Variability in serum sodium concentration and prognostic significance in severe traumatic brain injury: a multi-center observational study

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This study followed the STROBE recommendation for observational studies (appendix 1)

Abstract

Background/Objective: Dysnatremia is common in severe traumatic brain injury (TBI) patients and may contribute to mortality. However, serum sodium variability has not been studied in TBI patients. We hypothesized that such variability would be independently associated with mortality.

Methods: We collected 6-hourly serum sodium levels for the first 7 days of ICU admission from 240 severe TBI patients in 14 neurotrauma ICUs in Europe and Australia. We evaluated the association between daily serum sodium standard deviation (dNa_{SD}), an index of variability, and 28-day mortality.

Results: Patients were 46 ± 19 years of age with a median initial GCS of 6 [4 – 8]. Overall hospital mortality was 28%. Hypernatremia and hyponatremia occurred in 64% and 24% of patients, respectively. Over the first 7 days in ICU, serum sodium standard deviation was 2.8 [2.0 – 3.9] mmol/L. Maximum daily serum sodium standard deviation (dNa_{SD}) occurred at a median of 2 [1-4] days after admission. There was a significant progressive decrease in dNa_{SD} over the first 7 days (coefficient -0.15 95%CI [-0.18 - -0.12], p<0.001). After adjusting for baseline TBI severity, diabetes insipidus, the use of osmotherapy, the occurrence of hypernatremia and hyponatremia and center, dNa_{SD} was significantly independently associated with 28-day mortality (HR 1.27 95%CI (1.01-1.61), p=0.048).

Conclusions: Our study demonstrates that daily serum sodium variability is an independent predictor of 28-day mortality in severe TBI patients. Further prospective investigations are

necessary to confirm the significance of sodium variability in larger cohorts of TBI patients and test whether attenuating such variability confers outcome benefits to such patients.

Introduction

Serum sodium concentration is tightly regulated in humans. However, severe traumatic brain injury (TBI) patients are at high-risk of developing dysnatremia due to the use of hyperosmolar therapy, diabetes insipidus[1] and inappropriate water retention. As both hypernatremia and hyponatremia have been reported to be independently associated with mortality and worse outcome in TBI patients[2–4], serum sodium management appears an important therapeutic target in patients with raised intracranial pressure. However, given their potential to induce osmotic injury to neurons [5–7], it would seem plausible that, independent of hypo or hypernatremia, changes in sodium concentration may be at least as pathophysiologically important as the serum sodium concentration itself.

Outside the context of TBI, in order to gain further insights into the association between serum sodium disorders and outcome, several authors have considered serum sodium variability over time [8,9]. In these studies, serum sodium variability was associated with mortality independently of the serum sodium level itself. We therefore hypothesized that, in a population of severe TBI patients, serum sodium variability would be associated with mortality regardless of the occurrence of hyponatremia and hypernatremia. In order to test this hypothesis, in an international multicenter cohort study of severe TBI patients, we sought to assess the daily variability of serum sodium over the first 7 days of intensive care unit (ICU) stay and its relationship with 28-day mortality.

Methods

We have provided a STROBE (Strengthening the reporting of observational studies in epidemiology) checklist in Supplementary Appendix 1. Ethics approval for contribution to this dataset was obtained locally by each center.

Study population

We retrospectively collected data on previously managed patients in 14 Intensive Care Units (ICUs) treating TBI patients. The description of data collection has been described previously [10]. Two centers were from Australia (both from Melbourne), and the remaining 12 were from Europe (London and Cambridge, UK; Paris and Nice, France; Valencia, Spain; Lausanne, Switzerland; Brussels, Belgium; Monza, Italy; Berlin, Germany; Rotterdam, The Netherlands; Solna, Sweden and Innsbruck, Austria).

We included the first 20 patients admitted to each center in 2015 (except two centers that included 14 and 10 patients, respectively). Inclusion criteria were age ≥ 18 years, severe TBI as defined by a Glasgow Coma Scale (GCS) of 8 or less after resuscitation but before sedation, and an intracranial pressure (ICP) monitor in place for at least 72 hours. Patients dying within 48 hours of ICU admission were excluded in order to focus on those with a potentially salvageable injury.

