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Early serum sodium dynamics and acute brain dysfunction in critically ill patients with impaired consciousness at admission: a retrospective cohort study

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Abstract

Introduction: Dysnatremia is common in critically ill patients, but the neurological relevance of early sodium dynamics is unclear.

Aim of the study: To evaluate whether sodium variability during the first 72 hours of intensive care is associated with acute brain dysfunction (ABD).

Material and Methods: This retrospective cohort study included 96 adults with an admission Glasgow Coma Scale (GCS) score ≤13 in an intensive care unit (ICU); the full verified cohort of 109 patients formed a sensitivity cohort. The sodium variability index (SVI) was the maximum minus minimum serum sodium within 72 hours. ABD was defined as delirium, seizures, and/or coma. The primary model included SVI, Acute Physiology and Chronic Health Evaluation (APACHE) II score, admission sodium, and neurological diagnosis.

Results: ABD occurred in 58 patients (60.4%). Median SVI was lower with ABD (4 vs. 7 mmol/L; p = 0.031). Higher SVI was associated with lower odds of ABD (adjusted odds ratio [OR] per 1 mmol/L 0.827; 95% confidence interval [CI] 0.722–0.947). Estimates were similar with Firth regression (OR 0.838), in the full cohort (OR 0.855), and after excluding patients with admission GCS ≤8 (OR 0.821) or who received sedation (OR 0.841), and were attenuated by adjustment for persistent hyponatremia (OR 0.858; 95% CI 0.736–0.999).

Conclusions: Lower early sodium variability, mainly reflecting a smaller sodium rise, was associated with ABD after adjustment for illness severity. Because the timing of ABD relative to sodium changes could not be established, these hypothesis-generating findings do not indicate prediction or causation.

Keywords: acute brain dysfunction; sodium variability; hyponatremia; critical illness; intensive care unit; delirium; serum sodium; biomarkers

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Introduction

Dysnatremia is among the most common electrolyte disturbances in critically ill adults, affecting approximately 20–40% of patients at intensive care unit (ICU) admission and an even greater proportion during ICU stay [1-5]. Both hypo- and hypernatremia are associated with adverse outcomes, although these associations largely reflect illness severity [1-5].

The central nervous system is particularly vulnerable to disturbances in sodium homeostasis. Hyponatremia may cause cerebral edema and neurological manifestations ranging from delirium to seizures [6-10], and fluctuations in serum sodium may also disturb cerebral osmotic homeostasis [5-8].

Acute brain dysfunction (ABD), commonly manifesting as delirium, seizures, or coma, is a frequent complication of critical illness and is independently associated with prolonged ICU stay, increased mortality, and persistent cognitive impairment among survivors [11-14]. Reliable early biochemical markers associated with ABD remain limited [11,15].

Most studies of dysnatremia have focused on static sodium measurements [1-5]. More recently, sodium variability has been associated with adverse outcomes independently of baseline sodium in hospitalized, surgical ICU, and neurocritical populations [16-24]. However, most of these studies examined mortality or global outcomes, and the association of sodium variability with organ-specific neurological complications

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has received little attention.

Failure to restore normonatremia early in critical illness may also reflect persistent disruption of sodium homeostasis, but its association with acute brain dysfunction has not been systematically investigated.

We therefore investigated the association between early sodium dynamics and acute brain dysfunction in critically ill adults, using the sodium variability index (SVI), defined as the difference between the maximum and minimum serum sodium concentrations during the first 72 hours of ICU stay, and, descriptively, persistent hyponatremia (maximum sodium <135 mmol/L) during the same period. We hypothesized that lower early sodium variability would be associated with acute brain dysfunction after adjustment for illness severity.

