BMJ Open

The association between intensive care unit-acquired hypernatraemia and mortality in critically ill patients with cerebrovascular diseases: a single centre cohort study in Japan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016248
Article Type:	Research
Date Submitted by the Author:	02-Feb-2017
Complete List of Authors:	Imaizumi, Takahiro; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology Nakatochi, Masahiro; Nagoya Daigaku Igakubu Fuzoku Byoin, Statistical Analysis Section, Center for Advanced Medicine and Clinical Research Fujita, Yoshiro; Chubu Rosai Byoin, Nephrology and Rheumatology Nomura, Rie; Toyohashi Shimin Byoin, Department of Nephrology Watanabe, Kenshi; Toyohashi Shimin Byoin, Department of Nephrology Maekawa, Michitaka; Toyohashi Shimin Byoin, Department of Nephrology Yamakawa, Taishi; Toyohashi Shimin Byoin, Department of Nephrology Katsuno, Takayuki; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology Maruyama, Shoichi; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Renal medicine, Epidemiology
Keywords:	cerebrovascular disease, EPIDEMIOLOGY, hypernatraemia, intensive care unit, restricted cubic spline

1

The association between intensive care unit-acquired hypernatraemia and mortality in critically ill patients with cerebrovascular diseases: a single centre cohort study in Japan

Takahiro Imaizumi[1], Masahiro Nakatochi[2], Yoshiro Fujita[3], Rie Nomura[4], Kennshi Watanabe[4], Michitaka Maekawa[4], Taishi Yamawaka[4], Takayuki Katsuno[1], Shoichi Maruyama[1*]

Affiliations

1 Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

2 Statistical Analysis Section, Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan

3 Department of Nephrology and Rheumatology, Chubu Rosai Hospital, Nagoya, Japan

4 Department of Nephrology, Toyohashi Municipal Hospital, Toyohashi, Japan

* Corresponding author: Shoichi Maruyama, Ph.D. Department of Nephrology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Tel.: +81-(0)52-744-2192. Fax: +81-(0)52-744-2209.

E-mail: marus@med.nagoya-u.ac.jp

Word count: 3590

ABSTRACT

Objectives: Hypernatraemia is one of the major electrolyte disorders associated with mortality among critically ill patients in intensive care units (ICUs). It is unclear whether this applies to patients with cerebrovascular diseases in whom high sodium concentrations may be allowed in order to prevent cerebral oedema. This study aimed to examine the association between ICU-acquired hypernatraemia and the prognosis of patients with cerebrovascular diseases.

Design: A retrospective cohort study.

Setting: The incidence of ICU-acquired hypernatraemia was assessed retrospectively in a single tertiary care facility in Japan.

Participants: Adult patients (≥ 18 years old) whose length of stay in ICU was > 2 days, and those whose serum sodium concentrations were 130–149 mEq/L on admission to ICU were included.

Outcome measures: 28-day in-hospital mortality risk was assessed by Cox regression analysis. Hypernatraemia was defined as serum sodium concentration ≥ 150 mEq/L. Using multivariate analysis, we examined whether ICU-acquired hypernatraemia and the main symptom present at ICU admission were associated with mortality among ICU patients. We also evaluated how the maximum and minimum sodium concentrations during ICU stay were associated with mortality, using restricted cubic splines.

Results: Of 1756 patients, 121 developed ICU-acquired hypernatraemia. Multivariate Cox proportional hazard analysis revealed an association between ICU-acquired hypernatraemia and 28-day mortality (adjusted hazard ratio [HR], 3.07 [95% confidence interval (CI), 2.12–4.44]). The interaction between ICU-acquired hypernatraemia and cerebrovascular disease was significantly associated with 28-day mortality (HR, 3.03 [95% CI, 1.29–7.15]). The restricted cubic splines analysis of maximum serum sodium concentration in ICU patients determined a threshold maximum of 147 mEq/L. There was no significant association between minimum sodium

concentration and mortality.

Conclusions: ICU-acquired hypernatraemia was associated with an increased mortality rate among critically ill patients with cerebrovascular diseases; the threshold maximum serum sodium concentration associated with mortality was 147 mEq/L.

Key words: cerebrovascular disease, epidemiology, hypernatraemia, intensive care unit, restricted cubic spline

Strengths and limitations of this study:

- We determined that ICU-acquired hypernatremia is associated with mortality interactively with other symptoms in critically ill patients, especially in those with cerebrovascular diseases.
- We determined the optimal serum sodium concentration range for ICU-admitted patients with cerebrovascular diseases by investigating the association between mortality and the maximum and minimum serum sodium concentration during the ICU stay.
- The data collected for the study were specific to the time when the patients were admitted to ICU; hence, we were not able to determine whether patients developed hypernatraemia after being discharged from ICU.

INTRODUCTION

Hypernatraemia is a common electrolyte disturbance occurring in patients who admitted to medical, surgical, and neurological intensive care units (ICUs). Previous studies showed that ICU-acquired hypernatraemia (IAH) is an independent predictor of increased mortality (1–5). Hypernatraemia has been shown to be a risk factor for mortality in patients admitted to ICU for sepsis (6), and in patients admitted to neurological ICU (7–10). On the other hand, hypernatraemia on admission was not associated with mortality among patients with respiratory failure (11). Thus, whether the effect of hypernatraemia on mortality is augmented by the coexisting clinical condition at the time of ICU admission remains unclear.

Hypernatraemia is common among the patients with neurological symptoms; it is also a risk factor for mortality. Critically ill patients with neurological diseases are susceptible to developing hypernatraemia for a variety of reasons, including an impaired thirst mechanisms and physical disability hindering voluntary drinking. Insensible loss of water may increase in patients with fever due to infectious or non-infectious causes. Moreover, hypernatraemia may be induced by the therapeutic use of osmotic diuretics or hypertonic saline to lower intracranial pressure (12); a study showed that a reduction in intracranial pressure was correlated with a rise in the serum sodium concentration (13). Thus, in patients receiving osmotic therapy, the ideal serum sodium concentration is difficult to determine. Hypernatraemia may be beneficial in controlling intracranial pressure, but it may be associated with increased morbidity and mortality among critically ill patients, including those with neurological conditions.

Few studies have targeted patients with cerebral infarction or spontaneous cerebral haemorrhage, and most of the prior studies were conducted among patients who admitted to neurological ICU (8–10). Prior studies concluded that the peak serum sodium concentration was a strong predictor for mortality. However, the cut-off point varied between studies, and these studies included not only

patients with cerebral infarction and spontaneous cerebral haemorrhage, but also those with traumatic brain injury and other neurological diseases.

The objective of this study was to investigate whether the IAH was associated with mortality interactively with other symptoms, especially cerebrovascular diseases (CVD). We also investigated the optimal serum sodium concentration range for patients admitted to ICU. The findings of this study may have implications for the choice of therapeutic and maintenance fluids administered to critically ill patients with neurological conditions.

SUBJECTS AND METHODS

Study design and setting

This was a retrospective cohort study conducted among patients admitted to ICU in Toyohashi Municipal Hospital from 1 January 2013 to 31 December 2015. Toyohashi Municipal Hospital is a tertiary referral hospital. The ICU manages both medical and surgical patients and is staffed by non-intensivists. The timing of and interval between laboratory examinations are determined by each doctor. Blood samples of planned laboratory examination are drawn between 5 and 6 a.m. under starved conditions. Some ICU beds are also used as recovery beds for patients admitted from emergency department; such patients are usually discharged from ICU within 2 days.

Using the data from these patients, we first examined whether IAH was associated with mortality using survival analysis. Second, we added a subgroup analysis of the main symptom on admission. Third, we examined the association between mortality and the maximum and minimum sodium concentrations during ICU stay to find the optimal cut-off value among patients with CVD. The outcome of interest was 28-day in-hospital mortality.

Study population and definitions

Adult patients (≥ 18 years old) whose length of stay in ICU was > 2 days, and those whose serum sodium concentrations were 130–149 mEq/L on admission to ICU were included. We excluded patients whose initial serum sodium concentration results were missing and brain-dead patients admitted to the ICU for planned organ donation.

If a patient was admitted to the ICU more than once during one hospital admission, data were obtained from the first ICU admission that was longer than 2 days in duration or from the admission during which the patient developed IAH. Patients who developed hypernatraemia outside of the ICU were not classified as cases of IAH.

The study protocol was approved by the ethics committee of Toyohashi municipal hospital (No. 248) and the study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Hypernatraemia was defined as a serum sodium concentration ≥ 150 mEq/L. IAH was defined as hypernatraemia occurring ≥ 12 hours after ICU admission in patients with a normal serum sodium concentration at ICU admission. Patients who developed hypernatraemia within the first 12 hours of ICU admission were excluded.

Data collection

The following data were recorded: age, sex, vital signs, Glasgow Coma Scale (GCS) score, and Acute Physiology And Chronic Health Evaluation II (APACHE-II) score (14) on admission to ICU; main symptoms at ICU admission; biochemical parameters; and ICU exposures, such as mechanical ventilation or renal replacement therapy. The main symptom at ICU admission was classified into the following categories: sepsis, respiratory failure, neurological symptom, acute kidney injury (AKI), and other medical conditions. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, as represented by an increase in the Sepsis-related Organ Failure Assessment (SOFA) score (≥ 2 points) (15). Respiratory failure was

defined as P/F ratio < 200 or the need for mechanical ventilation due to respiratory insufficiency. The neurological category included CVD, traumatic head injury, refractory status epilepticus, encephalopathy, and meningoencephalitis without sepsis. It was divided into two groups: CVD (including ischemic cerebral infarction and spontaneous cerebral haemorrhage) and other neurological diseases. AKI was defined in accordance with the Kidney Disease: Improving Global Outcome (KDIGO) guidelines (16), as follows:

1. An increase in serum creatinine level of ≥ 0.3 mg/dL (≥ 26.5 mmol/L) within 48 hours; or
2. An increase in serum creatinine level to ≥ 1.5 times above its baseline value, known or presumed to have occurred within the preceding 7 days; or
3. A urine volume < 0.5 mL/kg/h for 6 hours.

Among patients with CVD, we also reviewed the modified Rankin scale score on admission and the type of CVD (ischemic cerebral infarction, spontaneous cerebral haemorrhage, and subarachnoid haemorrhage). The modified Rankin scale is a validated measurement of the overall handicap scale for patients who have suffered a stroke (17,18). The scale was assessed by trained neurologists on admission. A score of ≤3 indicates favourable neurological function (19).