Data collection

Each center retrospectively collected demographic, clinical and biochemical data. Baseline admission data included age, sex, GCS, pupil reactivity, hemoglobin, blood glucose levels and brain computed tomography CT-scan findings as required to calculate the Marshall score and illness severity scores: injury severity score (ISS), Acute Physiology and Chronic Health Evaluation

score (APACHE-II) and International Mission for Prognosis and Analysis of Clinical trial in TBI score (IMPACT-score, core + CT + lab) for each patient.

We collected six-hourly serum sodium concentrations from ICU admission until 7 days, or death, whichever came first. We collected data on important aspects of TBI care including neurosurgery (clot evacuation, extra-ventricular drainage, decompressive craniectomy) as well as the use of osmotherapy[10], barbiturate coma and hypothermia (less than 35°C) and daily total desmopressin administered. Finally, we collected outcome data including ICU and hospital mortality, and ICU and hospital length of stay.

Definition of serum sodium variability

We defined daily serum sodium variability as the daily standard deviation of serum sodium measurements (dNa_{SD}) for each individual for each day over the first seven days of admission. We also calculated serum sodium variability as the standard deviation of all serum sodium measurements taken during the seven-day period (Na_{SD}) after admission for each patient. We defined patients with high sodium variability as those having a Na_{SD} greater than the median Na_{SD} for the whole cohort. We used this threshold since no data are available on serum sodium variability in TBI patients.

Generation of variables

Natremia on admission was defined as the first available sodium concentration after admission to ICU. Hyponatremia and hypernatremia were defined as at least one serum sodium value below 135 mmol/L or above 145 mmol/L, respectively[11]. The minimum and maximum sodium (Na_{min} and Na_{max}) concentrations for each patient were taken to be the lowest and highest measured serum sodium concentrations over the first 7 days of their ICU stay. Mean

serum sodium concentration was calculated for each patient as the mean (Na_{mean}) of all serum sodium measurements taken during the seven-day period. Since serum sodium was measured 6-hourly, Na_{mean} was equivalent to a time-weighted average serum sodium. We also calculated daily maximum sodium (dNa_{max}), daily minimum sodium (dNa_{min}), daily mean serum sodium (dNa_{mean}) for each of the 7 first days of admission.

We defined two thresholds for acute serum sodium changes (increases or decreases) as changes of 3 or 6 mmoles between two serum sodium measures (i.e. over 6 hours), corresponding to rates of change higher than 0.5 and 1.0 mmol/L/h respectively[11].

We defined $center_{high}$ as the center with the highest mean serum sodium over the first 7 days of ICU stay and $center_{low}$ as the center with the lowest mean serum sodium over the first 7 days. We used desmopressin administration as a surrogate marker of central diabetes insipidus[12].

Missing data

Patients with 50% or more missing data were not included in the analysis. For patients with less than 50% missing data, we interpolated missing serum sodium values by assigning the mean value of the previous and the next available serum sodium measure.

Serum sodium measurement

Serum sodium measurement was performed by blood gas analyzers in each ICU, except in two centers where a small number of samples were sent to the central lab. In each center, analyzer maintenance was performed as recommended by the manufacturer with at least one daily autocalibration.

Statistical analysis

We expressed quantitative variables as means (standard deviation) or medians [interquartile range] while categorical variables were expressed as counts (proportion). We compared

normally-distributed variables with a t-test and used a Chi-square test to compare proportions. For non-normally distributed variables, we used the Mann-Whitney test.

We analyzed the effect of time on dNa_{SD} with a linear mixed model with time as a fixed effect and patient as a random effect. In order to assess changes in six-hourly serum sodium over time in $center_{low}$, $center_{high}$ and the remaining centers, we built 2 linear mixed models to compare $center_{low}$ with the remaining centers and $center_{high}$ with the remaining centers over the first 7 days of ICU admission, by considering center as a fixed effect and patient as a random effect.

To compare the impact of mannitol and HTS on serum sodium measurements in univariate analysis, we used a linear mixed model with mannitol and HTS as 2 different fixed effects (and included an interaction between mannitol and HTS) and patient as a random effect.

In order to assess sensitivity to missing sodium measures, we conducted all linear mixed models in the whole cohort and in the subpopulation of patients without missing sodium measures.