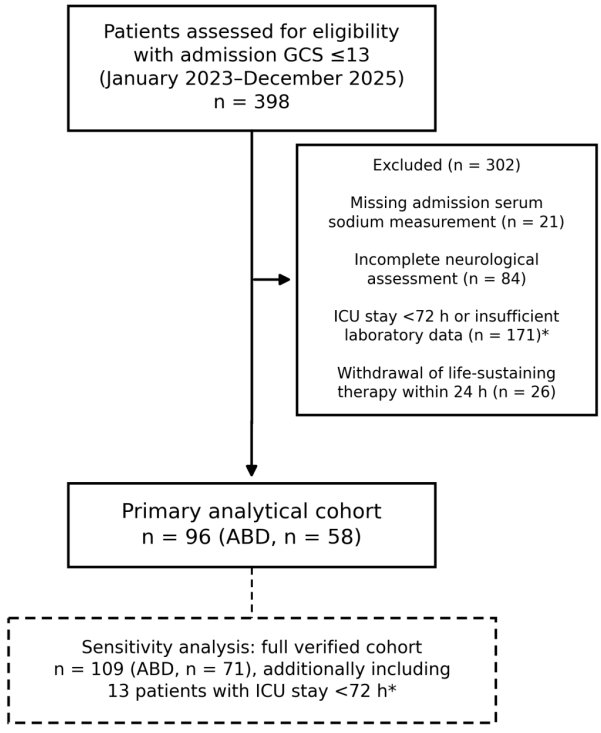
Materials and methods

Study design and setting

This retrospective cohort study was conducted in the adult intensive care unit of a tertiary referral hospital. Consecutive adult patients admitted between January 2023 and December 2025 were screened for eligibility. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Study population

A total of 398 patients were assessed for eligibility. Adult patients (≥18 years) with an admission Glasgow Coma Scale score of 13 or lower, selected to include patients with impaired consciousness at ICU admission, were eligible if serum sodium at ICU admission was available and laboratory and clinical data could be retrieved for at least the first 72 hours. Of the 302 patients excluded, 21 lacked an admission sodium measurement, 84 had incomplete neurological assessment, 171 had an ICU stay shorter than 72 hours or insufficient laboratory data, and 26 had life-sustaining therapy withdrawn within the first 24 hours. After applying the eligibility criteria, 96 patients comprised the primary analytical cohort (Figure 1). During data verification for this revision, we identified 13 patients who had been included in the original analysis although they did not meet the 72-hour criterion (12 died and 1 was transferred after 39–70 hours); they were excluded from the primary analysis, and the main analyses were repeated in the full verified cohort of 109 patients as sensitivity analyses.



* Includes 13 patients identified during data verification who had been included in the originally submitted analysis despite an ICU stay <72 h (died, n = 12; transferred, n = 1).

Figure 1. Flow diagram of patient screening and selection. Of 398 patients with an admission

Glasgow Coma Scale (GCS) score of 13 or lower assessed for eligibility between January 2023 and December 2025, 302 were excluded (missing admission serum sodium, n = 21; incomplete neurological assessment, n = 84; ICU stay <72 hours or insufficient laboratory data, n = 171; withdrawal of life-sustaining therapy within the first 24 hours, n = 26), leaving a primary analytical cohort of 96 patients. The full verified cohort (n = 109), which additionally includes 13 patients with an ICU stay <72 hours identified during data verification, was analyzed as a sensitivity analysis. ABD, acute brain dysfunction; ICU, intensive care unit.

Data collection

Clinical and laboratory data were retrospectively extracted from electronic medical records using standardized predefined case report forms. Collected variables included age, sex, primary diagnosis at ICU admission, illness severity assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, neurological status, organ support at ICU admission, and clinical outcomes.

Laboratory variables included serum sodium at ICU admission and all sodium measurements during the first 72 hours, together with admission potassium, chloride, creatinine, urea, glucose, lactate, C-reactive protein, procalcitonin, and albumin. During revision, the dataset was re-verified against the source medical records; this led to correction of several values and to identification of the 13 patients described above (details in Appendix A), and all analyses were repeated on the verified dataset.

Definitions

Sodium measurements and sodium variability. Serum sodium was measured at ICU admission and thereafter according to clinical practice. The minimum (Na_min) and maximum (Na_max) concentrations during the first 72 hours, including the admission value, were identified, and early sodium variability was quantified as the sodium variability index (SVI):

SVI = Na_max − Na_min

This range can be calculated from routine data; because it may depend on the number of measurements, this number was included as a covariate in the eight-variable model. Net change (last value within 72 hours minus admission sodium), the largest change within any 24-hour interval, and the number of changes in direction were derived from all time-stamped values (Appendix A, Section A.5).

Failure of sodium normalization (persistent hyponatremia) was defined as a maximum sodium concentration <135 mmol/L during the first 72 hours; it was analyzed descriptively and in a sensitivity analysis.