Statistical analysis

Clinical characteristics were compared between IAH and non-IAH patients using the Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Continuous variables are expressed as the median (interquartile range) and categorical variables are expressed as number and proportion, as appropriate. Cumulative probabilities of mortality were calculated using the Kaplan–Meier method. To identify predictors of 28-day in-hospital mortality, the log-rank test and uni- and multivariate Cox proportional hazards models were employed. Survival time was calculated as the time from ICU admission to death (either in ICU or in hospital).

Data for patients with a hospital stay longer than 28 days were censored at 28 days. IAH was included in the regression model as a time-dependent prognostic factor.

The multivariate analysis was adjusted for age, sex, APACHE-II score, AKI, sepsis, emergency surgery prior to the ICU admission, mechanical ventilation, and initiation of renal replacement therapy. The proportional hazards assumption for covariates was tested using scaled Schoenfeld residuals.

We also performed a subgroup analysis of the main symptoms on ICU admission, as defined above. A multivariate Cox regression analysis was performed to examine whether IAH, the symptoms, and the interaction between IAH and symptoms, were associated with mortality among ICU patients, adjusted for age, sex, APACHE-II score, use of mechanical ventilation, and initiation of renal replacement therapy. When we considered the interaction, we centred each variables by subtracting the mean value from each variables to reduce the multi-collinearity, and we calculated the interaction terms.

To assess the association between the maximum and minimum sodium concentrations and mortality, we performed a multivariate binary logistic regression analysis and restricted cubic splines (RCS)(20). The multivariate logistic regression analysis was adjusted for age, sex, APACHE-II score, GCS, length of ICU stay, types of CVD, and favourable neurological condition (defined as modified Rankin scale score ≤ 3) on ICU admission. In the RCS model, the association between predictor and outcome was assessed using cubic polynomials and linear terms. In this study, we set 3 knots to analyse the associations between predictor and outcome, placed on the 10^{th}, 50^{th}, and 90^{th} percentile of the predictor value range.

Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using Stata statistical software, version 14.1 (STATA Corp., College Station, TX, USA; http://www.stata.com)

RESULTS

Study participants

During the study period, 7205 patients were admitted to the ICU. The following exclusions were made: 5233 patients were discharged from the ICU within 2 days of admission, 122 patients had a serum sodium concentration outside the normal range on ICU admission, 88 patients had missing data, 5 patients developed hypernatraemia before ICU admission, and 1 patient was a deceased organ transplant donor. The final cohort comprised 1756 patients who were normonatraemic on admission to the ICU. Figure 1 shows the selection of the study participants and IAH cases. There were 121 cases of IAH, with a median serum sodium concentration of 152 mEq/L (interquartile range [IQR]: 150–153 mEq/L). The median serum sodium concentration of those who did not develop IAH was 142 mEq/L (IQR: 138–144 mEq/L).

Table 1 compares the baseline demographic data, medical exposures in ICU, and outcomes between patients who developed hypernatraemia and those who did not. The incidence of IAH was 6.9% (121 /1756). In terms of main symptom category, 11.6% (45/388) of patients with sepsis, 10.0% (46/461) of patients with respiratory failure, 9.5% (33/346) of patients with CVD, and 11.2% (45/403) of patients with AKI developed IAH. Among IAH cases, sepsis and neurological diseases were common reasons for ICU admission. A significantly higher proportion of patients with IAH required mechanical ventilation. ICU and in-hospital mortality were higher and the length of ICU stay was longer among IAH cases.

10

Table 1. Baseline characteristics, exposures in ICU, and outcomes

Category	Variables	IAH cases (n = 121)	non-IAH cases (n = 1635)	P value
Characteristics	Age (years)	71 (61–78)	69 (58–79)	0.38
	Male	85 (70.3)	1016 (62.1)	0.075
	Body mass index (kg/m^2)	20.1 (17.7–23.5)	21.5 (18.8–24.3)	0.069
	APACHE-II score	19 (13–24)	12 (8–18)	< 0.001*
	Glasgow coma scale score	12 (4–15)	15 (13–15)	< 0.001*
	Systolic blood pressure (mmHg)	125 (91–163)	135 (104–164)	0.082
	Pulse rate (/ min)	101 (84–116)	91 (76–110)	< 0.001*
	Body temperature (□)	36.7 (36.2–37.3)	36.8 (36.3–37.4)	0.26
Admission laboratory data	Na (mEq/L)	142 (138–144)	141 (138–143)	0.017*
	K (mEq/L)	4.0 (3.5–4.7)	4.0 (3.7–4.5)	0.65
	Blood glucose (mg/dL)	158 (120–198)	142 (115–186)	0.12
	BUN (mg/dL)	23 (15–45)	18 (13–27)	0.005*
	Creatinine (mg/dL)	1.05 (0.72–1.77)	0.86 (0.67–1.25)	< 0.001*
Main symptom	Sepsis	45 (37.2)	343 (21.0)	< 0.001*

11

at ICU admission	Respiratory failure	46 (38.0)	415 (25.4)	0.002*
	Neurological	45 (37.2)	501 (30.6)	0.13
	CVD	33 (27.3)	313 (19.1)	0.030*
	non-CVD	12 (9.9)	188 (11.5)	0.60
	Acute kidney injury	45 (37.2)	358 (21.9)	< 0.001*
	Other medical conditions	7 (5.8)	307 (18.8)	< 0.001*
Interventions	Surgery prior to ICU admission			0.23
	Elective surgery	4 (3.3)	102 (6.2)	
	Emergency surgery	26 (21.5)	278 (17.0)	
	Renal replacement therapy	11 (9.1)	128 (7.8)	0.62
	Mechanical ventilation	86 (71.1)	606 (37.1)	< 0.001*
Outcomes	Length of ICU admission (days)	9 (5,15)	4 (3,6)	< 0.001*
	All cause hospital mortality	56 (46.3)	193 (11.9)	< 0.001*
	All cause 28-day mortality	42 (35.0)	145 (8.9)	< 0.001*

ICU: intensive care unit; IAH: ICU-acquired hypernatraemia; APACHE: Acute Physiology And Chronic Health Evaluation; BUN: blood urea nitrogen; CVD: cerebrovascular disease.

Continuous data are presented as the median (interquartile range). Categorical data are presented as n (%). * $P < 0.05$

Outcomes of patients with IAH

The cumulative probabilities of mortality using the Kaplan–Meier method are shown in Supplementary Figure 1. Patients with IAH had a poorer prognosis. A univariate and multivariate Cox proportional hazard analysis revealed that IAH was associated with 28-day mortality (adjusted hazard ratio [HR], 3.23 [95% confidence interval (CI), 2.22–4.71]).

Interaction between IAH and clinical symptoms

We examined the association between 28-day mortality and the interaction between IAH and the clinical symptoms, as shown in Table 2. IAH was associated with 28-day mortality in all categories. There was significant association among patients with neurological symptoms, particularly patients with CVD. Among patients with neurological symptoms, the adjusted HRs of IAH, symptom, and the interaction term were 2.52 (1.59–3.97), 0.94 (0.62–1.42), and 2.31 (1.09–4.90), respectively. In patients with CVD, the adjusted HRs of IAH, symptom, and the interaction terms were 2.64 (1.72–4.04), 0.72 (0.42–1.25), and 3.03 (1.29–7.15), respectively. Figure 2 shows the association between mortality and the interaction between IAH and CVD.

Table 2 Multivariate analysis of the interaction between IAH and clinical symptoms

Symptom	Variable	HR[1]	95% confidence interval	P value
Sepsis	IAH	3.64	2.50–5.29	< 0.001*
	Sepsis	1.30	0.94–1.81	0.112
	Interaction	0.52	0.25–1.07	0.076
Neurological	IAH	3.27	2.25–4.76	< 0.001*
	Neurological	0.99	0.67–1.46	0.95
	Interaction	2.31	1.09–4.90	0.029*
CVD	IAH	3.30	2.26–4.82	< 0.001*
	CVD	0.78	0.47–1.30	0.34
	Interaction	3.03	1.29–7.15	0.011*
Respiratory	IAH	3.69	2.49–5.47	< 0.001*
	Respiratory failure	1.38	0.96–1.98	0.079
	Interaction	0.73	0.37–1.48	0.39
AKI	IAH	3.64	2.51–5.30	< 0.001*
	AKI	1.01	0.71–1.42	0.97
	Interaction	0.56	0.27–1.17	0.12

[1]Adjusted for age, gender, APACHE-II score, renal replacement therapy, and mechanical ventilation

* $P < 0.05$

IAH: ICU-acquired hypernatraemia; CVD: cerebrovascular diseases; AKI: acute kidney injury.

Maximum and minimum serum sodium concentrations and mortality

The clinical characteristics of patients with CVD are shown in Table 3. In this study, there were 93 patients with subarachnoid haemorrhage, 159 with cerebral haemorrhage, and 94 with ischemic stroke patients. Among the patients with CVD, the median modified Rankin scale score was 4 (3–5), and the median value of the maximum and minimum serum sodium concentrations were 143 (141–145) mEq/L and 141 (139–142) mEq/L, respectively. Twenty-eight patients in those with CVD died within 28 days.

The RCS analysis showed a U-shaped association between mortality and the maximum sodium concentration (Figure 3A). The curve's nadir was between 141 and 146 mEq/L. On the other hand, the minimum sodium concentration was not significantly associated with mortality, although the RCS also demonstrated a U-shaped association (Figure 3B).

Table 3. Clinical characteristics of CVD patients (n = 346)

Variables	Median (IQR) or n (%)
Age (years)	67 (58–78)
Male	192 (55.5)
Type of CVD	
Subarachnoid haemorrhage	93 (26.9)
Cerebral haemorrhage	159 (46.0)
Ischemic stroke	94 (27.2)
APACHE-II score on admission	11 (8–16)
Modified Rankin scale score on admission	4 (3–5)
GCS score on admission	13 (10–15)
Maximum sodium in ICU (mEq/L)	143 (141–145)
Minimum sodium in ICU (mEq/L)	141 (139–142)
Length of ICU admissions (days)	4 (3–6)
Modified Rankin scale at discharge	3 (2–4)
All cause hospital mortality	29 (8.4)
All cause 28-day mortality	28 (8.1)

CVD: cerebrovascular disease; IQR: interquartile range; APACHE: Acute Physiology And Chronic Health Evaluation; GCS: Glasgow Coma Scale

Continuous data are median (IQR). Categorical data are n values (%).

DISCUSSION

In this study on hypernatraemia in critically ill patients, we made two important clinical observations. First, IAH was associated with high mortality among critically ill patients, especially those with CVD. Second, using RCS analysis, the optimal serum sodium target concentration for patients with CVD was determined to be ≤ 146 mEq/L.