We first compared in a univariate analysis the characteristics of survivors and non survivors. We then examined the relationship between 28-day mortality and variables that had a p-value <0.10 in univariate analysis (dNa_{SD} as a measure of daily sodium variability, dNa_{max}, dNa_{min}) by applying a Cox proportional-hazards regression model. This model analyzed the relationship between time to mortality (up to 28 days) and these variables. We adjusted the model for baseline risk of death (IMPACT score) and for other known confounding risk factors for death (diabetes insipidus, osmotherapy, hypernatremia and hyponatremia)[2,13]. Diabetes insipidus was considered as a daily time-dependent variable whose value was 0 and became 1 on the first day desmopressin was given. Hypertonic saline and mannitol were both considered as time-dependent variables whose values were 1 on the days they were given and 0 on the days they were not administered. Hypernatremia and hyponatremia were considered as time-dependent covariates with an assigned value of 0 on those days when they were absent and a value of 1 if at least one serum

sodium measure was higher than 145 mmol/L (hypernatremia) or below 135 mmol/L (hyponatremia) that day. By adjusting for the occurrence of daily hyponatremia and hypernatremia, we aimed to investigate whether daily fluctuations in serum sodium as quantified by daily serum sodium standard deviation are associated with outcome regardless of the level of the serum sodium level they fluctuate around. To account for variations in dNa_{SD} (i.e., daily variations in Na_{SD}), we considered dNa_{SD} as a continuous time-varying variable whose daily value was included in the model. This approach limits the risk of « survivor treatment selection bias » that would have been encountered if sodium variability had been considered as a time-fixed variable [14]. We accounted for center effect by adding center as a random effect in the multivariable Cox proportional hazard regression model. In order to assess sensitivity of our Cox model to missing serum sodium measures, we also applied, as recommended elsewhere [15], a multiple imputation method for missing data in repeated measurements using a fully conditionnal specification method for regularly spaced data (MICE package for R) and calculated hazard ratios from this imputed dataset.

The two-sided level of significance was fixed at 5%. We analyzed results using R open source software 3.4.1 (http ://www.R-project.org).

Results

General characteristics of study patients

We collected data on 262 patients. We excluded 22 patients because of more than 50% missing sodium values. From the 240 patients included in the analysis, we obtained 5,806 serum sodium measurements. We collected serum sodium over a median of 6 [5-7] days. There were 185 missing serum sodium measures (3.2%) in 57 patients that were imputed according to the study protocol. Additional description of missing sodium measures is provided in Table 1 of the Supplementary Appendix 2.

The characteristics of the study population are described in Table 1. Patients were predominantly middle-aged males with a median Injury Severity Score of 30 [25-41]. Median GCS prior to sedation was 6 [4-8]. One third had at least one fixed pupil at hospital admission. About one-third of patients underwent neurosurgery for clot evacuation. Overall hospital mortality was 28%. A comparison of characteristics in patients without missing sodium and those with missing sodium measures is provided in table 2 of the Supplementary Appendix 2.

General description of serum sodium

Table 1 summarizes serum sodium values of the study population. Hypernatremia and hyponatremia occurred in 153 (64%) and 58 (24%) patients respectively. Moreover, 74 (48%) of those developing hypernatremia had received hypertonic saline over the first 7 days of admission. When considering the mean serum sodium by center over the first 7 days of admission, the median Na_{mean} was 143.1 [142.7-144.4] mmol/L with differences of greater than 10 mmol/L between some centers. Serum sodium levels were significantly different between $center_{low}$, $center_{high}$ and all other centers over time (Figure 1 of the Supplementary Appendix 3, p<0.001). Similar results were found when excluding patients with missing sodium measures

(Table 1 of the Supplementary Appendix 3). The evolution of ICP over the first 7 days of admission is shown in Supplementary Appendix 4.

Serum sodium variability

Over the first 7 days of ICU stay, median Na_{SD} was 2.8 [2.0 – 3.9] mmol/L. Median dNa_{SD} was 1.3 [0.8-1.9] mmol/L. Maximum dNa_{SD} occurred at a median of 2 [1-4] days after admission. Figure 1 shows dNa_{SD}, dNa_{mean}, dNa_{max} and dNa_{min} over the first seven days of admission. There was a significant progressive decrease in dNa_{SD} over the first 7 days (coefficient -0.15 95%CI [-0.18 - -0.12], p<0.001). Similar results were found when excluding patients with missing sodium measures (Supplementary Appendix 5).

A comparison of patients experiencing Na_{SD} higher than 2.8 mmol/L (i.e. median Na_{SD} in the cohort over the first 7 days in ICU) with those having Na_{SD} lower than 2.8 mmol/L is shown in Table 2. Patients with high Na_{SD} received more desmopressin and osmotherapy and had higher ISS. Moreover, patients with high Na_{SD} were more likely to experience hyper and hyponatremia (Table 2).