Acute brain dysfunction. The primary outcome, ABD, was defined as delirium, seizures, and/or coma at any time during ICU stay. Delirium was identified from physician documentation and bedside assessments, including the Confusion Assessment Method for the ICU (CAM-ICU) when available; sedation and consciousness were assessed with the Richmond Agitation–Sedation Scale (RASS). Seizures were identified from physician documentation. Coma was identified from contemporaneous physician documentation of coma accompanied by a GCS score ≤8. Sedation at any time during the ICU stay was recorded; the frequency of CAM-ICU assessments and the timing of sedation relative to neurological assessments were not systematically recorded. Patients were classified as having ABD if at least one manifestation occurred.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR); categorical variables as counts (%). Comparisons between patients with and without ABD used the Mann–Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Crude associations were described with univariable logistic regression. The prespecified eight-variable model included age, APACHE II score, invasive mechanical ventilation, sedation, SVI, cumulative fluid balance, number of sodium measurements, and any sodium-modifying therapy; Glasgow Coma Scale was not included because it is part of the APACHE II score and may lie on the pathway to ABD. Because this model had approximately 4.75 events per variable (38 patients in the smaller outcome group), we specified during revision a restricted model with four variables selected on clinical grounds as potential confounders: SVI, APACHE II score, admission sodium, and neurological admission diagnosis (acute ischemic stroke or intracerebral hemorrhage), corresponding to approximately 9.5 events per variable. In the primary cohort, 12 patients had acute ischemic stroke and 16 had intracerebral hemorrhage. The restricted model, fitted in the primary cohort, is the primary adjusted analysis; it was also fitted with Firth penalized-likelihood regres-

sion, and the eight-variable model is presented as a secondary analysis.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, multicollinearity was assessed with variance inflation factors, and there were no missing values in the primary cohort. Both models were internally validated with 1,000 bootstrap resamples (optimism-corrected C-statistic and calibration slope).

Sensitivity analyses repeated the main models in the full verified cohort (n = 109); excluded patients who received sedation at any time during the ICU stay, because sedation may interfere with outcome ascertainment; added osmotherapy (hypertonic saline and mannitol), persistent hyponatremia, or admission Glasgow Coma Scale score (a partial check for brain dysfunction present at admission) to the restricted model; and examined neurological and non-neurological diagnoses separately. Minimum and maximum sodium were each entered in place of SVI to identify which part of the sodium profile accounted for the association. Analyses were also repeated after excluding patients with an admission GCS score ≤8, without coma in the composite outcome, with coma counted only in patients who never received sedation, and within admission sodium categories, and alternative measures of sodium change replaced SVI (Appendix A, Table A.2). Alternative model specifications, the individual components of ABD, and the correlation between APACHE II score and the number of sodium measurements are reported in Appendix A.

The precise timing of onset of delirium, seizures, or coma relative to individual sodium measurements could not be reliably established from the retrospective records; ABD may therefore have preceded, coincided with, or followed the sodium changes captured by SVI, and the analyses were designed to assess association rather than temporal prediction.

All analyses reported in this revised manuscript were performed on the verified dataset using R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria); Firth penalized logistic regression was performed with the logistf package. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective design of the study, the Ethics Committee of Azerbaijan Medical University waived the requirement for ethical approval. Owing to the retrospective observational design and the use of fully anonymized data, the requirement for written informed consent was waived in accordance with applicable institutional policies and national regulations.

Results

Study population and baseline characteristics

Of 96 patients in the primary cohort, 58 (60.4%) had ABD (Table 1). Patients with ABD had higher APACHE II scores, lower admission Glasgow Coma Scale scores, more frequent sedation, and higher admission glucose; hospital mortality was also higher in patients with ABD (16 of 58 [27.6%] vs. 2 of 38 [5.3%]; p = 0.007). Admission sodium, other laboratory variables, vasopressor use, fluid balance, sodium-modifying therapies, and the number of sodium measurements did not differ significantly between groups. The most frequent admission diagnoses were COVID-19 pneumonia, intracerebral hemorrhage, acute heart failure, sepsis, and acute ischemic stroke (Appendix A, Table A.3).

Table 1. Baseline characteristics, early sodium dynamics, and early ICU management according to acute brain dysfunction status

Variable	No ABD (n = 38)	ABD (n = 58)	P value
Baseline characteristics			
Age, years	67.5 (58.0–76.5)	65.5 (53.5–78.75)	0.799
Male sex, n (%)	24 (63.2)	28 (48.3)	0.152
APACHE II score	20.0 (17.0–28.75)	25.5 (21.0–30.0)	0.013
Glasgow Coma Scale at ICU admission	12 (11–13)	11 (9–12)	0.001
RASS score at ICU admission	0 (0–0)	0 (0–1)	0.007
Sedation during ICU stay, n (%)	3 (7.9)	24 (41.4)	<0.001
Invasive mechanical ventilation, n (%)	12 (31.6)	28 (48.3)	0.105
Vasopressor use, n (%)	18 (47.4)	28 (48.3)	0.931
Sodium at ICU admission, mmol/L	136 (130–139)	135 (129.25–140)	0.842

