# Appendix A. Supplementary material

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

## A.1. Data verification

Before the revised analyses, the dataset was re-verified against the source medical records. This led to the following changes: correction of the minimum 72-hour sodium value in three patients, in whom the admission sodium value had not been included; coding of any sodium-modifying therapy as administration of diuretics, hypertonic saline, and/or mannitol during the first 72 hours (the variable had previously been incomplete); correction of two data-entry errors (one chloride value and one RASS score); correction of ICU and hospital length-of-stay values in 21 patients and of ventilation duration in 2 patients; and identification of 13 patients who had been included in the originally submitted analysis although their ICU stay was shorter than 72 hours (12 died and 1 was transferred after 39–70 hours). Five admission laboratory values (creatinine in two patients, lactate in two, and procalcitonin in one) that were missing from the earlier analysis file were confirmed against the records. In accordance with the stated eligibility criteria, the 13 patients were excluded from the primary analysis (n = 96), and the main analyses were repeated in the full verified cohort (n = 109). All analyses were performed in R version 4.6.1.

## A.2. Model diagnostics and internal validation

Variance inflation factors ranged from 1.221 to 1.526 in the restricted model and from 1.045 to 1.177 in the eight-variable model. In internal validation with 1,000 bootstrap resamples, the restricted model had an apparent C-statistic of 0.720, an optimism-corrected C-statistic of 0.674, and a calibration slope of 0.78; the corresponding values for the eight-variable model were 0.791, 0.725, and 0.66. Adding SVI increased the apparent C-statistic from 0.655 to 0.720 in the restricted model and from 0.763 to 0.791 in the eight-variable model. In the full verified cohort, the restricted model had an apparent C-statistic of 0.716, an optimism-corrected C-statistic of 0.679, and a calibration slope of 0.80 (eight-variable model: 0.811, 0.754, and 0.70).

## A.3. Alternative model specifications

Across alternative specifications in the primary cohort, the inverse association between SVI and ABD was directionally consistent: unadjusted OR 0.900; adjusted for APACHE II score, OR 0.864; additionally adjusted for sedation, OR 0.887; restricted model, OR 0.827; eight-variable model, OR 0.860 (Table A.1). Adjustment for APACHE II score produced the largest single change in the estimate, suggesting that illness severity may have masked part of the crude association; this pattern should be interpreted cautiously in a small sample. APACHE II score was not correlated with the number of sodium measurements (Spearman's $\rho = -0.11$, $p = 0.27$).

## A.4. Individual components of acute brain dysfunction

Among the 58 patients with ABD in the primary cohort, delirium was documented in 36, seizures in 21, and coma in 18 (not mutually exclusive). In univariable analyses, SVI was not significantly associated with delirium (OR 0.950, 95% CI 0.854–1.056; $p = 0.340$), seizures (OR 0.902, 95% CI 0.786–1.035; $p = 0.140$), or coma (OR 0.940, 95% CI 0.820–1.078; $p = 0.378$). With the restricted-model covariates, the estimates were all in the same direction as for the composite outcome (Table A.1). The association was strongest for coma, the only component with a confidence interval excluding 1; because coma is the component most likely to overlap with impaired consciousness at admission and with sedation, we performed additional analyses excluding patients with an admission GCS ≤8, removing coma from the composite outcome, and counting coma only in patients who never received sedation (Section A.5, Table A.2); estimates were similar in each. The component analyses should not be interpreted as evidence of a component-specific association. These analyses were limited by the small number of events per component.