Serum sodium decreased by at least 0.5 mmol/L/h in 3.3 % of 6-hourly episodes (i.e. 14% of days with such a rapid decrease in serum sodium), and by at least 1.0 mmol/L in 0.5 % of 6-hourly episodes. Serum sodium increased by at least 0.5 mmol/L/h in 5.3% of 6-hourly episodes (i.e. 21% of days with such a rapid increase in serum sodium), and by at least 1.0 mmol/L/h in 1.0 % of 6-hourly episodes (Table 1). Acute six-hourly increases in serum sodium (i.e. six-hourly increase of more than 0.5 or 1.0 mmol/L/h) occurred more often in patients with high Na_{SD}. ICU and hospital mortality were higher in patients with a high Na_{SD} than those with a low Na_{SD} but it did not reach statistical significance.

Both mannitol and hypertonic saline affected dNa_{SD} in the same way (Supplementary Appendix 6). HTS was associated with the occurrence of hypernatremia, an increased Na_{mean} and Na_{max} while mannitol was associated with the occurrence of hyponatremia and with more common acute serum sodium changes (Supplementary Appendix 6). Similar results were found when excluding patients with missing sodium measures (Supplementary Appendix 6). 2 centers exclusively used mannitol, 3 centers exclusively used hypertonic saline whereas 9 centers used both agents.

Relationship between serum sodium variability and outcome

General characteristics and serum sodium levels of survivors and non-survivors are presented in Table 3. Na_{max} and Na_{mean} were significantly different between survivors and non-survivors. Na_{min} and Na_{SD} were not significantly different between survivors and non-survivors. Acute increases in six-hourly measured serum sodium (i.e. a rise in six-hourly serum sodium of more than 0.5 or 1.0 mmol/L/h) were significantly more common in non-survivors than survivors while hyponatremia and hypernatremia were not.

When individually including variables that had a p-value <0.10 in univariate analysis between survivors and non survivors (dNa_{max}, dNa_{min}, dNa_{SD}) in a Cox proportional hazards model for mortality, adjusted for baseline severity (IMPACT score), the occurrence of diabetes insipidus, the use of osmotherapy, and the occurrence of hypernatremia or hyponatremia, only dNa_{SD} was significantly associated with 28-day mortality (HR 1.27 95%CI (1.01-1.61), p=0.048, Table 4). Of note, hypernatremia and hyponatremia were not independently associated with 28-day mortality in this model (HR 1.73 95%CI (0.94-3.20), p=0.08 and 0.74 (0.24-2.28), p=0.60 respectively). Similar results were found when applying the same Cox proportional hazards

model to data imputed with a multiple imputation method for missing data in repeated measurements using a fully conditionnal specification method for regularly spaced data (Supplementary Appendix 7).

Discussion

Key findings

In an international multi-center study, we aimed to analyze daily serum sodium variability over the first seven days of ICU stay, and its relationship with 28-day mortality. We found that sodium variability was highest during the first 2 days after admission and progressively decreased thereafter. We also found that variability of serum sodium (as reflected by its daily standard deviation), even after adjustment for TBI severity, diabetes insipidus, osmotherapy, hyponatremia and hypernatremia, was a significant predictor of mortality. To our knowledge, this is a novel finding in severe TBI patients.

Relationship with previous studies

Severe TBI leads to disorders of serum sodium and water handling [16]. While some factors such as the use osmotherapy, the use of fluids with high sodium content, and choice of nutritional preparations are at the discretion of the physician, other factors are trauma-related, such as the occurrence of posterior pituitary dysfunction[17,18]. In the latter case, a deficit in antidiuretic hormone (ADH) secretion results in water loss and hypernatremia, whereas excessive ADH secretion leads to water retention and the risk of hyponatremia[19]. In TBI patients, the prevalence of hyponatremia and hypernatremia has been reported between 15 to 55% [4,13,20–22] and 30 to 50%, [2,23,24] respectively. In keeping with these studies, we found that 24% of patients experienced hyponatremia. Our finding that 64% of patients experienced hypernatremia during the period of observation is higher than previously described, and likely explained by the greater frequency of measurement in our study.