Variable	No ABD (n = 38)	ABD (n = 58)	P value
Potassium, mmol/L	3.75 (3.50–4.68)	4.10 (3.50–4.58)	0.816
Chloride, mmol/L	104 (102–107.75)	104.5 (102–107.75)	0.866
Creatinine, µmol/L	83.0 (55.25–99.25)	83.5 (60.0–107.5)	0.579
Urea, mmol/L	14 (8–18)	15 (10–19)	0.241
Glucose, mmol/L	7 (5.25–9.0)	9 (7–11.75)	<0.001
Lactate, mmol/L	2.0 (1.3–3.0)	2.0 (1.23–3.0)	0.756
C-reactive protein, mg/L	69 (10.75–126.0)	76 (34.25–146.25)	0.556
Procalcitonin, ng/mL	0.13 (0.085–0.195)	0.13 (0.08–0.20)	0.907
Albumin, g/L	30 (22–32)	27.5 (20.5–32)	0.405
Admission hyponatremia (Na <135 mmol/L), n (%)	15 (39.5)	27 (46.6)	0.494
Admission hypernatremia (Na >145 mmol/L), n (%)	0 (0.0)	1 (1.7)	1.000
Early sodium dynamics (first 72 h)			
Sodium variability index (SVI), mmol/L	7 (4–10)	4 (3–7.75)	0.031
Persistent hyponatremia within the first 72 h, n (%)	2 (5.3)	11 (19.0)	0.070
Number of serum sodium measurements during the first 72 h	8 (6–10)	8 (6–10)	0.952
Early ICU management (first 72 h)			
Cumulative fluid balance, mL	1387.5 (240.25–2254.25)	1363.5 (67.5–2600.0)	0.911
Diuretic therapy, n (%)	20 (52.6)	28 (48.3)	0.676
Hypertonic saline administration, n (%)	5 (13.2)	8 (13.8)	0.929
Mannitol administration, n (%)	13 (34.2)	16 (27.6)	0.489

Data are presented as median (IQR) or number (%). Groups were compared as described in the Methods; Fisher's exact test was used for persistent hyponatremia and admission hypernatremia. ABD was defined as delirium, seizures, and/or coma during ICU stay. Persistent hyponatremia (failure of sodium normalization) was defined as a maximum serum sodium <135 mmol/L during the first 72 hours. There were no missing data. ABD, acute brain dysfunction; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQR, interquartile range; RASS, Richmond Agitation–Sedation Scale; SVI, sodium variability index.

Early sodium variability

Median SVI was lower in patients with ABD than in those without ABD (4 [IQR 3–7.75] vs. 7 [IQR 4–10] mmol/L; p = 0.031; Figure 2). Admission, minimum, and maximum sodium concentrations did not differ significantly between groups (Figure 3); median maximum sodium was 140.5 mmol/L in both groups, although its lower quartile was lower in patients with ABD (135 vs. 138 mmol/L; p = 0.147). Persistent hyponatremia occurred in 11 of 58 patients with ABD (19.0%) and 2 of 38 without ABD (5.3%; p = 0.070); these patients had a narrower sodium range than other patients (median SVI 3 vs. 6 mmol/L).

Univariable associations with acute brain dysfunction

In univariable analysis (Table 2), SVI was inversely associated with ABD (OR 0.900 per 1 mmol/L increase; 95% CI 0.810–0.999; p = 0.048), whereas admission sodium and admission hyponatremia were not.

Multivariable analysis

In the restricted model (n = 96; 58 events), higher SVI was associated with lower odds of ABD (adjusted OR 0.827 per 1 mmol/L increase; 95% CI 0.722–0.947; p = 0.006); higher APACHE II score was also associated