**Table A.1. Sensitivity analyses of the association between the sodium variability index and acute brain dysfunction**

| Analysis | Patients (events) | OR for SVI per 1 mmol/L (95% CI) | P value |
|---|---|---|---|
| Primary cohort | | | |
| Crude | 96 (58) | 0.900 (0.810–0.999) | 0.048 |
| Restricted model (primary)* | 96 (58) | 0.827 (0.722–0.947) | 0.006 |
| Restricted model, Firth penalized regression | 96 (58) | 0.838 (0.730–0.950) | 0.005 |
| Eight-variable model (secondary)† | 96 (58) | 0.860 (0.756–0.978) | 0.021 |
| SVI + APACHE II score | 96 (58) | 0.864 (0.770–0.970) | 0.013 |
| SVI + APACHE II score + sedation | 96 (58) | 0.887 (0.788–0.998) | 0.047 |
| Restricted model + hypertonic saline and mannitol | 96 (58) | 0.820 (0.713–0.943) | 0.005 |
| Restricted model + persistent hyponatremia | 96 (58) | 0.858 (0.736–0.999) | 0.048 |
| Restricted model + admission Glasgow Coma Scale¶ | 96 (58) | 0.822 (0.709–0.951) | 0.009 |
| Patients who never received sedation during the ICU stay* | 69 (34) | 0.841 (0.721–0.982) | 0.029 |
| Non-neurological admission diagnoses‡ | 68 (39) | 0.864 (0.739–1.010) | 0.066 |
| Neurological admission diagnoses‡ | 28 (19) | 0.752 (0.562–1.005) | 0.054 |
| Component outcome: delirium§ | 96 (36) | 0.922 (0.808–1.053) | 0.230 |

| Analysis | Patients (events) | OR for SVI per 1 mmol/L (95% CI) | P value |
|---|---|---|---|
| Component outcome: seizures§ | 96 (21) | 0.843 (0.708–1.004) | 0.055 |
| Component outcome: coma§ | 96 (18) | 0.809 (0.671–0.976) | 0.027 |
| Full verified cohort, including 13 patients with ICU stay <72 h | | | |
| Crude | 109 (71) | 0.906 (0.820–1.001) | 0.051 |
| Restricted model* | 109 (71) | 0.855 (0.758–0.966) | 0.012 |
| Restricted model, Firth penalized regression | 109 (71) | 0.864 (0.765–0.967) | 0.011 |
| Eight-variable model† | 109 (71) | 0.856 (0.755–0.971) | 0.016 |
| Restricted model + persistent hyponatremia | 109 (71) | 0.889 (0.780–1.013) | 0.077 |
| Restricted model + admission Glasgow Coma Scale¶ | 109 (71) | 0.849 (0.743–0.970) | 0.016 |

* SVI, APACHE II score, admission sodium, and neurological admission diagnosis (acute ischemic stroke or intracerebral hemorrhage; in the primary cohort, 12 patients had acute ischemic stroke and 16 had intracerebral hemorrhage). † Age, APACHE II score, invasive mechanical ventilation, sedation, SVI, cumulative fluid balance, number of sodium measurements, and any sodium-modifying therapy. ‡ Adjusted for APACHE II score and admission sodium. § Restricted-model covariates; outcome = individual component. ¶ Partial check for brain dysfunction present at ICU admission; because coma is a component of ABD, this adjustment partly conditions on the outcome. Firth confidence intervals are profile-likelihood intervals. 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.

## A.5. Additional analyses performed in response to peer review

In response to reviewers' comments, the following analyses were performed in the primary cohort (Table A.2). Of the 18 patients classified as having coma, 11 had a GCS score ≤8 at ICU admission, all of whom were classified as having ABD, and 7 had an admission GCS score of 9–13 and a lowest recorded GCS score ≤8 (3 of them received sedation). Because coma was identified from physician documentation accompanied by a GCS score ≤8, patients with an admission GCS ≤8 were excluded in one analysis, coma was removed from the composite outcome in another, and in a third coma was counted only in patients who never received sedation. Among the 85 patients with an admission GCS of 9–13 (47 with ABD), median SVI was 4 (IQR 3–7.5) mmol/L in patients with ABD and 7 (4–10) mmol/L in those without ABD (p = 0.039). Sedation was recorded as any sedation during the ICU stay; its timing relative to neurological assessments and the frequency of CAM-ICU assessments were not systematically recorded.

The pattern of sodium change was characterized from all time-stamped sodium values within 72 hours. Relative to admission sodium, 8 patients had a bidirectional profile (a rise and a fall of ≥3 mmol/L each), 46 a net rise, 2 a net fall (net change ≥3 mmol/L), and 40 a stable profile; ABD occurred in 2, 26, 2, and 28 of these patients, respectively. Median net change (last value within 72 hours minus admission sodium) was 2 (IQR 0–4) mmol/L in patients