Our study shows that even within academic centers in Europe and Australia there is marked variability in serum sodium levels according to center. Such high variability between centers should be interpreted in the context of previous conflicting results in TBI patients[5,25,26], which suggests that the optimal level of serum sodium remains unclear. Similar to what has been described in general ICU patients[8,27], serum sodium variability was highest over the first 2 days in our cohort of severe TBI patients and the extent of serum sodium variability was similar in our study population to that previously reported in burns patients[27]. Studies of serum sodium report a greater occurrence of dysnatremias in neuro-critical care patients[2,20,24] compared to general ICU patients[8,28,29]. Accordingly, risk factors for increased dNa_{SD} included osmotherapy and desmopressin administration.

As expected, mannitol was associated with more common hyponatremia whereas HTS led to a higher incidence of hypernatremia. Mannitol-induced hyponatremia is a non-hypotonic hyponatremia and may thus not have the same meaning as true hyponatremia. Mannitol was also associated with more acute changes in serum sodium than HTS. Whether this relates to the osmotic drug in itself or some unmeasured confounders remains to be investigated.

Unlike absolute sodium concentration[2,4,23], any association that may exist between serum sodium variability and outcome has not been investigated in TBI patients. In our study, after adjusting for baseline severity and previously described key confounding factors influencing serum sodium level[2], serum sodium variability, as assessed by dNa_{SD}, was associated with 28-day mortality. Moreover, this association was independent of the occurrence of daily hyponatremia and hypernatremia, which suggests that fluctuations in sodium leading to an increased dNa_{SD} are associated with mortality at any sodium level. Serum sodium standard

deviation does not capture the rate of serum sodium change. However, those patients with high serum sodium variability had more periods of rapid sodium change, raising the possibility that acute variations in sodium might partly account for the relationship between dNa_{SD} and outcome. Indeed, a retrospective analysis of the subset of TBI patients in the SAFE study who received the relatively hypotonic (260 mOsm/L) 4% albumin solution rather than 0.9% sodium chloride as resuscitation fluid, raised the possibility that the mechanism of increased mortality in those receiving albumin was related to episodes of increased ICP [30] induced by rapid changes in osmolarity.

Implications of study findings

Our findings imply that, in TBI patients, serum sodium variability is independently associated with mortality. This variability is highest during the first 2 days of ICU stay. Mannitol use potentially leads to greater sodium changes than hypertonic saline. As dNa_{SD} is potentially a modifiable risk factor for mortality, further investigation is needed to determine whether attenuation of such variability may be beneficial to patients.

Strengths and limitations

Our study has several strengths. It is the first international multicenter study describing the independent association of dNa_{SD} with mortality. Thus, across a wide spectrum of behavior and sodium management, our findings still hold and have external validity within such a spectrum of practice. Moreover, serum sodium was measured six-hourly during the first week after ICU admission and on more than 5,000 occasions, providing the most robust and detailed assessment to date of serum sodium changes over time in TBI patients. In addition, we collected daily use of osmotherapy as well as desmopressin, allowing us to account for important causes of sodium

variability that may have confounded the association of serum sodium with death in other studies.

We acknowledge several limitations. This is a retrospective study with all the inherent limitations of such studies. However, sodium levels are objective, reproducible, and not subject to selection or ascertainment bias, and mortality is a clear patient-centered outcome. We had 3.2% missing sodium measures, nonetheless, our findings were robust to different approaches to imputation and linear mixed models were not sensitive to missing sodium measures. We did not measure neurological outcome. This would have required systematic follow-up at 6 months or one year. This shortcoming will have to be addressed in future studies of sodium variability. As this study was not a randomized controlled trial, we can make no inferences as to causality. While we adjusted for TBI severity, we could not adjust for ICP elevations, which are a major clinical variable triggering therapeutic interventions, potentially including intentional changes in serum sodium. Thus, it remains possible that serum sodium variability is simply a marker of illness severity. However, if this is the case, such variability appears to be a more powerful risk factor than hypernatremia and hyponatremia and should be taken into account in future predictive models for mortality in TBI patients.

Conclusion

In summary, in an international multicenter study, we found that serum sodium variability, as reflected by its daily standard deviation, has an independent association with mortality, after adjustment for TBI severity and key confounders. Further prospective investigations are necessary to confirm the significance of sodium variability in larger cohorts of TBI patients and test whether attenuating such variability confers outcome benefits to such patients.