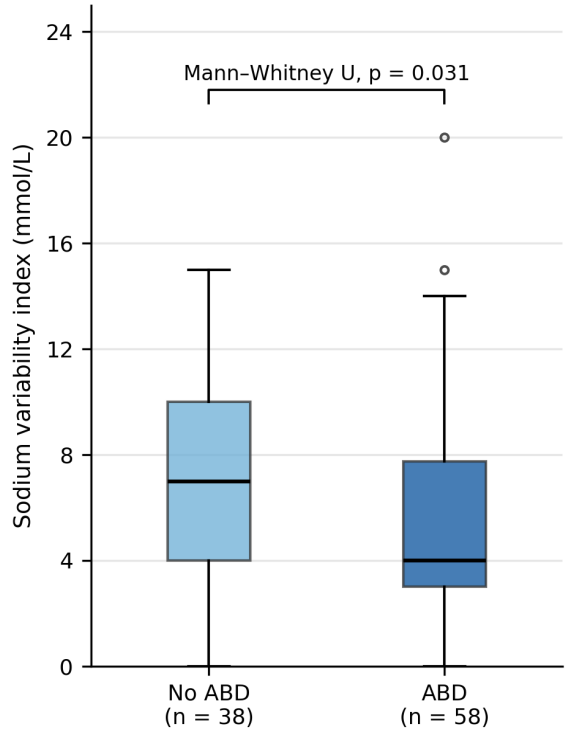


Figure 2. Distribution of the sodium variability index (SVI) during the first 72 hours after ICU admission according to the presence of acute brain dysfunction (ABD). Primary cohort (n = 96). Tukey boxplots. Groups were compared using the Mann–Whitney U test (p = 0.031). ICU, intensive care unit.

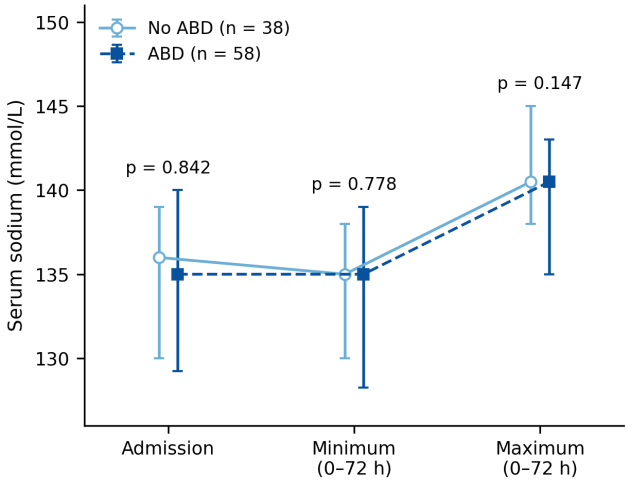


Figure 3. Early serum sodium profile according to acute brain dysfunction (ABD) status in the primary cohort (n = 96). Points represent the median serum sodium concentration at ICU admission, the minimum concentration during the first 72 hours, and the maximum concentration during the first 72 hours; these three summary values are not an evenly spaced time series and do not imply a fixed temporal sequence within the 72-hour window. Error bars indicate the interquartile range (IQR). P values represent between-group comparisons at each point using the Mann–Whitney U test. ABD, acute brain dysfunction; ICU, intensive care unit.

with ABD (adjusted OR 1.104 per point; 95% CI 1.018–1.198; p = 0.017), whereas admission sodium and neurological admission diagnosis were not (Table 2). The estimate was similar with Firth regression (OR 0.838; 95% profile-likelihood CI 0.730–0.950; p = 0.005) and in the eight-variable model (OR 0.860; 95% CI 0.756–0.978; p = 0.021), in which sedation was also associated with ABD. Bootstrap validation indicated some overfitting (optimism-corrected C-statistic 0.674 and calibration slope 0.78 for the restricted model; 0.725 and 0.66 for the eight-variable model; Appendix A).

Sensitivity analyses

The association was similar in the full verified cohort of 109 patients (restricted model OR 0.855; 95% CI 0.758–0.966; p = 0.012), in patients who never received sedation (OR 0.841; 95% CI 0.721–0.982), and after adding osmotherapy (OR 0.820; 95% CI 0.713–0.943) or admission Glasgow Coma Scale score (OR 0.822; 95% CI 0.709–0.951) to the restricted model; the latter adjustment should be interpreted cautiously because coma is a component of ABD. Adding persistent hyponatremia attenuated the estimate (OR 0.858; 95% CI 0.736–0.999), more so in the full cohort (OR 0.889; 95% CI 0.780–1.013). When entered in place of SVI, maximum sodium was inversely associated with ABD (OR 0.832 per 1 mmol/L; 95% CI 0.717–0.964; p = 0.015), whereas minimum sodium was not (OR 1.287; 95% CI 0.924–1.792; p = 0.135). Crude maximum sodium, however, did not differ significantly between groups. Estimates were in the same direction in neurological and non-neurological subgroups and for each component of ABD (Appendix A, Table A.1).

