviewers for their insightful and helpful comments.

References

[1] Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. Lancet 2018;392(10154):1257–68. doi:10.1016/S0140-6736(18)31878-6.
[2] Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46(7):2032–60. doi:10.1161/STR.0000000000000069.
[3] Gross BA, Jankowitz BT, Friedlander RM. Cerebral intraparenchymal hemorrhage: a review. JAMA 2019;321(13):1295–303. doi:10.1001/jama.2019.2413.
[4] Human T, Cook AM, Anger B, Bledsoe K, Castle A, Deen D, et al. Treatment of hyponatremia in patients with acute neurological injury. Neurocrit Care 2017;27(2):242–8. doi:10.1007/s12028-016-0343-x.
[5] Carcel C, Sato S, Zheng D, Heeley E, Arima H, Yang J, et al. Prognostic Significance of hyponatremia in acute intracerebral hemorrhage: pooled analysis of the intensive blood pressure reduction in acute cerebral hemorrhage trial studies. Crit Care Med 2016;44(7):1388–94. doi:10.1097/CCM.0000000000001628.
[6] Boland T, Henderson GV, Gibbons FK, Brouwers HB, Greenberg SM, Raffeld M, et al. Hypernatremia at hospital discharge and out of hospital mortality following primary intracerebral hemorrhage. Neurocrit Care 2016;25(1):110–16. doi:10.1007/s12028-015-0234-6.
[7] Berend K, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes. Eur J Intern Med 2012;23(3):203–11. doi:10.1016/j.ejim.2011.11.013.
[8] Neyra JA, Canepa-Escaro F, Li X, Manllo J, Adams-Huet B, Yee J, et al. Association of hyperchloremia with hospital mortality in critically Ill septic patients. Crit Care Med 2015;43(9):1938–44. doi:10.1097/CCM.0000000000001161.
[9] Suetrong B, Pisitsak C, Boyd JH, Russell JA, Walley KR. Hyperchloremia and moderate increase in serum chloride are associated with acute kidney in-

jury in severe sepsis and septic shock patients. Crit Care 2016;20(1):315. doi:10.1186/s13054-016-1499-7.
[10] Lee JY, Hong TH, Lee KW, Jung MJ, Lee JG, Lee SH. Hyperchloremia is associated with 30-day mortality in major trauma patients: a retrospective observational study. Scand J Trauma Resusc Emerg Med 2016;24(1):117. doi:10.1186/s13049-016-0311-7.
[11] Mao W, Wu J, Zhang H, Zhou J, Ye B, Li G, et al. Increase in serum chloride and chloride exposure are associated with acute kidney injury in moderately severe and severe acute pancreatitis patients. Pancreatology 2019;19(1):136–42. doi:10.1016/j.pan.2018.11.006.
[12] Oh TK, Do SH, Jeon YT, Kim J, Na HS, Hwang JW. Association of preoperative serum chloride levels with mortality and morbidity after noncardiac surgery: a retrospective cohort study. Anesth Analg 2019;129(6):1494–501. doi:10.1213/ANE.0000000000003958.
[13] Huang K, Hu Y, Wu Y, Ji Z,, Wang S,, Lin Z,, et al. Hyperchloremia is associated with poorer outcome in critically Ill stroke patients. Front Neurol 2018;9:485. doi:10.3389/fneur.2018.00485.
[14] Ditch KL, Flahive JM, West AM, Osgood ML, Muehlschlegel S. Hyperchloremia, not concomitant hypernatremia, independently predicts early mortality in critically Ill moderate-severe traumatic brain injury patients. Neurocrit Care 2020;33(2):533–41. doi:10.1007/s12028-020-00928-0.
[15] Riha HM, Erdman MJ, Vandigo JE, Kimmons LA, Goyal N, Davidson KE, et al. Impact of moderate hyperchloremia on clinical outcomes in intracerebral hemorrhage patients treated with continuous infusion hypertonic saline: a pilot study. Crit Care Med 2017;45(9) e947–947. doi:10.1097/CCM.0000000000002522.
[16] Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. Sci Data 2016;3:160035. doi:10.1038/sdata.2016.35.
[17] Johnson AE, Stone DJ, Celi LA, Pollard TJ. The MIMIC code repository: enabling reproducibility in critical care research. J Am Med Inform Assoc 2018;25(1):32–9. doi:10.1093/jamia/ocx084.
[18] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84. doi:10.1159/000339789.
[19] Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: chloride in critical illness. Crit Care 2010;14(4):226. doi:10.1186/cc9052.
[20] Thongprayoon C, Cheungpasitporn W, Cheng Z, Qian Q. Chloride alterations in hospitalized patients: prevalence and outcome significance. PLoS ONE 2017;12(3):e0174430. doi:10.1371/journal.pone.0174430.
[21] Bandak G, Kashani KB. Chloride in intensive care units: a key electrolyte. F1000Res 2017;6:1930. doi:10.12688/f1000research.11401.1.
[22] Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. J Crit Care 2011;26(2):175–9. doi:10.1016/j.jcrc.2010.04.013.
[23] Barhight MF, Brinton J, Stidham T, Soranno DE, Faubel S, Griffin BR, et al. Increase in chloride from baseline is independently associated with mortality in critically ill children. Intensive Care Med 2018;44(12):2183–91. doi:10.1007/s00134-018-5424-1.
[24] de Vasconcellos K, Skinner DL. Hyperchloraemia is associated with acute kidney injury and mortality in the critically ill: a retrospective observational study in a multidisciplinary intensive care unit. J Crit Care 2018;45:45–51. doi:10.1016/j.jcrc.2018.01.019.
[25] Rass V, Ianosi BA, Wegmann A, Gaasch M, Schiefecker AJ, Kofler M, et al. Delayed resolution of cerebral edema is associated with poor outcome after nontraumatic subarachnoid hemorrhage. Stroke 2019;50(4):828–36. doi:10.1161/STROKEAHA.118.024283.
[26] Nagami GT. Hyperchloremia – why and how. Nefrologia 2016;36(4):347–53. doi:10.1016/j.nefro.2016.04.001.
[27] Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. Balanced crystalloids versus saline in critically Ill adults. N Engl J Med 2018;378(9):829–39. doi:10.1056/NEJMoa1711584.
[28] Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock 1998;9(5):364–8. doi:10.1097/00024382-199805000-00009.
[29] Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, et al. Balanced crystalloids versus saline in noncritically Ill adults. N Engl J Med 2018;378(9):819–28. doi:10.1056/NEJMoa1711586.
[30] Sadan O, Singbartl K, Kandiah PA, Martin KS, Samuels OB. Hyperchloremia is associated with acute kidney injury in patients with subarachnoid hemorrhage. Crit Care Med 2017;45(8):1382–8. doi:10.1097/CCM.0000000000002497.
[31] Zhou Y, Wang Y, Wang J, Anne Stetler R, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. Prog Neurobiol 2014;115:25–44. doi:10.1016/j.pneurobio.2013.11.003.
[32] Sadan O, Singbartl K, Kraft J, Plancher JM, Greven A, Kandiah P, et al. Low-chloride- versus high-chloride-containing hypertonic solution for the treatment of subarachnoid hemorrhage-related complications: the ACETatE (A low ChloriE hyperTonic solution for brain Edema) randomized trial. J Intens Care 2020;8:32. doi:10.1186/s40560-020-00449-0.