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Figure 1
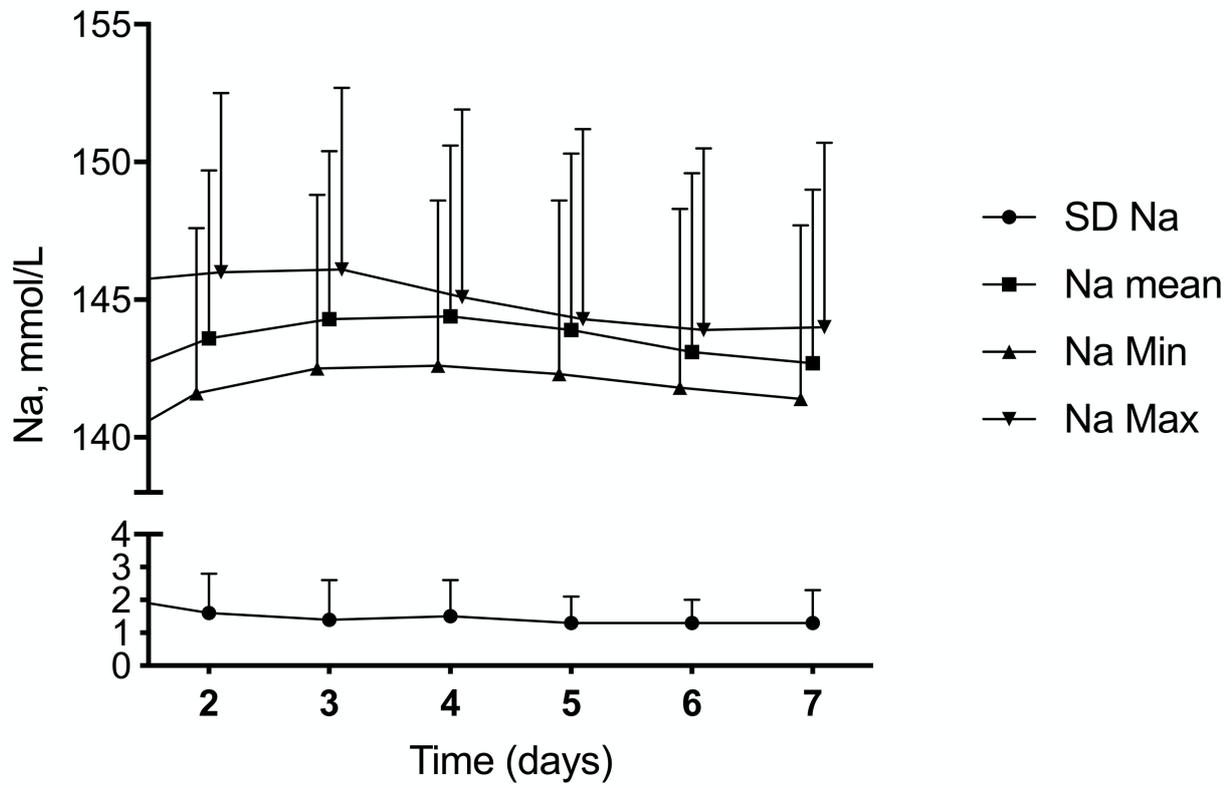
Table 1 : Clinical and serum sodium characteristics of the study population.