After exclusion of the 11 patients with an admission GCS score ≤8, all of whom had ABD, the estimate was similar (n = 85; OR 0.821; 95% CI 0.707–0.954), as it was when coma was removed from the outcome (OR 0.854; 95% CI 0.746–0.978) or counted only in patients who never received sedation (OR 0.837; 95% CI 0.732–0.958). Bidirectional sodium fluctuation was uncommon (8 of 96 patients); net change and the larg-

Table 2. Univariable and multivariable logistic regression analyses of factors associated with acute brain dysfunction

Variable	Crude OR (95% CI)	P value	Adjusted OR, restricted model (95% CI)*	P value
Age, per 1-year increase	0.996 (0.966–1.027)	0.789	—	—
Male sex	0.544 (0.236–1.257)	0.154	—	—
APACHE II score, per 1-point increase	1.089 (1.017–1.166)	0.015	1.104 (1.018–1.198)	0.017
Glasgow Coma Scale, per 1-point increase	0.649 (0.491–0.857)	0.002	—	—
RASS score at ICU, per 1-point increase	1.166 (0.886–1.534)	0.273	—	—
Sedation	8.235 (2.268–29.908)	0.001	—	—
Invasive mechanical ventilation	2.022 (0.859–4.761)	0.107	—	—
Vasopressor use	1.037 (0.457–2.352)	0.931	—	—
Neurological admission diagnosis‡	1.570 (0.621–3.968)	0.341	1.230 (0.405–3.733)	0.715
Admission sodium, per 1 mmol/L increase	0.995 (0.935–1.058)	0.866	0.947 (0.871–1.030)	0.204
Admission hyponatremia	1.335 (0.582–3.063)	0.495	—	—
Admission hypernatremia	Not estimable	—	—	—
Sodium variability index, per 1 mmol/L increase	0.900 (0.810–0.999)	0.048	0.827 (0.722–0.947)	0.006

Variable	Crude OR (95% CI)	P value	Adjusted OR, restricted model (95% CI)*	P value
Persistent hyponatremia within the first 72 h	4.213 (0.878–20.206)	0.072	—	—
Cumulative fluid balance, per 1000 mL increase	1.020 (0.793–1.312)	0.878	—	—
Diuretic therapy	0.840 (0.370–1.905)	0.676	—	—
Hypertonic saline administration	1.056 (0.318–3.509)	0.929	—	—
Mannitol administration	0.733 (0.303–1.773)	0.490	—	—
Number of sodium measurements, per additional measurement	0.989 (0.836–1.170)	0.901	—	—
Any sodium-modifying therapy†	0.937 (0.372–2.361)	0.891	—	—

Binary logistic regression; continuous variables per one-unit increase. Primary cohort (n = 96). * The restricted multivariable model included SVI, APACHE II score, admission sodium, and neurological admission diagnosis (58 events). Other models are reported in the text and Appendix A (Table A.1). † Any sodium-modifying therapy was defined as administration of diuretics, hypertonic saline, and/or mannitol during the first 72 hours. Admission hypernatremia was not estimable because it occurred in only one patient, in the ABD group, resulting in complete separation. ‡ Acute ischemic stroke or intracerebral hemorrhage; in the primary cohort, 12 patients had acute ischemic stroke and 16 had intracerebral hemorrhage. ABD, acute brain dysfunction; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RASS, Richmond Agitation–Sedation Scale; SVI, sodium variability index.

est 24-hour change were associated with ABD in the same direction as SVI, and among patients with normal admission sodium the OR adjusted for APACHE II score was 0.795 (95% CI 0.643–0.982) (Appendix A, Table A.2).

Discussion

In this retrospective cohort study of critically ill patients with an admission Glasgow Coma Scale score of 13 or lower, lower sodium variability during the first 72 hours of ICU admission was associated with ABD after adjustment for illness severity. The direction and magnitude of the association were similar across alternative models and sensitivity analyses, including the full verified cohort, although estimates were imprecise. Because the timing of ABD relative to sodium measurements could not be established, these findings describe an association and do not indicate that sodium variability predicts or contributes to ABD.

Early sodium variability and acute brain dysfunction

Previous studies have mainly related admission sodium, ICU-acquired dysnatremia, or correction rate to mortality and other global outcomes [1-4]; we examined the early sodium range in relation to a composite neurological outcome. Estimates for delirium, seizures, and coma were all in the same direction; the association was strongest for coma, the component most likely to overlap with impaired consciousness at admission and with sedation, although estimates were similar after excluding patients with an admission GCS score ≤8 and when coma was counted only in patients who never received sedation; the composite remained the primary outcome. The crude association was borderline and strengthened after adjustment for illness severity, which is compatible with confounding by severity but may also reflect chance or model instability in a small sample.