A prior study showed that a serum sodium concentration >160 mEq/L was an independent risk factor for mortality for patients in the neurological ICU (10). Another study showed that a serum sodium concentration >147.55 mEq/L was the optimal cut-off among patients in the neurological

ICU (8). In the present study, we showed that 146 mEq/L was the upper limit of serum sodium concentration among critically ill patients with CVD admitted to ICU. To our knowledge, this is the first report to show a threshold serum sodium concentration in patients with CVD admitted to ICU.

Hypernatraemia occurs when the total amount of body sodium increases and/or total body water is lost (21). The latter factor can be caused by loss of electrolyte-free water induced by administration of osmotic diuretics and urea-induced osmotic diuresis (22). Patients in ICU are often ventilated, sedated, and immobilized because of their medical condition and treatment; hence, water intake tends to be limited. There are several specific reasons for the development of hypernatraemia among patients with CVD. First, in most neurological ICUs, hypernatraemia is intentionally induced in such patients to treat brain oedema or to reduce elevated intracranial pressure (23). To reduce intracranial pressure, hypertonic saline or osmotic diuretics are commonly administered. An osmotic diuretic (glycerol) was administered to all the patients with CVD in our cohort. According to a previous report, hypernatraemia is more likely to develop in patients who undergo osmotic diuresis (10). Second, hypothalamic or pituitary gland dysfunction is a common secondary cause for sodium or water imbalance, such as central diabetes insipidus. Hypernatraemia might reflect severity in patients with such conditions. In our cohort, it was not possible to identify from the retrospective chart review the aetiology of hypernatraemia in most cases of IAH, but some might have been iatrogenic. Initial treatment of hypernatraemia is often inadequate, and sometimes treatment is delayed (21). Thus, prevention, early detection, and early treatment of IAH may be an indicator of clinical quality of care. Our findings will encourage clinicians who regularly see patients with CVD to monitor serum sodium concentrations more closely.

Hypernatraemia was shown to be associated with increased mortality among the patients with CVD. Hypernatraemia is associated with various neuromuscular manifestations, such as muscle weakness (24), that can prolong the length of ICU stay and duration of mechanical ventilation (9).

These factors, in turn, can lead to infection and other complications.

In this study, we could not identify the lower limit of sodium concentration, but we showed that the lower threshold of maximum serum sodium concentration was 141 mEq/L. Hence, a serum sodium concentration <141 mEq/L may be associated with mortality in patients with CVD, possibly because lower serum sodium concentration might cause brain oedema. Thus, we assume that the serum sodium concentration should be controlled at a relatively higher level.

There were several limitations to this study. First, due to the retrospective nature, the timing of and interval between examining blood samples were not decided *a priori*, thus, we might have missed some cases of IAH or those with lower concentrations of sodium. Second, it is possible that we underestimated the number of patients with IAH, both because we excluded patients who were admitted to ICU for <2 days and because once patients were discharged from ICU, we were not able to determine whether they developed hypernatraemia.

In the present study, we clearly demonstrated that hypernatraemia is a significant risk factor for mortality in critically ill patients, especially those with CVD. We also demonstrated that the serum sodium concentration cut-off point for increased mortality risk among patients with CVD was 147 mEq/L. These findings will be helpful for clinicians who manage critically ill patients with CVD. However, multi-centre, prospective studies should be conducted to assess the usefulness of this threshold in practice.

ACKNOWLEDGMENTS

The authors acknowledge the physicians and patients of Toyohashi Municipal Hospital, who contributed to this study. The authors also express gratitude to Ms. Megumi Matsushita (medical assistant) for extracting the electrical data from the medical records of the study patients, and to Mr. Shozo Nakamura (clinical engineer), Mr. Shin'ichi Miura (clinical engineer), and Mr. Hironori

Aoyama (clinical engineer) for offering the lists of patients who were mechanically ventilated or received renal replacement therapy.

Contributors

TI, MN, and SM: study concept and design; TI, RN and TY: acquisition of clinical data; TI, MN, YF, and SM: analysis and interpretation of data; KW, MM, and TK: critical revision of the manuscript for important intellectual content; TI, MN, and SM: drafting of the manuscript and statistical analysis; SM: study supervision.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

The Department of Nephrology, Nagoya University Graduate School of Medicine, received research promotion grants from Astellas, Alexion, Otsuka, Kyowa Hakko Kirin, Daiichi Sankyo, Dainippon Sumitomo, Takeda, Torii, Pfizer, and Mochida.

The Department of Nephrology, Toyohashi Municipal Hospital received research grants from Kyowa Hakko Kirin, Otsuka, Chugai, Astellas, Takeda, Torii, and Asahikasei.

The Center for Advanced Medicine and Clinical Research, Nagoya University Hospital and Chubu Rosai Hospital received no research grants or donations.

REFERENCES

1. Lindner G, Funk GC, Schwarz C et al. Hypernatremia in the Critically Ill Is an Independent

Risk Factor for Mortality. American Journal of Kidney Diseases 2007; 50: 952–7.

2. Hoorn EJ, Betjes MGH, Weigel J, et al. Hypernatraemia in critically ill patients: Too little water and too much salt. Nephrology Dialysis Transplantation 2008; 23: 1562–8.

3. O'Donoghue SD, Dulhunty JM, Bandeshe HK, et al. Acquired hypernatraemia is an independent predictor of mortality in critically ill patients. Anaesthesia 2009; 64: 514–20.

4. Darmon M, Timsit JF, Francais A et al. Association between hypernatraemia acquired in the ICU and mortality: A cohort study. Nephrology Dialysis Transplantation 2010; 25: 2510–5.

5. Waite MD, Fuhrman SA, Badawi O, et al. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. Journal of Critical Care 2013; 28: 405–12.

6. Ni H, Hu X, Huang X et al. Risk Factors and Outcomes in Patients With Hypernatremia and Sepsis. The American Journal of the Medical Sciences 2016; 351: 601–5.

7. Beseoglu K, Etminan N, Steiger HJ, et al. The relation of early hypernatremia with clinical outcome in patients suffering from aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 2014; 123: 164–8.

8. Hu B, Han Q, Mengke N et al. Prognostic value of ICU-acquired hypernatremia in patients with neurological dysfunction. Medicine 2016; 95: e3840.

9. Zhang YZ, Qie JY, Zhang QH. Incidence and mortality prognosis of dysnatremias in neurologic critically ill patients. European Neurology 2015; 73: 29–36.

10. Aiyagari V, Deibert E, Diringer MN. Hypernatremia in the neurologic intensive care unit: how high is too high? Journal of Critical Care 2006; 21: 163–72.

11. Bihari S, Peake SL, Bailey M, et al. Admission high serum sodium is not associated with increased intensive care unit mortality risk in respiratory patients. Journal of Critical Care 2014; 29: 948–54.

12. Jeon S-B, Koh Y, Choi HA, et al. Critical care for patients with massive ischemic stroke. Journal of stroke 2014; 16: 146–60.

13. Qureshi AI, Suarez JI, Bhardwaj A et al. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: Effect on intracranial pressure and lateral displacement of the brain. Critical care medicine 1998; 26: 440–6.

14. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Critical care medicine 1985; 13: 818–29.

15. Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801–10.

16. Kellum J a, Lameire N, Aspelin P et al. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney international supplements 2012; 2: 1–138.

17. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604–7.

18. Shinohara Y, Minematsu K, Amano T, et al. Modified Rankin Scale with Expanded Guidance Scheme and Interview Questionnaire: Interrater Agreement and Reproducibility of Assessment. Cerebrovascular Diseases 2006; 21: 271–8.

19. Nichol G, Leroux B, Wang H et al. Trial of Continuous or Interrupted Chest Compressions during CPR. The New England journal of medicine 2015; 373: 2203–14.

20. Nieboer D, Vergouwe Y, Roobol MJ et al. Nonlinear modeling was applied thoughtfully for risk prediction: the Prostate Biopsy Collaborative Group. Journal of clinical epidemiology 2015; 68: 426–34.

21. Polderman KH, Schreuder WO, Strack van Schijndel RJ, et al. Hypernatremia in the intensive care unit: an indicator of quality of care? Critical care medicine 1999; 27: 1105–8.

22. Lindner G, Schwarz C, Funk GC. Osmotic diuresis due to urea as the cause of

hypernatraemia in critically ill patients. Nephrology Dialysis Transplantation 2012; 27: 962–67.

23. Ryu JH, Walcott BP, Kahle KT et al. Induced and Sustained Hypernatremia for the Prevention and Treatment of Cerebral Edema Following Brain Injury. Neurocritical Care 2013; 19: 222–31.

24. Knochel JP. Neuromuscular manifestations of electrolyte disorders. The American journal of medicine 1982; 72: 521–35

Figure Legends

Figure 1. Flow chart of patients admitted during the study period.

Figure 2. Kaplan–Meier survival curves of the interaction between intensive care unit (ICU)-acquired hypernatraemia and cerebrovascular diseases.

Figure 3. Association between maximum/minimum sodium concentration and mortality by restricted cubic spline model in patients with cerebrovascular diseases.

A. Maximum sodium concentration and 28-day mortality. (Reference: 144 mEq/L)

B. Minimum sodium concentration and 28-day mortality. (Reference: 141 mEq/L)

Supplementary Figure 1. Kaplan–Meier survival curves of patients with and without intensive care unit (ICU)-acquired hypernatraemia.