Variable	Value
Clinical characteristics	
Age, years	46 ± 19
Weight, kg	76 ± 13
Male, n (%)	186 (78)
GCS prior to sedation	6 [4 – 8]
At least one fixed pupil at admission, n(%)	79 (33)
Marshall score	3 [2 – 5]
Injury Severity Score	30 [25 – 41]
APACHE II Score	19 [15 – 24]
Extended IMPACT predicted 6 month-mortality, %	25 [14 – 39]
Neurosurgery (for clot evacuation), n(%)	90 (38)
Extra-ventricular drain, n(%)	82 (34)
Hypothermia ≤ 35°C, n(%)	59 (26)
Barbiturate, n(%)	27 (11)
Decompressive craniectomy, n(%)	70 (29)
ICU mortality, n(%)	57 (24)
Hospital mortality, n(%)	66 (28)
First Natremia in ICU	
Admission natremia, mmol/L	140 [137-143]
Hypernatremia within the first 7 days	
Hypernatremia >145 mmol/L, n(%)	153/240 (64)
Time from admission to hypernatremia >145 mmol/L, h	24 [12 - 60]
Hyponatremia within the first 7 days	
Hyponatremia <135 mmol/L, n(%)	58/240 (24)
Time from admission to hyponatremia <135 mmol/L, h	24 [6 - 111]
Acute Serum Sodium changes within the first 7 days *	
Serum sodium increase > 0.5 mmol/L/h, n(%)	294/5566 (5.3)
Serum sodium increase > 1 mmol/L/h, n(%)	55/5566 (1.0)
Serum sodium decrease > 0.5 mmol/L/h, n(%)	186/5566 (3.3)
Serum sodium decrease > 1.0 mmol/L/h, n(%)	26/5566 (0.5)
Serum sodium according to center within the first 7 days	
Mean serum sodium (all centers, Na_{mean}), mmol/L	143 ± 5
Mean Serum Sodium ($center_{high}$), mmol/L	149 ± 6
Mean Serum Sodium ($center_{low}$), mmol/L	138 ± 4
Serum sodium extreme values within the first 7 days	
Minimum Serum Sodium (Na_{min}), mmol/L	137 [135 – 140]
Maximum Serum Sodium (Na_{max}), mmol/L	147 [144 - 152]
Serum sodium variability within the first 7 days	
Standard deviation of serum sodium (Na_{SD}), mmol/L	2.8 [2.0 – 3.9]

* Acute changes in serum sodium are given in number of six-hourly period of time with rate of change greater than 0.5 or 1 mmol/L/h. Data are reported as mean ± SD, median [interquartile ranges] or n (proportion). APACHE = acute physiology and chronic health evaluation, EVD = extraventricular drain, GCS = Glasgow Coma Scale, ICU = intensive care unit, IMPACT = international mission for prognosis and analysis of clinical trials in TBI, ISS = injury severity score. $center_{high}$ = the single center with the highest mean serum sodium level over the first 7 days of admission, $center_{low}$ = the single center with the lowest mean serum sodium level over the first 7 days of admission. Na_{max}= maximum serum sodium over 7 days of admission, Na_{mean} = mean serum sodium over 7 days of admission, Na_{min} = minimum serum sodium over 7 days of admission, Na_{SD} = standard deviation of serum sodium over 7 days of admission.

Table 2: General and serum sodium characteristics in patients with high Na_{SD} and low Na_{SD}

Variable	High Na_{SD} (n=120)	Low Na_{SD} (n=120)	p
Age	43 [28-59]	46 [32-66]	0.08
APACHE II	19 [15-24]	21 [16-24]	0.29
ISS	34 [25-43]	27 [25-35]	0.001
Extended IMPACT predicted 6 month-mortality, %	26 [15-41]	23 [14-38]	0.34
Diabetes Insipidus, n(%)	26 (21.7)	9 (7.5)	0.002
Osmotherapy, n(%)	85 (70.8)	55 (45.8)	<0.001
HTS, n(%)	62 (51.7)	36 (30.0)	<0.001
Mannitol, n(%)	54 (45.0)	38 (31.7)	0.03
EVD, n(%)	49 (40.8)	33 (27.5)	0.03
Neurosurgery, n(%)	44 (36.7)	46 (38.3)	0.79
Admission serum sodium, mmol/L	140 [137-144]	140 [138-143]	0.92
Na_{mean}, mmol/L	145.3 ± 6.1	141.6 ± 3.4	<0.001
Hypernatremia, n(%)	99 (82.5)	54 (45)	<0.001
Hyponatremia, n(%)	39 (32.5)	19 (15.8)	0.002
Na_{max}, mmol/L	152 [147-157]	145 [143-148]	<0.001
Na_{min}, mmol/L	137 [134-140]	137 [136-140]	0.06
Acute Serum Sodium changes within the first 7 days*			
Serum sodium increase > 0.5 mmol/L/h, n(%)	95/2836 (3.3)	59/2730 (2.2)	0.007
Serum sodium increase > 1 mmol/L/h, n(%)	40/2836 (1.4)	5/2730 (0.2)	<0.001
Serum sodium decrease > 0.5 mmol/L/h, n(%)	77/2836 (2.7)	32/2730 (1.2)	<0.001
Serum sodium decrease > 1.0 mmol/L/h, n(%)	20/2836 (0.7)	3/2730 (0.1)	<0.001
Na_{SD}, mmol/L	3.9 [3.4-4.8]	2.0 [1.7-2.4]	<0.001
ICU length of stay, days	15 [7-21]	13 [9-19]	0.74
Hospital length of stay, days	21 [8-34]	20 [13-30]	0.95
ICU mortality, n(%)	33 (27.5)	24 (20)	0.17
Hospital mortality, n(%)	38 (31.7)	28 (23.3)	0.15