The interpretation of lower, rather than greater, sodium variability is not straightforward. Marked or rapid sodium shifts can alter cerebral water balance and neuronal function [6-10], but SVI captures only the maximum-to-minimum range, not the direction, rate, or timing of change. In our cohort, the association was explained in adjusted analyses by maximum rather than minimum sodium: for a given admission sodium, patients with ABD tended to have a smaller upward excursion, whereas nadir values were similar. Crude maximum sodium, however, did not differ significantly between groups, so this pattern requires confirmation. Bidirectional fluctuation was uncommon, so SVI mainly reflected the size of a unidirectional, usually upward, change. Persistent hyponatremia attenuated the association, particularly in the full cohort, in which the confidence interval included 1, suggesting that it may account for a substantial part of the association. However, the association had the same, imprecise, direction in patients with normal admission sodium, so incomplete correction of hyponatremia may explain part, but probably not all, of the finding. A smaller rise may also reflect management aimed at stable sodium values or more severe disturbance of water homeostasis. Reverse causation is also plausible: patients with established brain dysfunction, particularly those with neurological diagnoses, may have been managed with tighter sodium targets. Adjustment for neurological diagnosis and osmotherapy did not materially change the estimate, but these variables capture management intensity only crudely. Lower SVI may therefore be a marker of the patient's condition and management rather than a physiological mechanism, and the find-

ing should not be interpreted as evidence that a smaller sodium increase is protective or harmful.

Two MIMIC-IV studies found greater early sodium variability to be associated with higher mortality in intracerebral hemorrhage [23] and cerebral infarction [24]. Their populations, outcomes, and metrics (relative dispersion vs. absolute range) differed from ours, as in earlier work in traumatic brain injury [22], and studies comparing variability metrics within the same cohort are needed.

Admission sodium and admission hyponatremia were not associated with ABD, suggesting that a single measurement at ICU entry provides limited information about subsequent neurological status. Persistent hyponatremia was more frequent in patients with ABD, but only 13 patients met this definition, and it was examined only in a sensitivity analysis.

Illness severity, mechanical ventilation, and sedation

Higher APACHE II score was associated with ABD in both models [25], and sedation was associated with ABD in the eight-variable model. Sedation and mechanical ventilation are best regarded as markers of severity and treatment intensity: sedatives can contribute to delirium and obscure the distinction between pharmacological depression of consciousness and coma, and detailed data on sedative agents, doses, and depth of sedation were not available. Because sedation was recorded at any time during the ICU stay, it may partly reflect the outcome, which limits its interpretation as a covariate. Residual confounding by fluid composition, renal function, endocrine disturbances, intracranial pathology, and the dose and timing of osmotic therapies remains possible.

Clinical implications

SVI can be calculated from routine laboratory data, but these results cannot support treatment decisions; prospective studies with defined temporal sequencing are needed to determine whether it has any value for risk assessment.

Strengths and limitations

Strengths include a clinically relevant neurological outcome [11-14], a predefined observation window, and multiple complementary analyses, which nevertheless cannot overcome the limitations of the design and sample size.

Several limitations should be acknowledged. First, the retrospective single-center design limits causal inference and generalizability, and the small sample reduced precision. The eight-variable model had approximately 4.75 events per variable and a bootstrap calibration slope of 0.66; the restricted model (approximately 9.5 events per variable; calibration slope 0.78) was specified during revision and should be regarded as a check on the stability of the estimate rather than an independent confirmation. Second, the cohort was highly selected: 302 of 398 screened patients (76%) were excluded, including 84 for incomplete neurological assessment, a criterion related to outcome ascertainment; data on excluded patients were not available, so the direction of any resulting bias cannot be estimated. Third, the requirement for 72 hours of ICU observation may introduce survivor bias; the 13 patients who died or were transferred earlier all had ABD, and although results in the full cohort were similar, this concern remains. Fourth, ABD was identified from routine documentation at any time during the ICU stay rather than from time-stamped assessments. Because an admission Glasgow Coma Scale score of 13 or lower was an inclusion criterion, all patients had impaired consciousness at admission; ABD may therefore have been present before the sodium observation period, and the findings may not apply to patients with preserved consciousness. An analysis restricted to incident ABD was not possible, adjustment for admission Glasgow Coma Scale score and exclusion of patients with an admission score ≤8 only partly address this, and reverse causation or confounding by indication cannot be excluded. Fifth, CAM-ICU frequency and the timing of sedation relative to neurological assessments were not systematically recorded, so coma could not be fully distinguished from sedation, although estimates were similar in patients who never received sedation; hypoactive delirium may also have been under-recognized. Sixth, sodium was measured according to clinical need, and SVI does not distinguish gradual from abrupt change. Finally, the study did not test whether modifying sodium dynamics affects outcomes.