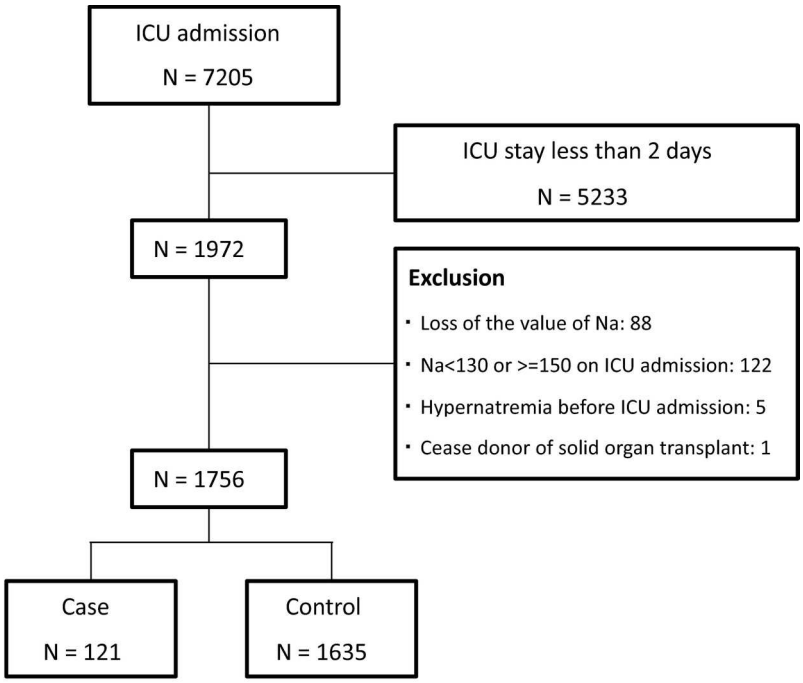
STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	none
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	none
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	none
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	none
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

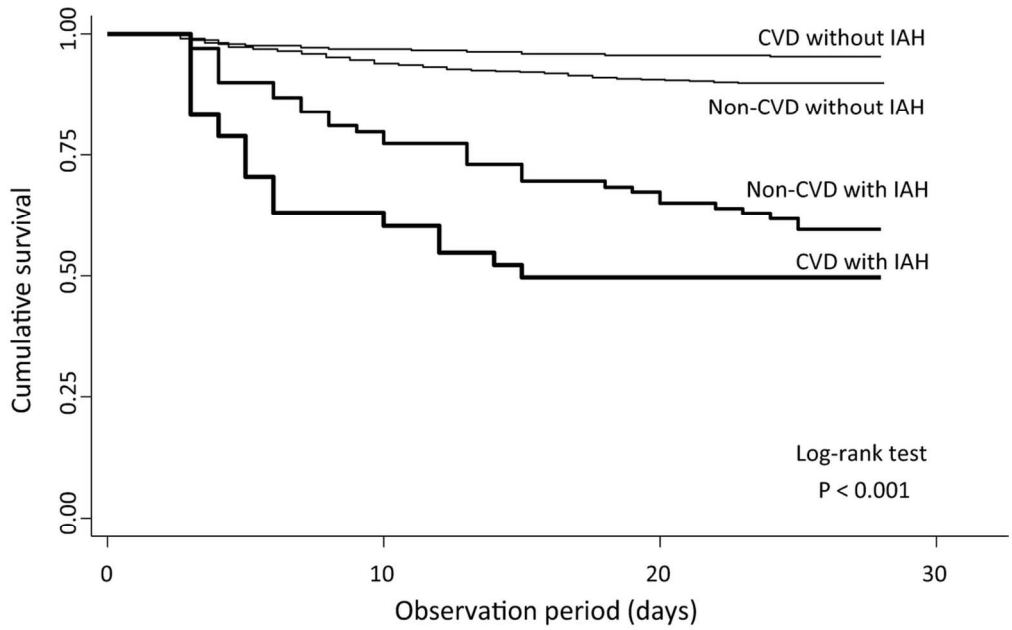
*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



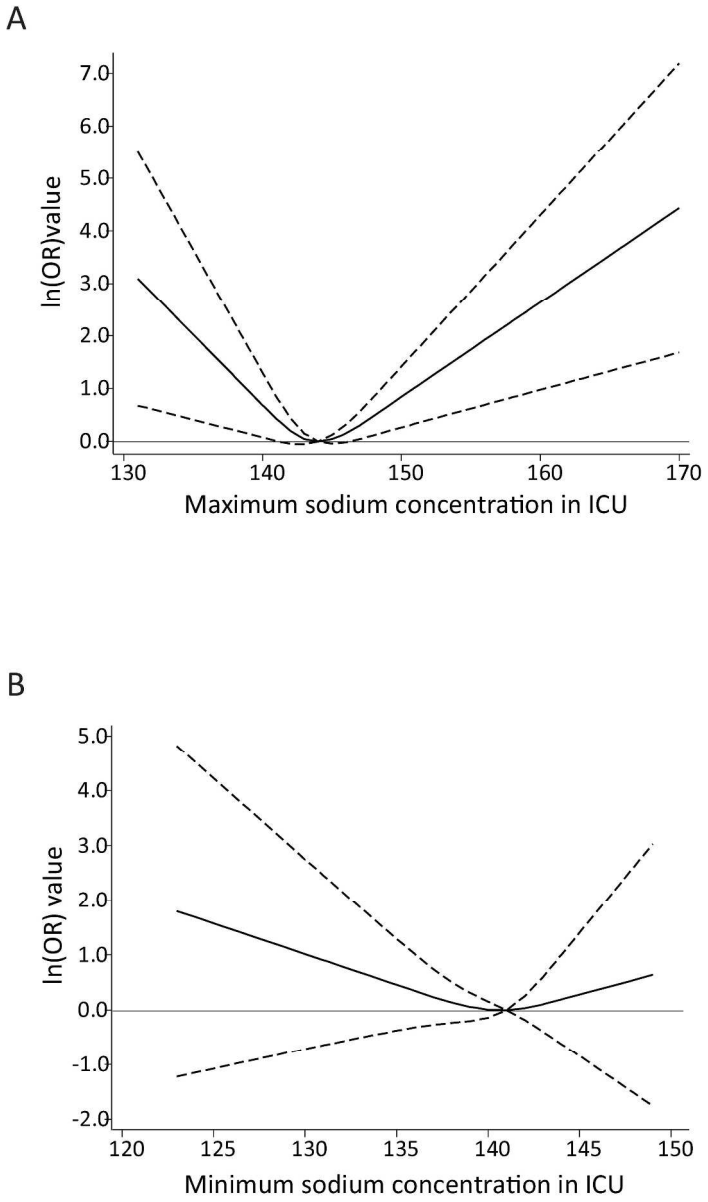
Flow chart of patients admitted during the study period.

180x165mm (300 x 300 DPI)



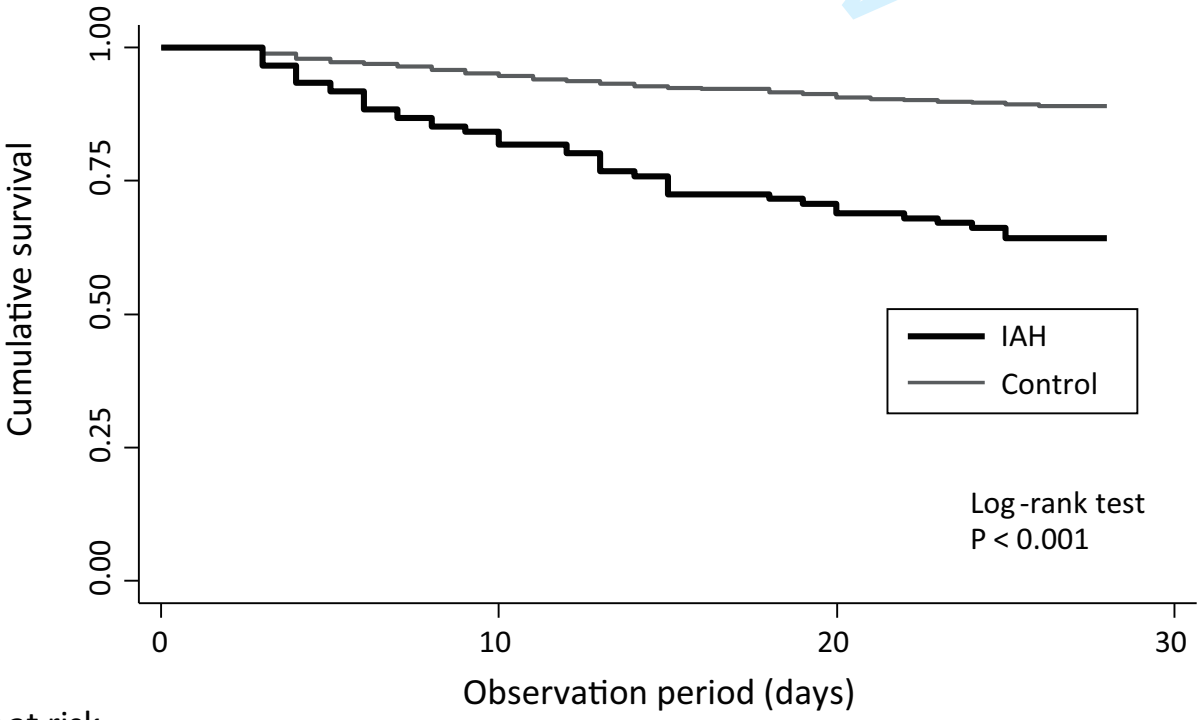
Kaplan–Meier survival curves of the interaction between intensive care unit (ICU)-acquired hypernatraemia and cerebrovascular diseases.

106x66mm (300 x 300 DPI)



Association between maximum/minimum sodium concentration and mortality by restricted cubic spline model in patients with cerebrovascular diseases.
A. Maximum sodium concentration and 28-day mortality. (Reference: 144 mEq/L)
B. Minimum sodium concentration and 28-day mortality. (Reference: 141 mEq/L)

213x368mm (300 x 300 DPI)



Number at risk

Control	1635	1372	916	0
IAH	121	102	79	0

BMJ Open

The association between intensive care unit-acquired hypernatraemia and mortality in critically ill patients with cerebrovascular diseases: a single centre cohort study in Japan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016248.R1
Article Type:	Research
Date Submitted by the Author:	13-Jun-2017
Complete List of Authors:	Imaizumi, Takahiro; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology Nakatochi, Masahiro; Nagoya Daigaku Igakubu Fuzoku Byoin, Statistical Analysis Section, Center for Advanced Medicine and Clinical Research Fujita, Yoshiro; Chubu Rosai Byoin, Nephrology and Rheumatology Nomura, Rie; Toyohashi Shimin Byoin, Department of Nephrology Watanabe, Kenshi; Toyohashi Shimin Byoin, Department of Nephrology Maekawa, Michitaka; Toyohashi Shimin Byoin, Department of Nephrology Yamakawa, Taishi; Toyohashi Shimin Byoin, Department of Nephrology Katsuno, Takayuki; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology Maruyama, Shoichi; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Renal medicine, Epidemiology
Keywords:	cerebrovascular disease, EPIDEMIOLOGY, hypernatraemia, intensive care unit, restricted cubic spline

1

The association between intensive care unit-acquired hypernatraemia and mortality in critically ill patients with cerebrovascular diseases: a single centre cohort study in Japan

Takahiro Imaizumi[1], Masahiro Nakatochi[2], Yoshiro Fujita[3], Rie Nomura[4], Kennshi Watanabe[4], Michitaka Maekawa[4], Taishi Yamawaka[4], Takayuki Katsuno[1], Shoichi Maruyama[1*]

Affiliations

1 Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

2 Statistical Analysis Section, Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan

3 Department of Nephrology and Rheumatology, Chubu Rosai Hospital, Nagoya, Japan

4 Department of Nephrology, Toyohashi Municipal Hospital, Toyohashi, Japan

* Corresponding author: Shoichi Maruyama, Ph.D. Department of Nephrology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Tel.: +81-(0)52-744-2192. Fax: +81-(0)52-744-2209.