* Acute changes in serum sodium are given in number of six-hourly period of time with rate of change greater than 0.5 or 1 mmol/L/h. High Na_{SD} was defined as Na_{SD} over the first 7 days of admission higher than median Na_{SD} (i.e. 2.8 mmol/L). Data are reported as mean ± SD, median [interquartile ranges] or n (proportion). APACHE = acute physiology and chronic health evaluation, EVD = extraventricular drain, HTS=hypertonic saline, ICU =

intensive care unit, IMPACT = international mission for prognosis and analysis of clinical trials in TBI, ISS = injury severity score, Na_{max} = maximum serum sodium over 7 days of admission, Na_{mean} = mean serum sodium over 7 days of admission, Na_{min} = minimum serum sodium over 7 days of admission, Na_{SD} = standard deviation of serum sodium over 7 days of admission.

Table 3: General characteristics and serum sodium variability in hospital survivors and non survivors.

Variable	Survivors (n=174)	Non survivors (n=66)	p
Extended IMPACT predicted 6 month-mortality, %	21 [13-33]	38 [26-51]	<0.001
Diabetes Insipidus, n(%)	21 (12)	14 (21)	0.073
Osmotherapy, n(%)	93 (53)	47 (71)	0.013
HTS, n(%)	73 (42)	25 (38)	0.566
Mannitol, n(%)	57 (33)	34 (53)	0.004
Admission serum sodium, mmol/L	140 [137-143]	140 [138-143]	0.513
Na$_{mean}$, mmol/L	142.9 $\pm$ 4.8	144.8 $\pm$ 6.3	0.035
Hypernatremia, n(%)	106 (61)	47 (71)	0.139
Hyponatremia, n(%)	43 (25)	15 (23)	0.748
Na$_{max}$, mmol/L	147 [144-151]	149 [144-155]	0.024
Na$_{min}$, mmol/L	137 [135-140]	137 [135-141]	0.228
Acute serum sodium changes within the first 7 days*			
Serum sodium increase > 0.5 mmol/L/h, n(%)	103/4108 (2.5)	51/1458 (3.5)	0.009
Serum sodium increase > 1 mmol/L/h, n(%)	27/4108 (0.7)	18/1458 (1.2)	0.034
Serum sodium decrease > 0.5 mmol/L/h, n(%)	78/4108 (1.9)	31/1458 (2.1)	0.590
Serum sodium decrease > 1.0 mmol/L/h, n(%)	17/4108 (0.4)	6/1458 (0.4)	0.991
Na$_{SD}$, mmol/L	2.7 [2.0-3.6]	2.9 [2.2-4.2]	0.065
Length of stay, days	24 [17-38]	9 [5-15]	-

* Acute changes in serum sodium are given in number of six-hourly period of time with rate of change greater than 0.5 or 1 mmol/L/h. Data are reported as mean $\pm$ SD, median [interquartile ranges] or n (proportion). EVD = extraventricular drain, HTS = hypertonic saline, ICU = intensive care unit, IMPACT = international mission for prognosis and analysis of clinical trials in TBI, ISS = injury severity score, Na$_{max}$= maximum serum sodium over 7 days of admission, Na$_{mean}$ = mean serum sodium over 7 days of admission, Na$_{min}$ = minimum serum sodium over 7 days of admission, Na$_{SD}$ = standard deviation of serum sodium over 7 days of admission

Table 4: Cox proportional hazards model for 28-day mortality

Variable	HR	95% CI Lower limit	95% CI Upper limit	P
dNa$_{SD}$	1.27	1.01	1.61	0.048
dNa$_{mean}$	1.05	0.99	1.10	0.096
dNa$_{max}$	1.05	0.99	1.11	0.070

Each variable was individually inserted into the model. Adjustment was made for IMPACT score, the occurrence of diabetes insipidus, daily use of osmotherapy, daily occurrence of hypernatremia and hyponatremia and center (as a random effect). CI = confidence interval, dNa$_{max}$= daily maximum serum sodium, dNa$_{mean}$ = daily mean serum sodium, dNa$_{SD}$ = daily standard deviation of serum sodium