CONCLUSIONS

In this retrospective cohort of critically ill adults with impaired consciousness at ICU admission, lower sodium variability during the first 72 hours of ICU stay, mainly reflecting a smaller sodium rise, was associated with acute brain dysfunction after adjustment for illness severity, whereas admission sodium was not.

Because the timing of brain dysfunction relative to sodium changes could not be established, these findings are hypothesis-generating and do not indicate prediction or causation. Prospective multicenter studies with standardized, time-stamped neurological assessments are needed.

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■ CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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■ References

1. Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Med. 2010;36(2):304-11.
2. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. Crit Care. 2008;12(6):R162.
3. Waite MD, Fuhrman SA, Badawi O, Zuckerman IH, Franey CS. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. J Crit Care. 2013;28(4):405-12.
4. Darmon M, Pichon M, Schwebel C, et al. Influence of early dysnatremia correction on survival of critically ill patients. Shock. 2014;41(5):394-9.
5. Marshall DC, Salciccioli JD, Goodson RJ, et al. The association between sodium fluctuations and mortality in surgical patients requiring intensive care. J Crit Care. 2017;40:63-8.
6. Sterns RH, Hix JK, Silver S. Management of hyponatremia in the ICU. Chest. 2013;144(2):672-9.
7. Giuliani C, Peri A. Effects of hyponatremia on the brain. J Clin Med. 2014;3(4):1163-77.
8. Kengne FG, Decaux G. Hyponatremia and the brain. Kidney Int Rep. 2018;3(1):24-35.
9. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014;170(3):G1-47.
10. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-42.
11. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825-73.
12. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753-62.
13. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306-16.
14. Liu SB, Wu HY, Duan ML, et al. Delirium in the ICU: how much do we know? A narrative review. Ann Med. 2024;56(1):2405072.
15. O'Keeffe F, Cervoni I, Ganau M, Prisco L. Serum biomarkers of delirium in critical illness: a systematic review of mechanistic and diagnostic evidence. Intensive Care Med Exp. 2025;13(1):90.
16. Sen S, Tran N, Chan B, Palmieri TL, Greenhalgh DG, Cho K. Sodium variability is associated with increased mortality in severe burn injury. Burns Trauma. 2017;5:34.
17. Thongprayoon C, Cheungpasitporn W, Yap JQ, Qian Q. Increased mortality risk associated with serum sodium variations and borderline hypo- and hypernatremia in hospitalized adults. Nephrol Dial Transplant. 2020;35(10):1746-52.
18. Chewcharat A, Thongprayoon C, Cheungpasitporn W, Mao MA, Thirunavukkarasu S, Kashani KB. Trajectories of serum sodium on in-hospital and 1-year survival among hospitalized patients. Clin J Am Soc Nephrol. 2020;15(5):600-7.
19. Grim CCA, Termorshuizen F, Bosman RJ, et al. Association between an increase in serum sodium and in-hospital mortality in critically ill patients. Crit Care Med. 2021;49(12):2070-9.
20. Liang S, Sun L, Zhang Y, et al. Sodium fluctuation as a parameter in predicting mortality in general hospitalized patients. Front Med (Lausanne). 2024;11:1399638.
21. Nasser A, Chaba A, Laupland KB, et al. ICU-acquired hypernatremia: prevalence, patient characteristics, trajectory, risk factors, and outcomes. Crit Care Resusc. 2024;26(4):303-10.
22. Harrois A, Anstey JR, van der Jagt M, et al. Variability in serum sodium concentration and prognostic significance in severe traumatic brain injury: a multicenter observational study. Neurocrit Care. 2021;34(3):899-907.
23. Sun S, Fei X, Gong K, Huang X. Dynamic sodium dysregulation predicts mortality in intracerebral hemorrhage: a retrospective cohort study of temporal variability and absolute thresholds. Neurosurg Rev. 2025;48(1):615.
24. Sun S, Fei X, Gong K, Huang X, Zhou X. Early serum sodium variability and mortality in critically ill patients with cerebral infarction: a retrospective cohort study. Eur J Med Res. 2026;31(1):416.
25. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.