E-mail: marus@med.nagoya-u.ac.jp

Word count: 3696

ABSTRACT

Objectives: Hypernatraemia is one of the major electrolyte disorders associated with mortality among critically ill patients in intensive care units (ICUs). It is unclear whether this applies to patients with cerebrovascular diseases in whom high sodium concentrations may be allowed in order to prevent cerebral oedema. This study aimed to examine the association between ICU-acquired hypernatraemia and the prognosis of patients with cerebrovascular diseases.

Design: A retrospective cohort study.

Setting: The incidence of ICU-acquired hypernatraemia was assessed retrospectively in a single tertiary care facility in Japan.

Participants: Adult patients (≥ 18 years old) whose length of stay in ICU was > 2 days, and those whose serum sodium concentrations were 130–149 mEq/L on admission to ICU were included.

Outcome measures: 28-day in-hospital mortality risk was assessed by Cox regression analysis. Hypernatraemia was defined as serum sodium concentration ≥ 150 mEq/L. Using multivariate analysis, we examined whether ICU-acquired hypernatraemia and the main symptom present at ICU admission were associated with time to death among ICU patients. We also evaluated how the maximum and minimum sodium concentrations during ICU stay were associated with mortality, using restricted cubic splines.

Results: Of 1756 patients, 121 developed ICU-acquired hypernatraemia. Multivariate Cox proportional hazard analysis revealed an association between ICU-acquired hypernatraemia and 28-day mortality (adjusted hazard ratio [HR], 3.07 [95% confidence interval (CI), 2.12–4.44]). The interaction between ICU-acquired hypernatraemia and cerebrovascular disease was significantly associated with 28-day mortality (HR, 3.03 [95% CI, 1.29–7.15]). The restricted cubic splines analysis of maximum serum sodium concentration in ICU patients determined a threshold maximum of 147 mEq/L. There was no significant association between minimum sodium

concentration and mortality.

Conclusions: ICU-acquired hypernatraemia was associated with an increased mortality rate among critically ill patients with cerebrovascular diseases; the threshold maximum serum sodium concentration associated with mortality was 147 mEq/L.

Key words: cerebrovascular disease, epidemiology, hypernatraemia, intensive care unit, restricted cubic spline

Strengths and limitations of this study:

- We determined that ICU-acquired hypernatremia is associated with mortality interactively with other symptoms in critically ill patients, especially in those with cerebrovascular diseases.
- We determined the optimal serum sodium concentration range for ICU-admitted patients with cerebrovascular diseases by investigating the association between mortality and the maximum and minimum serum sodium concentration during the ICU stay.
- The data collected for the study were specific to the time when the patients were admitted to ICU; hence, we were not able to determine whether patients developed hypernatraemia after being discharged from ICU.

INTRODUCTION

Hypernatraemia is a common electrolyte disturbance occurring in patients who admitted to medical, surgical, and neurological intensive care units (ICUs). Previous studies showed that ICU-acquired hypernatraemia (IAH) is an independent predictor of increased mortality (1–5). Hypernatraemia has been shown to be a risk factor for mortality in patients admitted to ICU for sepsis (6), and in patients admitted to neurological ICU (7–10). On the other hand, hypernatraemia on admission was not associated with mortality among patients with respiratory failure (11). Thus, whether the effect of hypernatraemia on mortality is augmented by the coexisting clinical condition at the time of ICU admission remains unclear.

Hypernatraemia is common among the patients with neurological symptoms; it is also a risk factor for mortality. Critically ill patients with neurological diseases are susceptible to developing hypernatraemia for a variety of reasons, including an impaired thirst mechanisms and physical disability hindering voluntary drinking. Insensible loss of water may increase in patients with fever due to infectious or non-infectious causes. Moreover, hypernatraemia may be induced by the therapeutic use of osmotic diuretics or hypertonic saline to lower intracranial pressure (12); a study showed that a reduction in intracranial pressure was correlated with a rise in the serum sodium concentration (13). Thus, in patients with CVD, the ideal serum sodium concentration is difficult to determine. Hypernatraemia may be beneficial in controlling intracranial pressure, but it may be associated with increased morbidity and mortality among critically ill patients, including those with neurological conditions.

Few studies have targeted patients with cerebral infarction or spontaneous cerebral haemorrhage, and most of the prior studies were conducted among patients who admitted to neurological ICU (8–10). Prior studies concluded that the peak serum sodium concentration was a strong predictor for mortality. However, the cut-off point varied between studies, and these studies included not only

patients with cerebral infarction and spontaneous cerebral haemorrhage, but also those with traumatic brain injury and other neurological diseases.

The objective of this study was to investigate whether the IAH was associated with mortality interactively with other symptoms, especially cerebrovascular diseases (CVD). We also investigated the optimal serum sodium concentration range for patients admitted to ICU. The findings of this study may have implications for the choice of therapeutic and maintenance fluids administered to critically ill patients with neurological conditions.

SUBJECTS AND METHODS

Study design and setting

This was a retrospective cohort study conducted among patients admitted to ICU in Toyohashi Municipal Hospital from 1 January 2013 to 31 December 2015. Toyohashi Municipal Hospital is a tertiary referral hospital. The ICU manages both medical and surgical patients and is staffed by non-intensivists. The timing of and interval between laboratory examinations are determined by each doctor. Blood samples of planned laboratory examination are drawn between 5 and 6 a.m. under starved conditions. Some ICU beds are also used as recovery beds for patients admitted from emergency department; such patients are usually discharged from ICU within 2 days.

Using the data from these patients, we first examined whether IAH was associated with mortality using survival analysis. Second, we added a subgroup analysis of the main symptom on admission. Third, we examined the association between mortality and the maximum and minimum sodium concentrations during ICU stay to find the optimal cut-off value among patients with CVD. The outcome of interest was 28-day in-hospital mortality.

Study population and definitions

Adult patients (≥ 18 years old) whose length of stay in ICU was > 2 days, and those whose serum sodium concentrations were 130–149 mEq/L on admission to ICU were included. We excluded patients whose initial serum sodium concentration results were missing and brain-dead patients admitted to the ICU for planned organ donation.

If a patient was admitted to the ICU more than once during one hospital admission, data were obtained from the first ICU admission that was longer than 2 days in duration or from the admission during which the patient developed IAH. Patients who developed hypernatraemia outside of the ICU were not classified as cases of IAH.

The study protocol was approved by the ethics committee of Toyohashi municipal hospital (No. 248) and the study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Hypernatraemia was defined as a serum sodium concentration ≥ 150 mEq/L. IAH was defined as hypernatraemia occurring ≥ 12 hours after ICU admission in patients with a normal serum sodium concentration at ICU admission. Patients who developed hypernatraemia within the first 12 hours of ICU admission were excluded.

Data collection

The following data were recorded: age, sex, vital signs, Glasgow Coma Scale (GCS) score, and Acute Physiology And Chronic Health Evaluation II (APACHE-II) score (14) on admission to ICU; main symptoms at ICU admission; biochemical variables; and ICU exposures, such as mechanical ventilation or renal replacement therapy. The main symptom at ICU admission was classified into the following categories: sepsis, respiratory failure, neurological symptom, acute kidney injury (AKI), and other medical conditions. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, as represented by an increase in the Sepsis-related Organ Failure Assessment (SOFA) score (≥ 2 points) (15). Respiratory failure was

defined as P/F ratio < 200 or the need for mechanical ventilation due to respiratory insufficiency. The neurological category included CVD, traumatic head injury, refractory status epilepticus, encephalopathy, and meningoencephalitis without sepsis. It was divided into two groups: CVD (including ischemic cerebral infarction and spontaneous cerebral haemorrhage) and other neurological diseases. AKI was defined in accordance with the Kidney Disease: Improving Global Outcome (KDIGO) guidelines (16), as follows:

1. An increase in serum creatinine level of ≥ 0.3 mg/dL (≥ 26.5 mmol/L) within 48 hours; or
2. An increase in serum creatinine level to ≥ 1.5 times above its baseline value, known or presumed to have occurred within the preceding 7 days; or
3. A urine volume < 0.5 mL/kg/h for 6 hours.

Among patients with CVD, we also reviewed the modified Rankin scale score on admission and the type of CVD (ischemic cerebral infarction, spontaneous cerebral haemorrhage, and subarachnoid haemorrhage). The modified Rankin scale is a validated measurement of the overall handicap scale for patients who have suffered a stroke (17,18). The scale was assessed by trained neurologists on admission. A score of ≤3 indicates favourable neurological function (19).

Statistical analysis

Clinical characteristics were compared between IAH and non-IAH patients using the Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Continuous variables are expressed as the median (interquartile range) and categorical variables are expressed as number and proportion, as appropriate. Cumulative probabilities of mortality were calculated using the Kaplan–Meier method. To identify predictors of 28-day in-hospital mortality, the log-rank test and uni- and multivariate Cox proportional hazards models were employed. Survival time was calculated as the time from ICU admission to death (either in ICU or in hospital).

Data for patients with a hospital stay longer than 28 days were censored at 28 days. IAH was included in the regression model as a time-dependent prognostic factor.

The multivariate analysis was adjusted for age, sex, APACHE-II score, AKI, sepsis, emergency surgery prior to the ICU admission, mechanical ventilation, and initiation of renal replacement therapy. The proportional hazards assumption for covariates was tested using scaled Schoenfeld residuals.

We also performed a subgroup analysis of the main symptoms on ICU admission, as defined above. A multivariate Cox regression analysis was performed to examine whether IAH, the symptoms, and the interaction between IAH and symptoms, were associated with mortality among ICU patients, adjusted for age, sex, APACHE-II score, use of mechanical ventilation, and initiation of renal replacement therapy. When we considered the interaction, we centred each variables by subtracting the mean value from each variables to reduce the multi-collinearity, and we calculated the interaction terms.

To assess the association between the maximum and minimum sodium concentrations and mortality, we performed a multivariate binary logistic regression analysis and restricted cubic splines (RCS)(20). The multivariate logistic regression analysis was adjusted for age, sex, APACHE-II score, GCS, length of ICU stay, types of CVD, and favourable neurological condition (defined as modified Rankin scale score ≤ 3) on ICU admission. In the RCS, the non-linear association between predictor and outcome was expressed as a spline curve combined cubic polynomials and linear terms. In this study, we set 3 knots to analyse the associations between predictor and outcome, placed on the 10^{th}, 50^{th}, and 90^{th} percentile of the predictor value range.

Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using Stata statistical software, version 14.1 (STATA Corp., College Station, TX, USA; http://www.stata.com)

RESULTS

Study participants

During the study period, 7205 patients were admitted to the ICU. The following exclusions were made: 5233 patients were discharged from the ICU within 2 days of admission, 122 patients had a serum sodium concentration outside the normal range on ICU admission, 88 patients had missing data, 5 patients developed hypernatraemia before ICU admission, and 1 patient was a deceased organ transplant donor. The final cohort comprised 1756 patients who were normonatraemic on admission to the ICU. Figure 1 shows the selection of the study participants and IAH cases. There were 121 cases of IAH, with a median serum sodium concentration of 152 mEq/L (interquartile range [IQR]: 150–153 mEq/L). The median serum sodium concentration of those who did not develop IAH was 142 mEq/L (IQR: 138–144 mEq/L). The median duration of IAH was 4 [3-8] days in total and 3 [2-8] days for patients with CVD.

Table 1 compares the baseline demographic data, medical exposures in ICU, and outcomes between patients who developed hypernatraemia and those who did not. The incidence of IAH was 6.9% (121 /1756). In terms of main symptom category, 11.6% (45/388) of patients with sepsis, 10.0% (46/461) of patients with respiratory failure, 9.5% (33/346) of patients with CVD, and 11.2% (45/403) of patients with AKI developed IAH. Among IAH cases, sepsis and neurological diseases were common reasons for ICU admission. A significantly higher proportion of patients with IAH required mechanical ventilation. ICU and in-hospital mortality were higher and the length of ICU stay was longer among IAH cases.

10

Table 1. Baseline characteristics, exposures in ICU, and outcomes

Category	Variables	IAH cases (n = 121)	non-IAH cases (n = 1635)	P value
Characteristics	Age (years)	71 (61–78)	69 (58–79)	0.38
	Male	85 (70.3)	1016 (62.1)	0.075
	APACHE-II score	19 (13–24)	12 (8–18)	< 0.001*
Main symptom	Sepsis	45 (37.2)	343 (21.0)	< 0.001*
at ICU admission	Respiratory failure	46 (38.0)	415 (25.4)	0.002*
	Neurological	45 (37.2)	501 (30.6)	0.13
	CVD	33 (27.3)	313 (19.1)	0.030*
	non-CVD	12 (9.9)	188 (11.5)	0.60
	Acute kidney injury	45 (37.2)	358 (21.9)	< 0.001*
	Other medical conditions	7 (5.8)	307 (18.8)	< 0.001*
Interventions	Surgery prior to ICU admission			0.23
	Elective surgery	4 (3.3)	102 (6.2)	
	Emergency surgery	26 (21.5)	278 (17.0)	
	Renal replacement therapy	11 (9.1)	128 (7.8)	0.62

11

	Mechanical ventilation	86 (71.1)	606 (37.1)	< 0.001*
Outcomes	Length of ICU admission (days)	9 (5,15)	4 (3,6)	< 0.001*
	All cause hospital mortality	56 (46.3)	193 (11.9)	< 0.001*
	All cause 28-day mortality	42 (35.0)	145 (8.9)	< 0.001*

ICU: intensive care unit; IAH: ICU-acquired hypernatraemia; APACHE: Acute Physiology And Chronic Health Evaluation; CVD: cerebrovascular disease.

Continuous data are presented as the median (interquartile range). Categorical data are presented as n (%). * $P < 0.05$

Outcomes of patients with IAH

The cumulative probabilities of mortality using the Kaplan–Meier method are shown in Supplementary Figure 1. Patients with IAH had a poorer prognosis. A univariate and multivariate Cox proportional hazard analysis revealed that IAH was associated with 28-day mortality (adjusted hazard ratio [HR], 3.23 [95% confidence interval (CI), 2.22–4.71]).

Interaction between IAH and clinical symptoms

We examined the association between 28-day mortality and the interaction between IAH and the clinical symptoms, as shown in Table 2. IAH was associated with 28-day mortality in all categories. There was significant association among patients with neurological symptoms, particularly patients with CVD. Among patients with neurological symptoms, the adjusted HRs of IAH, symptom, and the interaction term were 2.52 (1.59–3.97), 0.94 (0.62–1.42), and 2.31 (1.09–4.90), respectively. In patients with CVD, the adjusted HRs of IAH, symptom, and the interaction terms were 2.64 (1.72–4.04), 0.72 (0.42–1.25), and 3.03 (1.29–7.15), respectively. Figure 2 shows the association between mortality and the interaction between IAH and CVD.

Table 2 Multivariate analysis of the interaction between IAH and clinical symptoms

Symptom	Variable	HR[1]	95% confidence interval	P value
Sepsis	IAH	3.64	2.50–5.29	< 0.001*
	Sepsis	1.30	0.94–1.81	0.112
	Interaction	0.52	0.25–1.07	0.076
Neurological	IAH	3.27	2.25–4.76	< 0.001*
	Neurological	0.99	0.67–1.46	0.95
	Interaction	2.31	1.09–4.90	0.029*
CVD	IAH	3.30	2.26–4.82	< 0.001*
	CVD	0.78	0.47–1.30	0.34
	Interaction	3.03	1.29–7.15	0.011*
Respiratory	IAH	3.69	2.49–5.47	< 0.001*
	Respiratory failure	1.38	0.96–1.98	0.079
	Interaction	0.73	0.37–1.48	0.39
AKI	IAH	3.64	2.51–5.30	< 0.001*
	AKI	1.01	0.71–1.42	0.97
	Interaction	0.56	0.27–1.17	0.12

[1]Adjusted for age, gender, APACHE-II score, renal replacement therapy, and mechanical ventilation

* $P < 0.05$

IAH: ICU-acquired hypernatraemia; CVD: cerebrovascular diseases; AKI: acute kidney injury.

Maximum and minimum serum sodium concentrations and mortality

The clinical characteristics of patients with CVD are shown in Table 3. In this study, there were 93 patients had a subarachnoid haemorrhage, 159 had a cerebral haemorrhage, and 94 had suffered an ischemic stroke. Among those with CVD, 33 patients had IAH. Patients with IAH had significantly lower in GCS scores, and significantly higher in APACHE-II and modified Rankin scale scores than patients without IAH. Moreover, a significantly higher proportion of patients with IAH required mechanical ventilation. The incidence of AKI was not significantly higher in patients with IAH. Twenty-eight patients among those with CVD died within 28 days. ICU and in-hospital mortality rates were higher and the length of ICU stay was longer among patients with IAH.

The RCS analysis showed a U-shaped association between mortality and the maximum sodium concentration (Figure 3A). The curve's nadir was between 141 and 146 mEq/L. On the other hand, the minimum sodium concentration was not significantly associated with mortality, although the RCS also demonstrated a U-shaped association (Figure 3B).

15

Table 3. Clinical characteristics of CVD patients (n = 346)

Variables	All	IAH (n = 33)	Non-IAH (n = 313)	P value
Age (years)	67 (58–78)	65 (55-73)	67 (58-78)	0.33
Male	192 (55.5)	21 (63.64)	171 (54.63)	0.322
Type of CVD				0.49
Subarachnoid haemorrhage	93 (26.9)	11 (33.33)	82 (26.2)	
Cerebral haemorrhage	159 (46.0)	12 (36.36)	147 (46.96)	
Ischemic stroke	94 (27.2)	10 (30.3)	84 (26.84)	
Physical examination				
Body mass index (kg/m^2)	21.5 (18.8-24.4)	23.7 (21.1-26)	21.3 (18.8-24.3)	0.15
Systolic blood pressure (mmHg)	168 (146-195)	159 (135-212)	169 (147-193)	0.93
Pulse rate (/min)	81 (71.5-96)	96 (81-109)	80 (71-93)	<0.001
Body temperature (°C)	36.6 (36.2-37)	36.7 (36.2-37)	36.6 (36.2-37)	0.82
GCS score on admission	13 (10–15)	6 (4-13)	14 (11-15)	<0.001
APACHE-II score on admission	11 (8–16)	18 (12-22)	10 (7-15)	<0.001
Modified Rankin scale score on admission	4 (3–5)	5 (4-5)	4 (3-5)	<0.001
Favourable neurological condition*	176 (50.9)	4 (12.1)	172 (55.0)	<0.001
Laboratory data on admission				
Na	142 (140-143)	142 (141-144)	142 (140-143)	0.37
K	3.8 (3.5-4.2)	3.7 (3.3-4.1)	3.8 (3.6-4.2)	0.11
FBS	140.5 (117-178)	152 (124-190)	138 (116-176)	0.077
BUN	15 (12-19)	15 (12-20)	15 (12-19)	0.71

16

Cr	0.74 (0.6-0.91)	0.75 (0.66-0.94)	0.74 (0.6-0.9)	0.23
Maximum sodium in ICU (mEq/L)	143 (141–145)	154 (151-156)	143 (141-145)	<0.001
Minimum sodium in ICU (mEq/L)	141 (139–142)	141 (139-144)	141 (139-142)	0.29
AKI on admission	25 (7.2)	5 (15.2)	20 (6.4)	0.064
Surgery prior to ICU admission				0.047
Elective surgery	4 (1.2)	0 (0)	4 (1.3)	
Emergency surgery	104 (30.1)	16 (48.5)	88 (28.1)	
Renal replacement therapy	3 (0.9)	0 (0)	3 (1.0)	0.57
Mechanical ventilation	99 (28.6)	27 (81.8)	72 (23.0)	<0.001
Length of ICU admissions (days)	4 (3–6)	8 (5-13)	4 (3-5)	<0.001
Modified Rankin scale at discharge	3 (2–4)	5 (4-6)	3 (2-4)	<0.001
All cause hospital mortality	29 (8.4)	14 (42.4)	15 (4.8)	<0.001
All cause 28-day mortality	28 (8.1)	13 (39.4)	15 (4.8)	<0.001

CVD: cerebrovascular disease; IQR: interquartile range; APACHE: Acute Physiology And Chronic Health Evaluation; GCS: Glasgow Coma Scale

Continuous data are median (IQR). Categorical data are n values (%).

* A score of ≤3 indicates favourable neurological function

DISCUSSION

In this study on hypernatraemia in critically ill patients, we made two important clinical observations. First, IAH was associated with high mortality among critically ill patients, especially those with CVD. Second, using RCS analysis, a dose-response association between serum sodium concentration and mortality risk was observed, and the optimal serum sodium target concentration for patients with CVD was determined to be ≤ 146 mEq/L.