**Table A.2. Additional sensitivity analyses in the primary cohort (n = 96)**

| Analysis | Patients (events) | OR per unit (95% CI) | P value |
|---|---|---|---|
| Impaired consciousness at admission and sedation (exposure: SVI) | | | |
| Admission GCS ≤8 excluded, crude | 85 (47) | 0.897 (0.802–1.004) | 0.059 |
| Admission GCS ≤8 excluded, restricted model* | 85 (47) | 0.821 (0.707–0.954) | 0.010 |
| Admission GCS ≤8 excluded, restricted model, Firth penalized regression* | 85 (47) | 0.834 (0.715–0.955) | 0.008 |
| Coma removed from outcome (delirium and/or seizures), restricted model* | 96 (52) | 0.854 (0.746–0.978) | 0.022 |
| Coma counted only in patients who never received sedation, restricted model* | 96 (57) | 0.837 (0.732–0.958) | 0.010 |
| Patients who never received sedation, restricted model* | 69 (34) | 0.841 (0.721–0.982) | 0.029 |
| Pattern of sodium change (entered in place of SVI)† | | | |
| Net change, per 1 mmol/L | 96 (58) | 0.866 (0.739–1.014) | 0.074 |
| Largest change within any 24-hour interval, per 1 mmol/L | 96 (58) | 0.803 (0.673–0.958) | 0.015 |
| Number of direction changes, per change | 96 (58) | 0.961 (0.773–1.196) | 0.724 |
| SVI, restricted model + number of direction changes | 96 (58) | 0.825 (0.718–0.947) | 0.006 |
| Admission sodium categories (exposure: SVI)‡ | | | |
| Admission hyponatremia (<135 mmol/L), crude | 42 (27) | 0.875 (0.748–1.022) | 0.092 |
| Admission hyponatremia (<135 mmol/L), adjusted | 42 (27) | 0.852 (0.722–1.005) | 0.057 |
| Normal admission sodium (135–145 mmol/L), crude | 53 (30) | 0.856 (0.710–1.033) | 0.105 |
| Normal admission sodium (135–145 mmol/L), adjusted | 53 (30) | 0.795 (0.643–0.982) | 0.033 |

* SVI, APACHE II score, admission sodium, and neurological admission diagnosis. † Each variable entered in place of SVI in the restricted model, except the last row, in which the number of direction changes was added to the restricted model. Net change, last sodium value within 72 hours minus admission sodium; direction changes, changes in the sign of the difference between consecutive sodium values. ‡ Adjusted for APACHE II score only because of the small subgroups; one patient with admission hypernatremia is not shown. Firth confidence intervals are profile-likelihood intervals. ABD, acute brain dysfunction; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; GCS, Glasgow Coma Scale; OR, odds ratio; SVI, sodium variability index.

with ABD and 3 (1–6.75) mmol/L in those without ABD (p = 0.132), and the median largest change within any 24-hour interval was 4 (3–6) and 5.5 (3.25–7) mmol/L, respectively (p = 0.061). Median SVI in patients with and without ABD was 7 vs. 10 mmol/L among patients with admission hyponatremia (p = 0.056) and 4 vs. 5 mmol/L among those with normal admission sodium (p = 0.214); only one patient had admission hypernatremia.

## A.6. Admission diagnoses

**Table A.3. Admission diagnoses in the primary cohort (n = 96)**

| Admission diagnosis | Total, n (%) | No ABD (n = 38) | ABD (n = 58) |
|---|---|---|---|
| COVID-19 pneumonia | 22 (22.9) | 7 | 15 |
| Intracerebral hemorrhage | 16 (16.7) | 5 | 11 |
| Acute heart failure | 15 (15.6) | 8 | 7 |
| Sepsis | 14 (14.6) | 4 | 10 |
| Acute ischemic stroke | 12 (12.5) | 4 | 8 |
| Arrhythmia | 6 (6.3) | 5 | 1 |
| Respiratory failure (non-COVID) | 5 (5.2) | 4 | 1 |
| ARDS (non-COVID) | 4 (4.2) | 1 | 3 |
| Cardiogenic shock | 2 (2.1) | 0 | 2 |

Neurological admission diagnosis (acute ischemic stroke or intracerebral hemorrhage): 28 patients (29.2%). Among the 13 additional patients in the full verified cohort, 6 had COVID-19 pneumonia, 4 intracerebral hemorrhage, 2 sepsis, and 1 acute ischemic stroke. ABD, acute brain dysfunction; ARDS, acute respiratory distress syndrome.