A prior study showed that a serum sodium concentration >160 mEq/L was an independent risk factor for mortality for patients in the neurological ICU (10). Another study showed that a serum sodium concentration >147.55 mEq/L was the optimal cut-off among patients in the neurological ICU (8). In the present study, we showed that 146 mEq/L was the upper limit of serum sodium concentration among critically ill patients with CVD admitted to ICU. To our knowledge, this is the first report to show a threshold serum sodium concentration in patients with CVD admitted to ICU.

Hypernatraemia occurs when the total amount of body sodium increases and/or total body water is lost (21). The latter factor can be caused by loss of electrolyte-free water induced by administration of osmotic diuretics and urea-induced osmotic diuresis (22). Patients in ICU are often ventilated, sedated, and immobilized because of their medical condition and treatment; hence, water intake tends to be limited. There are several specific reasons for the development of hypernatraemia among patients with CVD. First, in most neurological ICUs, hypernatraemia is intentionally induced in such patients to treat brain oedema or to reduce elevated intracranial pressure (23). Evidence on the benefits of actively raising the serum sodium concentration and the active use of osmotic diuretics is lacking, especially for patients with CVD. Patients with lower GCS scores, or those with clinical evidence of trans tentorial herniation might be considered for intracranial pressure (ICP) monitoring and treatment according to the guidelines for the management of spontaneous intracranial haemorrhage (24). Methods of treating elevated ICP are

generally borrowed from traumatic brain injury guidelines as well. Osmotic diuretics or hypertonic saline may be used to treat acute elevations of ICP; hypertonic saline may be the more effective agent. However, this recommendation is effective only if ICP is monitored. Despite this, intravenous administration of hypertonic glycerol is commonly used in the treatment of acute stroke in Japan, often without concomitant ICP measurement (25). Actually, an osmotic diuretic (glycerol) was administered to all the patients with CVD in our cohort. According to a previous report, hypernatraemia is more likely to develop in patients who undergo osmotic diuresis (10). Second, hypothalamic or pituitary gland dysfunction is a common secondary cause for sodium or water imbalance, such as central diabetes insipidus. Hypernatraemia might reflect severity in patients with such conditions. In our cohort, it was not possible to identify from the retrospective chart review the aetiology of hypernatraemia in most cases of IAH, but some might have been iatrogenic. Initial treatment of hypernatraemia is often inadequate, and sometimes treatment is delayed (21). Thus, prevention, early detection, and early treatment of IAH may be an indicator of clinical quality of care. Our findings will encourage clinicians who regularly see patients with CVD to monitor serum sodium concentrations more closely.

Hypernatraemia was shown to be associated with increased mortality among the patients with CVD. Hypernatraemia is associated with various neuromuscular manifestations, such as muscle weakness (26), that can prolong the length of ICU stay and duration of mechanical ventilation (9). These factors, in turn, can lead to infection and other complications.

In this study, we could not identify the lower limit of sodium concentration, but we showed that the lower threshold of maximum serum sodium concentration was 141 mEq/L. Hence, a serum sodium concentration <141 mEq/L may be associated with mortality in patients with CVD, possibly because lower serum sodium concentration might cause brain oedema. Thus, we assume that the serum sodium concentration should be controlled at a relatively higher level.

There were several limitations to this study. First, due to the retrospective nature, the timing of and interval between examining blood samples were not decided *a priori*, thus, we might have missed some cases of IAH or those with lower concentrations of sodium. Second, it is possible that we underestimated the number of patients with IAH, both because we excluded patients who were admitted to ICU for <2 days and because once patients were discharged from ICU, we were not able to determine whether they developed hypernatraemia. Third, a single-centre study may be biased by local practice patterns, such as the use of osmotic diuretics or measurement of ICP. Fourth, since ICP measurement was not routinely performed, this study was unable to focus on patients with cerebral oedema. Nevertheless, osmotic diuretics such as glycerol are frequently administered in routine clinical practice in Japan. This might have contributed to hypernatraemia in some patients, leading a poor prognosis.

In the present study, we clearly demonstrated that hypernatraemia is a significant risk factor for mortality in critically ill patients, especially those with CVD. We also demonstrated that the serum sodium concentration cut-off point for increased mortality risk among patients with CVD was 147 mEq/L. These findings will be helpful for clinicians who manage critically ill patients with CVD. However, multi-centre, prospective studies should be conducted to assess the usefulness of this threshold in practice.

ACKNOWLEDGMENTS

The authors acknowledge the physicians and patients of Toyohashi Municipal Hospital, who contributed to this study. The authors also express gratitude to Ms. Megumi Matsushita (medical assistant) for extracting the electrical data from the medical records of the study patients, and to Mr. Shozo Nakamura (clinical engineer), Mr. Shin'ichi Miura (clinical engineer), and Mr. Hironori

Aoyama (clinical engineer) for offering the lists of patients who were mechanically ventilated or received renal replacement therapy.

Contributors

TI, MN, and SM: study concept and design; TI, RN and TY: acquisition of clinical data; TI, MN, YF, and SM: analysis and interpretation of data; KW, MM, and TK: critical revision of the manuscript for important intellectual content; TI, MN, and SM: drafting of the manuscript and statistical analysis; SM: study supervision.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

The Department of Nephrology, Nagoya University Graduate School of Medicine, received research promotion grants from Astellas, Alexion, Otsuka, Kyowa Hakko Kirin, Daiichi Sankyo, Dainippon Sumitomo, Takeda, Torii, Pfizer, and Mochida.

The Department of Nephrology, Toyohashi Municipal Hospital received research grants from Kyowa Hakko Kirin, Otsuka, Chugai, Astellas, Takeda, Torii, and Asahikasei.

The Center for Advanced Medicine and Clinical Research, Nagoya University Hospital and Chubu Rosai Hospital received no research grants or donations.

Data sharing statement

No additional data are available.

REFERENCES

1. Lindner G, Funk GC, Schwarz C et al. Hypernatremia in the Critically Ill Is an Independent Risk Factor for Mortality. American Journal of Kidney Diseases 2007; 50: 952–7.
2. Hoorn EJ, Betjes MGH, Weigel J, et al. Hypernatraemia in critically ill patients: Too little water and too much salt. Nephrology Dialysis Transplantation 2008; 23: 1562–8.
3. O'Donoghue SD, Dulhunty JM, Bandeshe HK, et al. Acquired hypernatraemia is an independent predictor of mortality in critically ill patients. Anaesthesia 2009; 64: 514–20.
4. Darmon M, Timsit JF, Francais A et al. Association between hypernatraemia acquired in the ICU and mortality: A cohort study. Nephrology Dialysis Transplantation 2010; 25: 2510–5.
5. Waite MD, Fuhrman SA, Badawi O, et al. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. Journal of Critical Care 2013; 28: 405–12.
6. Ni H, Hu X, Huang X et al. Risk Factors and Outcomes in Patients With Hypernatremia and Sepsis. The American Journal of the Medical Sciences 2016; 351: 601–5.
7. Beseoglu K, Etminan N, Steiger HJ, et al. The relation of early hypernatremia with clinical outcome in patients suffering from aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 2014; 123: 164–8.
8. Hu B, Han Q, Mengke N et al. Prognostic value of ICU-acquired hypernatremia in patients with neurological dysfunction. Medicine 2016; 95: e3840.
9. Zhang YZ, Qie JY, Zhang QH. Incidence and mortality prognosis of dysnatremias in neurologic critically ill patients. European Neurology 2015; 73: 29–36.
10. Aiyagari V, Deibert E, Diringer MN. Hypernatremia in the neurologic intensive care unit: how high is too high? Journal of Critical Care 2006; 21: 163–72.

11. Bihari S, Peake SL, Bailey M, et al. Admission high serum sodium is not associated with increased intensive care unit mortality risk in respiratory patients. Journal of Critical Care 2014; 29: 948–54.

12. Jeon S-B, Koh Y, Choi HA, et al. Critical care for patients with massive ischemic stroke. Journal of stroke 2014; 16: 146–60.

13. Qureshi AI, Suarez JI, Bhardwaj A et al. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: Effect on intracranial pressure and lateral displacement of the brain. Critical care medicine 1998; 26: 440–6.

14. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Critical care medicine 1985; 13: 818–29.

15. Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801–10.

16. Kellum J a, Lameire N, Aspelin P et al. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney international supplements 2012; 2: 1–138.

17. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604–7.

18. Shinohara Y, Minematsu K, Amano T, et al. Modified Rankin Scale with Expanded Guidance Scheme and Interview Questionnaire: Interrater Agreement and Reproducibility of Assessment. Cerebrovascular Diseases 2006; 21: 271–8.

19. Nichol G, Leroux B, Wang H et al. Trial of Continuous or Interrupted Chest Compressions during CPR. The New England journal of medicine 2015; 373: 2203–14.

20. Nieboer D, Vergouwe Y, Roobol MJ et al. Nonlinear modeling was applied thoughtfully for risk prediction: the Prostate Biopsy Collaborative Group. Journal of clinical epidemiology 2015; 68: 426–34.

21. Polderman KH, Schreuder WO, Strack van Schijndel RJ, et al. Hypernatremia in the intensive care unit: an indicator of quality of care? Critical care medicine 1999; 27: 1105–8.

22. Lindner G, Schwarz C, Funk GC. Osmotic diuresis due to urea as the cause of hypernatraemia in critically ill patients. Nephrology Dialysis Transplantation 2012; 27: 962–67.

23. Ryu JH, Walcott BP, Kahle KT et al. Induced and Sustained Hypernatremia for the Prevention and Treatment of Cerebral Edema Following Brain Injury. Neurocritical Care 2013; 19: 222–31.

24. Hemphill JC, Greenberg SM, Anderson CS et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Stroke 2015; 46: 2032–2060.

25. Toyoda K, Steiner T, Epple C et al. Comparison of the European and Japanese Guidelines for the Acute Management of Intracerebral Hemorrhage. Cerebrovascular Diseases 2013; 35: 419–429.

26. Knochel JP. Neuromuscular manifestations of electrolyte disorders. The American journal of medicine 1982; 72: 521–35

Figure Legends

Figure 1. Flow chart of patients admitted during the study period.

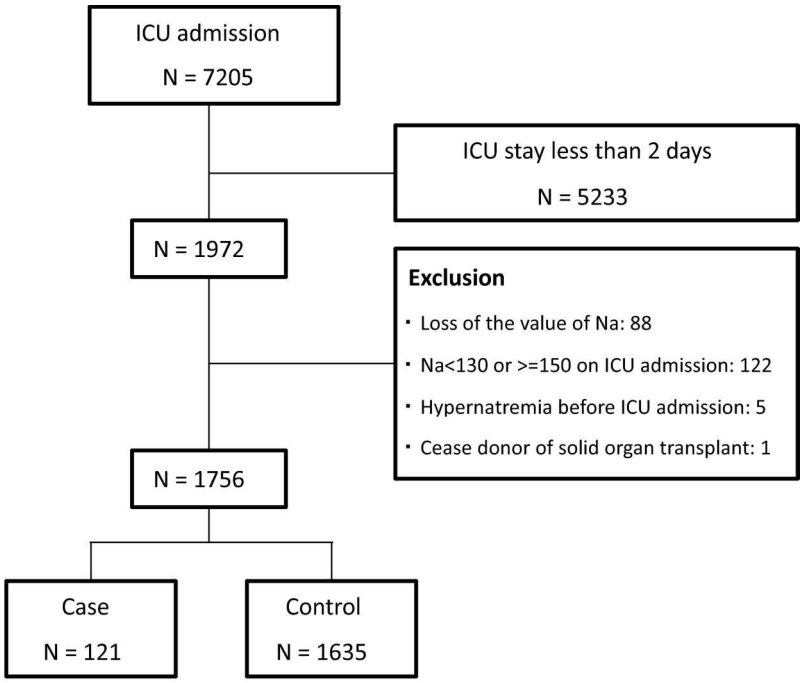
Figure 2. Kaplan–Meier survival curves of the interaction between intensive care unit (ICU)-acquired hypernatraemia and cerebrovascular diseases.

Figure 3. Association between maximum and minimum sodium concentration and mortality (adjusted odds ratio and 95% confidence intervals) by restricted cubic spline model (3 knots) in patients with cerebrovascular diseases. The dashed lines represent the 95% confidence intervals for the spline model.

A. Maximum sodium concentration and 28-day mortality. (Reference: 144 mEq/L) The curve's nadir was between 141 and 146 mEq/L.

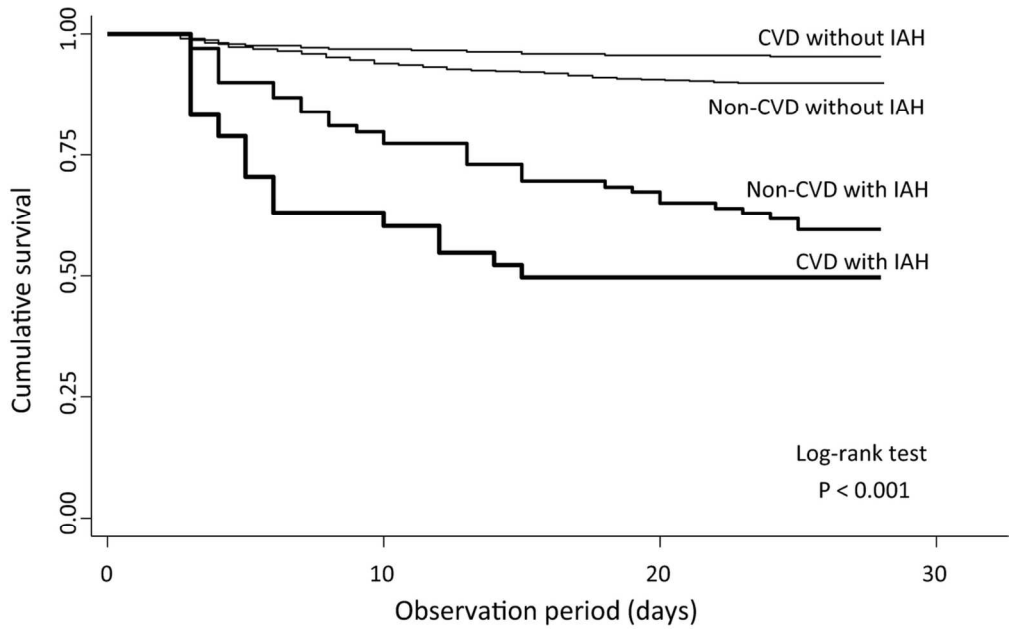
B. Minimum sodium concentration and 28-day mortality. (Reference: 141 mEq/L) The spline curve was not significantly associated with mortality.

Supplementary Figure 1. Kaplan–Meier survival curves of patients with and without intensive care unit (ICU)-acquired hypernatraemia.



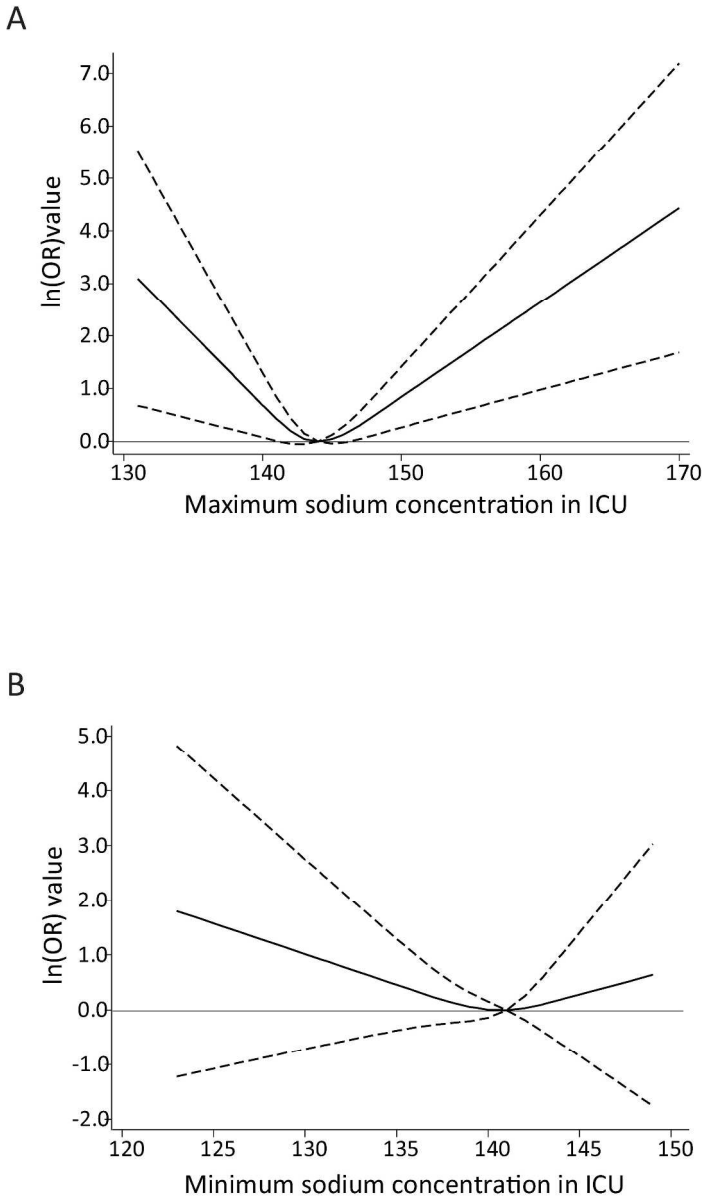
Flow chart of patients admitted during the study period.

180x165mm (300 x 300 DPI)



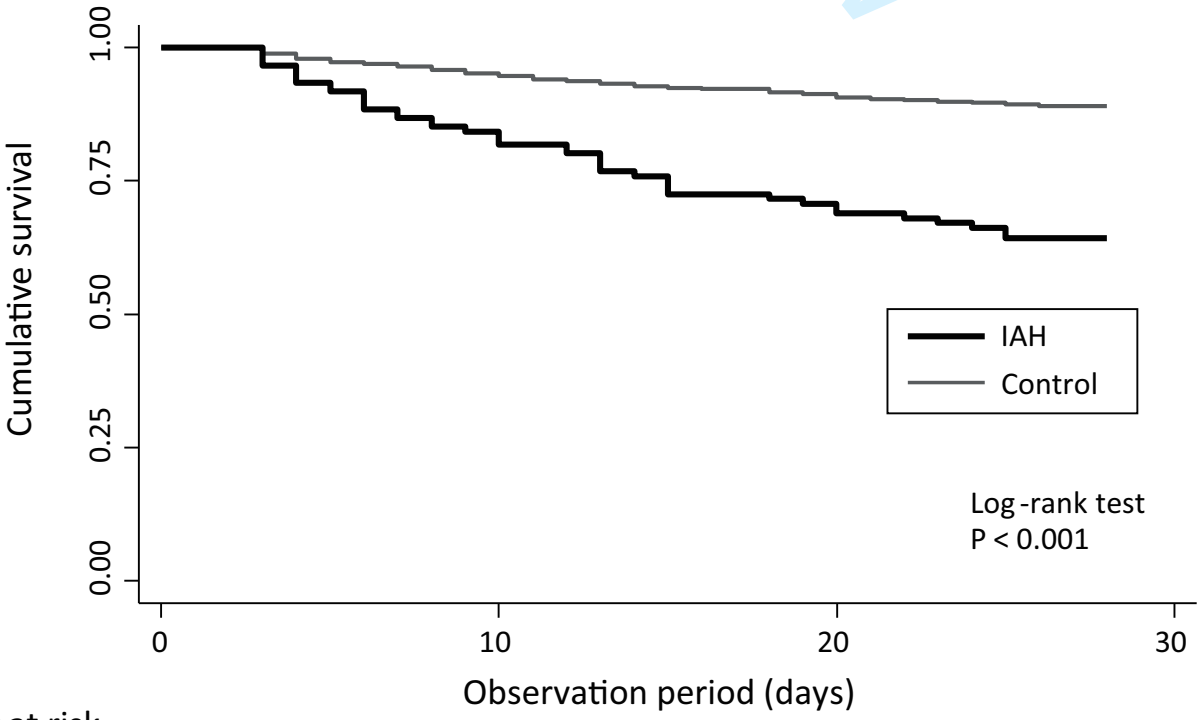
Kaplan–Meier survival curves of the interaction between intensive care unit (ICU)-acquired hypernatraemia and cerebrovascular diseases.

106x66mm (300 x 300 DPI)



Association between maximum/minimum sodium concentration and mortality by restricted cubic spline model in patients with cerebrovascular diseases.
A. Maximum sodium concentration and 28-day mortality. (Reference: 144 mEq/L)
B. Minimum sodium concentration and 28-day mortality. (Reference: 141 mEq/L)

213x368mm (300 x 300 DPI)



Number at risk

Control	1635	1372	916	0
IAH	121	102	79	0

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	none
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	none
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	none
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	none
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.